Srihari S. Naidu
Editor

Hypertrophic Cardiomyopathy

Foreword by
Bernard Gersh

Historical Context by
Eugene Braunwald

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Foreword

Hypertrophic cardiomyopathy (HCM) is a relatively new disease or group of diseases that seem to be a magnet for controversy in many aspects. It is an important clinical entity and together with bicuspid aortic valve is one of the two commonest monogenetic inherited cardiac diseases. What is so controversial also contributes to its fascination in that the disease entity is characterized by heterogeneity in regard to the clinical presentation, natural history, response to therapy, and the underlying genetic substrate.

This excellent book is a valuable contribution to the literature, and its appearance is particularly opportune given the publication of the recent ACCF/AHA guidelines in 2011—on which the Editor of this textbook, Dr. Srihari S. Naidu, and I served together—and the expected ESC guidelines in 2014. Such guidelines are a testament to the fact that we have reached a point in which there is much that we agree upon; but in addition, a reasonable body of evidence has also helped us to define our areas of disagreement, and all of these are well covered in this excellent book edited by Dr. Naidu with contributions from recognized experts in the field.

The list of contents emphasizes that this book encompasses the entire scope of hypertrophic cardiomyopathy and the issues that continue to stimulate vibrant and spirited discussion among those interested in this condition. It adds a level of detail as well as practical information that cannot be fully realized within national guidelines on the subject, and the chapter by Dr. Eugene Braunwald, whose seminal work in the 1960s taught us so much about this entity, is a classic and unique insight into a period of discovery and a wonderful contribution to this book.

What this book also emphasizes is that we are dealing with a very complex clinical syndrome, which serves to underscore the need for Centers of Excellence. Such centers need to have adequate patient volumes and the availability of experts in many different fields including clinical adult and pediatric cardiologists, up-to-date cardiac imaging expertise, interventional cardiologists and cardiac surgeons with expertise in surgical myectomy and alcohol septal ablation, electrophysiologists, geneticists, and genetic counselors. All Centers of Excellence need to provide unimpeded access to all forms of therapy and particularly the invasive modalities, whether this be on site or by a seamless mechanism of referral. In this regard, the chapter on constructing a Center of Excellence is a novel addition and will, I suspect, be particularly well received.

This is a dynamic field and ripe for further clinical and basic investigation and collaboration between centers nationally and internationally. I would emphasize the latter because despite the relative frequency of this disease entity, the majority of centers still see a limited number of patients, and the ability to collaborate across regions and countries will ensure the development of the databases we need for the future. In an era of large global trials in many areas of cardiovascular disease, hypertrophic cardiomyopathy is somewhat of an outlier in that it has not lent itself to many randomized trials. Drugs needed for the pharmacological treatment of symptomatic hypertrophic cardiomyopathy (beta blockers, calcium blockers, and disopyramide) are approximately 50 years old, and these have been evaluated in only a few small randomized trials.

In regard to the preferred method of septal reduction therapy in particular with surgical myectomy or alcohol septal ablation, we have no randomized trials, and none are likely to be performed in the future given the sample size and duration of follow-up required and the

already existing knowledge in regard to early outcomes. Guidelines and other statements have therefore had to rely upon a reasonable consensus. In this respect, the recent ACCF/AHA guidelines have concluded that in good surgical candidates, myectomy in experienced hands is the "gold standard." In poor or suboptimal surgical candidates, alcohol septal ablation is an excellent alternative. In patients who are deemed appropriate surgical candidates but who wish to decline surgery, alcohol septal ablation is reasonable but only after a full, detailed, informed, and balanced discussion between physician and patient. In all cases, it is essential that patients understand the pros and cons of both procedures. Indeed, the preferred method of septal reduction therapy has been the impetus for considerable and vigorous debate and remains a changing landscape.

It is intriguing to speculate upon the changes we might find in the second or third editions of this book. Part of the fascination of hypertrophic cardiomyopathy is that its knowledge base continues to unfold, and I suspect that some answers to the current research agenda proposed by the guidelines will be forthcoming in the near future. This research agenda does not lack for questions. From a genetic standpoint, we know little about the causes of hypertrophic cardiomyopathy both in patients who are mutation positive and mutation negative. Hopefully, the rapid technical innovations in genetics will likely bear fruit in this area in the near future. The link between the genotype and the phenotype needs further clarification in particular, as does the management and evaluation of genotype-positive/phenotype-negative patients. Whether genotyping will be a useful tool for the prognosis and risk stratification of sudden cardiac death and other sequelae such as heart failure remains to be determined. Although the role of genotyping for prognosis in current clinical practice is extremely limited with the exception of genetic counseling, it is likely that as geneticists are able to delve into the secrets of the hypertrophic genotype in more detail, genotyping as a prognostic tool may very well become a reality.

Ongoing studies using MRI will likely in the next few years clarify the clinical significance of myocardial fibrosis and the attributed risk of sudden cardiac death among other manifestations of the disease. Moreover, the entire area of risk stratification for prognosis including for sudden cardiac death and ICD implantation needs to be refined, and large collaborative studies are needed. There is also a need for new medical therapies, and this will depend upon an enhanced understanding of the basic physiology and energetics of the hypertrophied heart. Finally, as already alluded to, there is a particular need for comparative assessments of septal reduction strategies with longer-term follow-up, particularly after alcohol septal ablation.

So after 50 years of discovery and clinical investigations, the natural history of hypertrophic cardiomyopathy has been clarified; in regard to the pathophysiology of the role of obstruction, this is now well understood, but other mechanisms at play in this disease need further study. The use of molecular genetics in regard to genetic counseling should be a routine clinical tool in hypertrophic cardiomyopathy centers, but one gains the impression that we are just now seeing the tip of the genetic iceberg and that much more interesting information will emanate in the next few years. Finally, we do have a number of effective diagnostic, pharmaceutical, and invasive therapeutic approaches that need comparative studies. "We now know much more about what we do not know."

Dr. Naidu and his colleagues should be congratulated on this excellent and timely book. Hypertrophic cardiomyopathy has risen on the radar screen within national guidelines, clinical practice, and the mainstream media. I have no doubt that this book will be welcomed as a vital resource for both individual clinicians and Centers of Excellence interested in this fascinating disease and that we will see many future editions of this book, which will be considered as one of the definitive texts in the field.

Rochester, MN, USA Bernard J. Gersh, MD, ChB, DPhil, FRCP, MACC

Preface

Writing a textbook is no easy task. Indeed, it is oftentimes described as a labor of love, something that your passion must push forward lest you lose steam halfway through. Now at the culmination of what started almost 2 years ago, I will tell you that this is true. The desire to simply finish what has been started is not nearly enough; an author has to really want a book to be not only completed but also worthy of the time, effort, and inspiration that designed it. So what kept me going? I have often wondered how I came to this point in my career, where I care so deeply about a single disease that I would want to become instrumental in its course. It is, I think, an interesting story and one that I will now share with you. In doing so, perhaps you will understand a little bit of why I created this book and the void I was hoping to fill.

I first heard the term *hypertrophic cardiomyopathy* (HCM) in 1994 as part of my second-year cardiovascular pathophysiology course at Brown University Medical School. What was clear to me within just a few short weeks was that this was a remarkable disease. Not only was the physiology impossibly intricate, but the diverse symptomatology, differential age at presentation from childhood to the elderly, and genetic and social aspects as well as the diagnostic and therapeutic challenges made this disease uniquely appealing. To be clear, at the time, there was little in terms of treatment and only a relatively rudimentary understanding of diagnosis, physiology, and genetics. But that was part of what fascinated me—the feeling that despite years of progress, we remained in some ways at the beginning.

My next memory of HCM is from 1998 during internal medicine residency at Cornell Medical Center/New York Presbyterian Hospital in Manhattan. A senior resident was presenting a case during morning conference, and it turned out to be one of HCM. As he went around the room, I remember being able to articulate the underlying etiology of dynamic outflow tract obstruction, something I was quite proud of. He went on to describe the potential management options. At the time, dual-chamber pacing to reduce outflow tract obstruction was a leading concept having first been reported formally in 1992. In addition, he described a novel percutaneous approach to eliminating obstruction, alcohol septal ablation, which in early studies had been shown to mimic results of surgical septal myectomy. A few things stood out in my mind at this time. First, it appeared that HCM was extremely rare, this being the first case that we had seen during my 2 years of residency. Second, it seemed that neither surgical myectomy nor alcohol septal ablation was being performed with any regularity. And third, the disease was still fascinating to me—something I wanted to learn more about.

My own inroads into the management of HCM started in fellowship training at the University of Pennsylvania. Believe it or not, I went there initially to become a heart failure and transplant specialist. My interest in hemodynamics, physiology, and heart failure in particular was paramount up until the point that I stepped into the cardiac catheterization laboratory. As it turns out, I like to use my hands and soon realized that the hemodynamic and heart failure concepts I so loved were right there at the cath table. So it was that in 2000, I saw my first alcohol septal ablation performed by one of my mentors, Dr. John Hirshfeld. Here was a patient suffering from severe heart failure, unable to walk one block on a flat level without significant dyspnea

despite high-dose medications and unable to climb a flight of stairs without fear of passing out. The procedure went smoothly, and 3 days later the patient was transformed. His heart failure was vastly improved. It was surreal, and I have never forgotten.

Four years later, I graduated fellowship and took my first job as a faculty interventionalist back at my residency program, Cornell. My goals were to be an academic interventional cardiologist focusing on drug-eluting stents while becoming as good a clinician as I could. As it were, though, most academic institutions like their faculty to develop niches—areas of expertise that they could call their own, master, and develop. So it was that a patient presented to the emergency room with severe hypertrophic cardiomyopathy refractory to multiple and high-dose medications. Moreover, this patient had already undergone surgical myectomy 4 years prior, but the area of maximal septal-valve contact was clearly missed. His gradients were almost 300 mmHg with provocation, 100 mmHg resting, and the patient described ongoing severe symptoms that only worsened after surgery. This was my first alcohol septal ablation patient. Ten years later, I count him as not only a patient but a longtime friend, someone whose life has vastly improved due to my efforts.

Over the next few years, I became first the local and then the regional HCM expert. I read all the relevant original articles, all the reviews, and became intimately involved in every aspect of the disease from presentation to diagnosis and management. After moving to Winthrop University Hospital in 2006 as Director of the Cardiac Catheterization Laboratory, I created the HCM treatment center. What started as a handful of patients has now grown to almost 500. Over time, the Center has grown to include all aspects of diagnosis including cardiac MRI and genetics, electrophysiology, family screening, original research, randomized controlled trials, pediatrics, surgery, and alcohol septal ablation. We are now reaching into the community to raise awareness in high schools and impact statewide legislation. With all this, our national presence has grown with presentations at national meetings, live proctoring courses (Fig. 1), numerous grand rounds, as well as a biannual patient-centered regional conference.

Fig. 1 (**a**) Dr. Naidu with select faculty and participants from the first Annual Alcohol Septal Ablation Live Proctoring Course in 2014. (**b**) Dr. Naidu addresses the audience. (**c**) Dr. Naidu and Co-Director of the Live Course, Dr. George Hanzel, perform an alcohol septal ablation. (**d**) Dr. Michael Fifer (*right*) teaches from the viewing area

So where does this book come in? No one reads books anymore, I was once told—and to some extent, they are correct. But HCM is different, I think. In 2009, I was asked to serve on the first official American College of Cardiology (ACC)/American Heart Association (AHA) guideline on the diagnosis and management of HCM—I was to be the official representative of the Society for Cardiovascular Angiography and Interventions (SCAI). Although chosen to represent an interventional society, I brought all my insights as a medical director of a busy HCM program contributing as much as possible on all aspects. This was a transformative process for me. Working alongside luminaries such as guideline chair Dr. Bernard Gersh, I realized that those on the committee were part of a larger mission to (a) make sure our combined wisdom makes it to paper, (b) help physicians realize that HCM management is difficult and time consuming and should thus be done alongside an HCM Center of Excellence, and (c) make sure the recommendations we are writing are practical enough to be followed. Two years later, I was very proud of the group's efforts and culminating document. But something was missing.

It struck me at that point that there was no vehicle other than these newly created guidelines to explain why we do what we do for patients with this disease. We explained what to do and made dozens of formal recommendations, but the "why" and the "how" were limited—necessarily so as most were consensus driven. That's when I realized that books are still necessary for rare diseases. This is the way we put down in words what our experience has taught us. This is the way we can teach others. This is how we can grow the understanding, appeal, and impact of appropriately treating these patients and their families. This is where the details come. A book could be a blueprint not only for treating patients in a comprehensive yet practical way but also for creating and sustaining a Center of Excellence—and in doing so sustaining the optimal yet dynamic management of a rare disease.

This textbook is constructed purposefully to do this. After the foreword and this preface, we travel back in time to rediscover HCM, dive into the pathology, and tease out the nuances of diagnosis from echocardiography to cardiac MRI. A treat for the reader, Dr. Eugene Braunwald provides his firsthand account of encountering HCM. We discuss management including medications, pacemakers and defibrillators, and invasive septal reduction therapy—both surgical myectomy and alcohol septal ablation. Chapters on genetics, family screening, lifestyle concerns, and athletic screening are added given the ongoing controversies and differences of opinion on many of these. Advanced management including imaging, heart failure, and transplantation are also discussed in detail.

The chapters are meant to be practical, with each one starting off with key points of knowledge and ending with clinical pearls—the tiny morsels of information that only the experts have known about. The practical approach continues with dedicated chapters on creating a Center of Excellence and on case-based reviews and discussions. This last chapter takes you through the management of actual patients, showing over decades the nuances to diagnosis and management and the sometimes abrupt changes in the course of their diseases that necessitate correspondingly abrupt modifications in treatment. Through it all, the reader not only understands the dogma of HCM care as depicted in the guidelines but also the stuff between the cracks—the knowledge that not only separates the student from the teacher but the teacher from the master.

I would be remiss if I did not credit several individuals for making sure that HCM—the disease—was not "lost" after its discovery over 50 years ago and then for rapidly raising awareness and helping develop treatment options over the past two decades. Perhaps the two most influential would be Dr. Eugene Braunwald (Fig. 2) and Dr. Barry Maron. While the former helped describe the first cases and delineate the underlying pathophysiology, the latter took the disease in—like it was part of his family—and shepherded its rise and acceptance as well as the growth of other physicians with similar passion. As a result, there are now many HCM experts throughout the world with unique expertise that ranges from pathophysiology to medical therapy, genetics to imaging, alcohol septal ablation to surgery, and electrophysiology to transplantation. And patient-centered groups have also arisen right alongside providing that

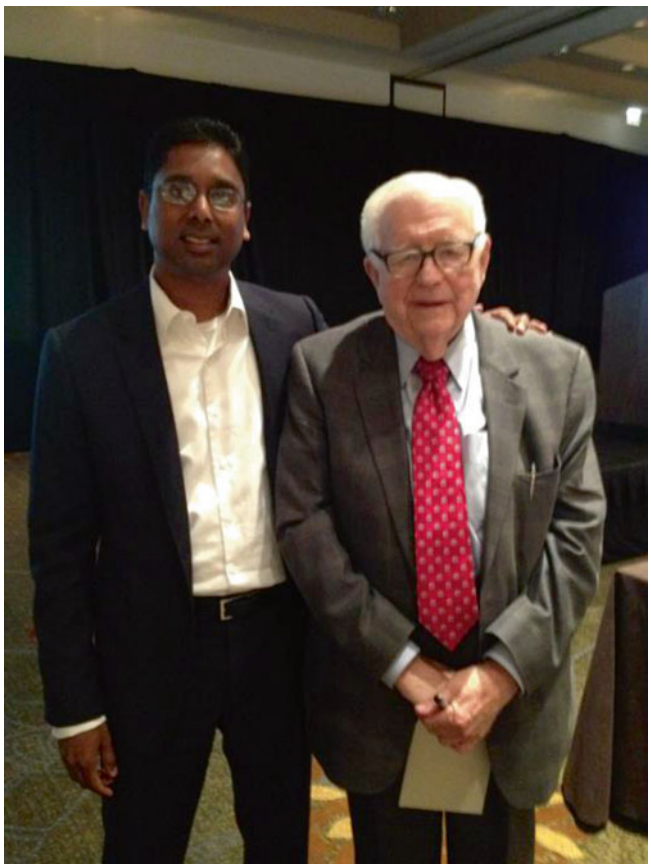

Fig. 2 Dr. Naidu and Dr. Braunwald at the 2013 HCM Summit

much-needed patient voice and drive for advocacy. Together, we form a very strong community tied by our deep passion for this disease and the patients and families that are affected by it—in essence, we are each other's extended family.

This book would not have been possible without several people who have inspired and supported me over the years. To my parents and sister, who quietly told me I could do anything and always stood by me even when I was my own worst enemy; to Vartan Gregorian, whose leadership style I think rubbed off on me; to John Hirshfeld, Howard Herrmann, Robert Wilensky, Daniel Kolansky, and Mariell Jessup, who inspired me to reach higher, focus, and be impactful in everything I do; to Kevin Marzo and Michael Niederman, who took a chance on me and let me fly; to Garry Schwall, who supported my interest in HCM right from the beginning; to Nicole Goldman, who keeps me on track with my patients; to Nina Naidu, who told me not just that I could do this but that I should; and to my son, Kiran Naidu, who makes me happy every single moment of my life and lets me take the time to enjoy it. This book is for all of you. And I thank you.

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Hypertrophic Cardiomyopathy: The Past, the Present, and the Future

1

Eugene Braunwald

Abstract

Patients with left ventricular hypertrophic cardiomyopathy (HCM) were described in the middle of the nineteenth century. Clinico-pathologic correlations carried out in the first half of the twentieth century revealed that HCM is characterized by familial occurrence, hypertrophy of the interventricular septum, dynamic obstruction to left ventricular outflow, impaired left ventricular filling, and rarely, sudden death or heart failure.

The clinical diagnosis can usually be confirmed by echocardiography. Treatment includes beta blockade and invasive therapy to reduce obstruction (septal myectomy or catheter induced alcohol septal ablation). In patients at high risk for sudden death, an implanted defibrillator is indicated. HCM is a disease of sarcomeric proteins; more than 1,500 mutations on ten genes have been described.

Future challenges include learning more about patients with characteristic mutations but normal phenotypes and the development of drugs that are specifically directed at the molecular abnormalities.

Keywords

Familial heart disease • Ventricular hypertrophy • Sudden death • Septal myectomy • Beta-blockade • Echocardiography • Implanted defibrillator

Hypertrophic cardiomyopathy (HCM) occurs once in about 500 births, is the most common familial heart disease, is seen in all races, both sexes, on all continents, and has been estimated by Maron et al to occur in at least 600,000 Americans [1]. HCM may present at any age, but it is now recognized as the most common cause of sudden cardiac death in athletes as well as in adolescents. Alternatively, it may be of no or little clinical import and is compatible with normal survival.

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This chapter traces the evolution of our understanding of this condition from its initial description in the mid-nineteenth century, and its emergence as a specific entity as a consequence of clinical-pathologic correlations in the first half of the twentieth century. With the development of left heart catheterization in the 1960s, many more patients with HCM were identified and its unique pathophysiology was described. At present, echocardiography is employed almost universally in diagnosis, while therapy involves the use of several drugs, interventions to relieve obstruction as well as the implantation of cardioverter/defibrillators to prevent sudden cardiac death. Beginning in the 1990s, advances in molecular genetics have greatly enhanced understanding of the fundamental mechanisms of HCM, but have also raised some important questions. Future efforts will involve the delineation of genotype-phenotype relations and more rigorous evaluation of currently available therapies.

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The Past

Clinical-Pathologic Observations

The Birth of HCM

Three patients with what now appears to have been HCM were described by French physicians in the late 1860s [2–4]. Perhaps of greatest interest is the case of a 75 year old woman reported by Liouville, who developed worsening dyspnea and was found to have a systolic heart murmur and died shortly after presentation [3]. The autopsy report stated: *"The left ventricle is enlarged and very thick. It has considerable concentric hypertrophy measuring 3.5–4 cm in width. When I insert my index finger from the ventricle toward the aortic outflow tract, my finger becomes tightly pinched in the myocardium, 1 cm below the aortic valve. The aortic valve itself does not appear to be stenosed or calcified. When I try to insert my thumb backward through the aortic valve toward the ventricle, it cannot reach my index finger that I have inserted from the opposite direction. This is due to the obstruction that is caused by the myocardial thickening that is situated below the level of the aortic valve* (my emphasis)."

Liouville's description of the combination of left ventricular hypertrophy and muscular subaortic stenosis leaves little doubt that this patient suffered from HCM. She lived for 75 years, an age that exceeded double the life expectancy at the time, and her clinical course appeared to have been benign for many years. Seven decades before the measurement of intraventricular pressures in patients, Liouville clearly articulated the concept of intraventricular obstruction.

In 1907, Schminke, a German pathologist, described the hearts of two women who had been in their fifties, both of which showed considerable left ventricular hypertrophy [5]. He wrote: *"Diffuse muscular hypertrophy of the left ventricular outflow tract causes an obstruction. The left ventricle has to work harder to overcome the obstruction. So, the primary hypertrophy will be accompanied by a secondary hypertrophy causing an incremental (further) narrowing of the outflow tract."* Thus, he proposed a vicious circle of ventricular hypertrophy leading to muscular obstruction, which stimulates more hypertrophy, leading to further obstruction, etc.

Sudden Death

The next key clinical-pathologic observation in the unfolding story of HCM was the association of ventricular hypertrophy of unknown etiology with sudden death in 1929 [6]. In 1944, Levy and von Glahn published an influential paper describing ten patients entitled "Cardiac Hypertrophy of Unknown Cause" [7]. This appears to have been the first series of patients with HCM observed clinically, studied by ECG and chest radiography and then at necropsy. Notably, three of their patients died suddenly. They wrote: *"These cases appear to form a clinical group of which the chief features are: marked cardiac hypertrophy, symptoms of cardiac insufficiency and occurrence of various types of arrhythmia. The hearts, at autopsy, all show hypertrophy of the muscle fibers."*

Familial Occurrence

An important milestone was the discovery of familial association in some patients with idiopathic left ventricular hypertrophy. In 1949, Evans reported five patients with idiopathic left ventricular hypertrophy who came from two families and termed the condition "Familial Cardiomegaly" [8]. In 1957, Teare, a London pathologist, described nine patients with massive hypertrophy of the interventricular septum, although little clinical information on these patients was provided except that eight of them had died suddenly; two of them were siblings. These two patients exhibited a characteristic triad of features: ventricular hypertrophy, familial association, and sudden death [9].

Thus, by the late 1950s, prior to the development of left heart catheterization, a syndrome was emerging which may be described as follows: Idiopathic left ventricular hypertrophy, often severe and usually involving primarily the interventricular septum, which could cause intraventricular obstruction, was sometimes familial, and could result in sudden death [10].

Elucidation of Pathophysiology

In 1955, Sir (later Lord) Russell Brock, a distinguished British cardiac surgeon, reported that congenital pulmonic valvular stenosis causes secondary subvalvular stenosis and following successful pulmonary valvotomy the obstruction moved from the valve to the subvalvular region [11]. He proposed that the same situation could occur in the left side of the heart, and indeed reported on patients with aortic valvular stenosis and others with longstanding hypertension who came to operation with what he considered to be secondary muscular subaortic stenosis. He termed this condition "acquired aortic subvalvular stenosis" [12] and considered it to be analogous to the muscular subpulmonic obstruction that he had described previously in patients with congenital pulmonic stenosis.

In 1958, A. Glenn Morrow, the Chief of Cardiac Surgery at the NIH, and I studied two young men with severe dyspnea and angina who had high subaortic pressure gradients and who we thought had congenital membranous subaortic stenosis, a relatively rare congenital anomaly. When Morrow opened the heart at the time of open-heart surgery and potassium-induced cardioplegia, no subaortic obstruction was observed, although the left ventricle appeared to be hypertrophied. We reported these two patients and stated that:

"*with the delineation of its clinical, hemodynamic, angiocardiographic and anatomic features, HCM*[1] *emerges as a specific entity which can be distinguished preoperatively from discrete valvular and subvalvular aortic stenosis*" [13]. At about the same time, Brock studied similar patients with hypertrophic subaortic obstruction, but without muscular hypertrophy secondary to aortic stenosis or longstanding hypertension. He wrote, also in 1959: "*That this is not an isolated case is made clear by the experience of Dr. Glenn Morrow who tells me he has operated on two similar cases in two young men in their early twenties; both survived. He has kindly allowed me to mention these prior to his own report of them (Morrow and Braunwald, Circulation, in press, 1959)*" [14].

Thus, by 1959, HCM had entered a new era, in which hemodynamic studies were employed for both diagnosis and elucidation of the pathophysiology of the condition. An increasing number of patients were discovered and attention focused on the obstruction to left ventricular outflow. It soon became apparent that the obstruction in these patients differed from the fixed discrete obstruction produced by aortic valvular, subaortic or supra aortic stenoses. Instead, in HCM left ventricular outflow tract obstruction was both dynamic and variable. Dynamic, in the sense that a variety of physiologic and pharmacologic stimuli altered its severity [15]. Interventions which reduce the size of the left ventricle (and, we presumed, the diameter of the outflow tract) were shown to increase the severity of obstruction [16]. Such interventions could also provoke obstruction in patients with HCM without obstruction in the basal state. These included: (1) an increase in left ventricular contractility, such as exercise or the administration of a positive inotropic agent (isoproterenol); and (2) a reduction in ventricular preload, such as sudden standing, the strain phase of the Valsalva maneuver or nitroglycerine administration. The opposite, i.e. transient reduction in severity or disappearance of obstruction, occurred with interventions that increased left ventricular volume, such as suddenly assuming the recumbent position, squatting, handgrip, or the infusion of a vasoconstrictor without inotropic properties (phenylephrine) [15].

The variability of the obstruction was evident in patients who had severe obstruction at one catheterization and far less or even no obstruction several days later [17]. In familial HCM, some affected individuals consistently exhibited obstruction while others in the same family with left ventricular hypertrophy had obstruction only on provocation; in still other members of the same family, although left ventricular hypertrophy was noted, obstruction was not present at baseline and could not be provoked [18]. Diastolic dysfunction was almost always present, with elevation of the left ventricular end diastolic pressure while the left ventricular end-diastolic volume was normal. Reduced compliance of the hypertrophied left ventricle was thought to play a role [19, 20]. The diastolic dysfunction could restrict inflow into either the left and/or right ventricle [21]. The unusual hemodynamic findings summarized above aroused widespread interest, and in the 1960s HCM became the "poster child" of how the then newly developed techniques of left heart catheterization could provide a new understanding of cardiac pathophysiology.

By the late 1960s, HCM was recognized with increasing frequency around the world and a clinical picture emerged which remains pertinent today [15, 22]. Patients can be of any age between infancy and advanced age, a family history with autosomal dominant inheritance is observed in about half; in others it appears to occur sporadically. In most patients the course is largely benign; indeed, many patients, particularly those detected in family studies (see below), or at the age of 60 or above [23], are asymptomatic and they remain so for their entire lives. Angina pectoris and exertional dyspnea are the most common symptoms and range from mild to severe. The most common cause of death is sudden [9, 22], which may be preceded by syncopal episodes [1, 24]; less frequently, death results from severe obstruction leading to frank systolic and/or diastolic heart failure [25, 26].

On examination, patients with obstruction to left ventricular outflow have a rapidly rising arterial pulse. A left ventricular lift and a double apical impulse are frequently present. A fourth heart sound is usually audible. A loud ($Gr \geq 3/6$) medium pitched ejection murmur may be heard along the left sternal border, where it may be accompanied by a thrill. The above mentioned interventions which increase obstruction, such as sudden standing, increase the intensity and duration of this murmur, while those which reduce obstruction, such as sudden squatting, diminish or even abolish the murmur [15]. Most patients with obstruction also have a holosystolic murmur of mitral regurgitation at the cardiac apex. The ECG typically shows left ventricular hypertrophy, and sometimes exhibits abnormally deep and wide Q waves, reflecting septal hypertrophy, rather than myocardial infarction [15]. Since the ECG is occasionally normal, electrocardiography is not an adequate screening test to exclude HCM, although a routine ECG showing the characteristic changes can lead to the discovery of unsuspected HCM.

The Present

Echocardiography

Until the development of echocardiography, left heart catheterization, with its accompanying discomfort, cost and risk (albeit low) was necessary for the diagnosis of HCM

[1] In this report, we referred to the condition as "functional aortic stenosis" and subsequently as "idiopathic hypertrophic subaortic stenosis" (IHSS). The preferred term now is hypertrophic cardiomyopathy (HCM), which is used throughout this chapter.

with obstruction. Obviously, catheterization is not ideal for screening, nor for regular follow up examinations. Therefore, when echocardiography became available as a clinical tool, it was quickly applied to patients with known or suspected HCM and filled an important void by permitting safe, painless and inexpensive non-invasive diagnosis [27]. This development ushered in what may be considered the "modern" era of HCM. Even the early M-mode echocardiograms provided a far more precise characterization of the severity of left ventricular hypertrophy than did the electrocardiogram and chest radiogram. Further, echocardiography demonstrated the characteristic asymmetry of ventricular hypertrophy; in most patients the ratio of the thickness of the septum to the posterior wall exceeded 1.3 [28]. An important echocardiographic finding, systolic anterior motion of the mitral valve (SAM), which made contact with the interventricular septum, was present in most HCM patients with obstruction [29] and the severity of obstruction correlated with the duration of this contact. Subsequently, two dimensional echocardiography refined the localization of the hypertrophy [30], and allowed recognition of a variety of uncommon but important subtypes, including apical HCM (in which severe hypertrophy predominates at the left ventricular apex), patients with heart failure secondary to severe concentric hypertrophy, patients with severe diastolic dysfunction, and those with left ventricular dilatation (usually patients who had previously had severe obstruction and subsequently developed overt heart failure [25, 26, 31]). Subsequently, the development of Doppler echocardiography allowed determination of the outflow tract pressure gradient [32], detection of the presence and severity of mitral regurgitation, and diastolic dysfunction with slowed relaxation and filling of the hypertrophied left ventricle [33].

Echocardiography is now universally used for screening persons suspected of having HCM, including adolescents who wish to participate in competitive sports, the relatives of patients with the clinical diagnosis of HCM, and of those with characteristic genotypes (see below). It is also employed in following patients with established HCM, and in assessing the effects of therapy.

During the past decade, cardiovascular magnetic resonance imaging (CMRI) has been employed with increasing frequency [34]. Although considerably more costly than echocardiography, CMRI provides tomographic imaging and greater spatial resolution. It is capable of detecting hypertrophy in the small fraction of patients in whom it cannot be detected by echocardiography, and can demonstrate apical aneurysms, as well as abnormalities of the mitral valve apparatus. Contrast enhanced CMRI may also show late enhancement, representing myocardial fibrosis, which, if extensive, may be responsible for ventricular arrhythmias and sudden death [35].

Treatment

Two modes of therapy for obstruction to left ventricular outflow – one pharmacologic, the other surgical – were developed in the 1960s.

Pharmacologic

Given the provocation and intensification of obstruction by a beta adrenergic agonist [16] and the development of beta blockers, in the 1960s it was logical to test these agents in patients with HCM and we found them to be effective, both hemodynamically [36] and clinically [37]. Recently, these drugs have been reported to reduce or prevent exercise-induced outflow tract obstruction [38]. Beta blockers continue to be "first line" pharmacotherapy in HCM and appear to reduce the severity of angina in about one half of patients [39, 40]. Other drugs that have also been reported to be useful in patients who do not tolerate or fail beta blockers are non-hydropyridine calcium channel blockers (verapamil or diltiazem) and disopyramide [40, 41]. The former can be substituted for a beta blocker, and the latter may be added cautiously.

Invasive Therapy

It is clear that outflow obstruction, when severe, is usually associated with symptoms and adverse clinical outcomes [42, 43]. In 1961, Morrow and Brockenbrough [44] and Kirklin and Ellis [45] developed left ventricular myectomy, a surgical procedure that was quite risky in the first decades of its use and therefore was limited to patients with severe obstruction who were seriously symptomatic. More recently, the procedure has become more extensive, more efficacious in the abolition of obstruction, as well as in the reduction of the associated mitral regurgitation, with surgical mortality rates to 2 % or less *when it is carried out by experienced surgical teams* [46, 47]. The indications for myectomy include the presence of severe obstruction (a systolic pressure gradient >50 mmHg at rest or with provocation) and the persistence of severe symptoms (angina, dyspnea, and/or syncope) despite pharmacologic therapy [1]. The majority of patients become asymptomatic or almost so, and the long term prognosis of survivors is excellent [48]. However, the number of surgical centers with substantial experience is relatively small and eligible patients must often be referred to a site at a distance from their homes.

In 1995, alcohol septal ablation (ASA), another technique for the treatment of obstruction in HCM, was introduced by Sigwart [49] and has gained popularity as an alternative to surgical myectomy [46, 50, 51]. Like myectomy, it appears to be effective in relieving obstruction, and its application should be limited to skilled interventionists, well trained in the performance of the procedure. Septal ablation is carried out by introducing a catheter into the first septal branch of the left

anterior coronary artery, inflating a balloon and injecting absolute alcohol distal to the balloon, thereby creating a septal infarction. Although the mortality from this procedure is low, atrio-ventricular block requiring a permanent pacemaker is required in about 15 % of patients, and in a small percentage of patients ventricular tachyarrhythmias occur [52, 53]. ASA has the distinct advantage of being percutaneous, with most patients discharged within 3 or 4 days and able to resume normal activity quickly. While a direct comparison between myectomy and ASA has not been carried out, operative and post operative survival appear to be similar between the two techniques, but relief of obstruction is slightly less complete with ASA and almost 10 % of patients require a repeat procedure [46, 54].

For patients with HCM with intractable heart failure despite the successful relief of obstruction [25, 26], cardiac transplantation may be an option. In those who are not candidates for transplantation or for whom a donor heart is unavailable, the implantation of a left ventricular assist device, either as a bridge to transplantation or as destination therapy, may be considered [55].

Prevention of Sudden Death

In 1929, Whittle described an asymptomatic 20 year old man who collapsed while riding a bicycle and died before reaching the hospital [6]. At post mortem examination he had marked left ventricular hypertrophy of unknown etiology. As noted above, three of the ten patients with unexplained severe left ventricular hypertrophy reported by Levy and von Glahn died suddenly [7], and eight of the nine patients studied at necropsy by Teare with massive hypertrophy of the ventricular septum had died suddenly [9]. Among the patients whom we studied prospectively at the NIH and described in 1968, ten died of HCM; six of these were sudden and unexpected and four were consequent to progressive heart failure [22]. Only one of the six sudden deaths occurred in a patient who had been symptomatic with severe obstruction in the basal state, while all four patients who died of heart failure had previously exhibited documented severe obstruction.

Sudden death is caused by ventricular fibrillation and remains the most common cause of death in HCM. Indeed, Maron has pointed out that it is the most common cause of non-violent death in adolescents and young adults [1]. Because of the occurrence of this complication during competitive sports, this activity should be prohibited in patients with HCM [39].

The development of the implantable cardioverter/defibrillator (ICD) by Mirowsky et al. in 1980 [56] represents a major step forward in reducing the risk of sudden cardiac death in selected patients with HCM [1]. As pointed out by Maron et al., the availability of this device has challenged clinicians to identify patients with HCM who are at risk of this usually fatal complication [57]. There is, of course, no argument about its use in secondary prevention, i.e. in patients who have survived an episode of cardiac arrest or sustained ventricular tachycardia. However, the ACC/AHA guidelines recommend that implantation of ICD should also be considered in patients with HCM in whom sudden death has occurred in a first degree relative, in patients with left ventricular wall thickness ≥30 mm; recent unexplained syncope; failure of the blood pressure to rise on an exercise stress test; and multiple episodes of non-sustained ventricular tachycardia [39]. Large areas of late gadolinium enhancement on cMRI is emerging as another risk factor for sudden death and may become an indication for ICD implantation as well [35].

Genetics

A familial association with idiopathic ventricular hypertrophy, likely HCM, was described in 1949 [9]. A large family of patients with familial HCM, of whom 77 were examined, was reported by Pare et al. in 1961 [58]. This family included six generations and the transmission was in Mendelian autosomal dominant fashion. In our series, 40 of 126 (32 %) patients were familial and demonstrated autosomal dominant inheritance [22]. C. Seidman and JG Seidman have pioneered the successful effort to uncover the genetic abnormality in HCM [59]. In 1990, they published a classic paper describing a mutation of a gene on chromosome 14 that encodes the beta cardiac myosin protein [60]. Since then, more than 1,500 mutations on ten other genes that encode other sarcomeric proteins (the myosin and actin proteins and the Z disc) associated with familial HCM have been identified [61, 62]. Such mutations have been found in about half of the patients with HCM; their expressivity is variable and the penetrance is age-related. Although it was hoped that the identification of these mutations could aid in risk stratification and became useful in guiding therapy, this now appears to be possible in only a small minority (approximately 5 %) of patients who present with double or compound mutations, and who are at high risk of adverse outcomes [61–63]. In a large majority of patients, identification of specific mutations has not been useful in risk stratification [62, 64], presumably because of genotypic and phenotypic heterogeneity [1]. However, it has been suggested that HCM patients with a sarcomeric gene mutation exhibit more derangement of left ventricular function than do patients without a detectable myofilament mutation [65].

Genetic testing should be carried out in patients in whom the clinical diagnosis of HCM has been established as well as in close relatives of patients with a specific sarcomeric mutation. Such testing can now be carried out rapidly, and using automated DNA sequencing techniques it is becoming progressively less expensive. It has been found to be useful in

identifying two groups of individuals [39, 61–66]. The first are the relatives of patients with a sarcomeric mutation who are without the mutation, so-called "gene negative" (G–) patients, who can be reassured that they will not develop HCM and who therefore do not need to be followed for this condition, nor modify their lifestyles. The second group are the relatives of patients with HCM who harbor the mutation, i.e. are gene positive (G+), and if these persons show no evidence of HCM by both clinical appraisal and imaging, they constitute a new category of patients, so-called genotype positive and phenotype negative (G+/P–) [67]. Such patients should be screened by echocardiography at yearly intervals until their mid twenties and at 3–5 year intervals thereafter to detect overt disease.

The Future

Pathobiology

A number of challenges regarding a more complete understanding of HCM remain. The first is to understand better the natural history of G+/P– subjects referred to above [67]. The identification of this group has enlarged dramatically, perhaps as much as doubled, the total number of persons with an HCM mutation. How many of them are likely to become P+ during their lives and at what age can routine follow ups in P– patients be discontinued? What is the first sign of P positivity in G+/P– persons? Is it ventricular hypertrophy or diastolic dysfunction (which has been termed "the quintessential pathophysiologic abnormality" in HCM) [63] or is it late enhancement on contrast enhanced CMRI? [35].

Are there any clinical risks associated with G+ persons in the absence of any abnormalities by echocardiography? Should they avoid participation in competitive sports? How should their genetic counseling be managed? Another challenge is to learn more about G–/P+ patients. How many have familial HCM whose mutations simply have not yet been discovered? How many have new mutations? How many are truly "sporadic?" Importantly, what are the natural histories of patients in each of these groups?

Therapy

There are many challenges for selecting and improving treatment. Although the drugs employed to reduce obstruction (beta blockers, non-pyridine calcium blockers and disopyramide) are considered to be beneficial [39] and are widely used, they have not been subjected to rigorous, placebo-controlled double blinded, randomized trials [40]. Such trials should not be too difficult to perform because using a crossover technique, each patient can be his/her own control with placebo periods alternating with various drugs and combinations. The end-points could be changes in symptoms, exercise capacity, and in outflow tract obstruction as well as adverse drug effects.

Similarly, there have been no rigorous comparisons between the two mechanical interventions – myectomy and ASA [46]. While it would be optimal to conduct a randomized trial, this is probably not possible because of the large sample size required, and the necessity of having well trained operators in both techniques available. Instead, consideration might be given to developing *prospective* registries in which detailed baseline characteristics are obtained to allow meaningful comparisons between similar groups of patients receiving the two interventions.

Finally, as the biochemical and biophysical consequences of the mutations responsible for the development of HCM become clear, it is possible that tailored therapy could be developed that actually improves the natural history of HCM [63]. Drugs that modify genetically-induced alterations in myocyte Ca^{2+} cycling, the Ca^{2+} sensitivity of contractile proteins, or the enhanced production of extracellular matrix might delay, or even prevent the development of HCM in G+/P– persons or retard the progression of patients with clinically evident HCM [68].

HCM was first recognized almost 150 years ago. We have learned an enormous amount about this fascinating condition, but the story is still incomplete. Future progress is likely to require the continued collaboration of scientists and clinicians with expertise in many fields, including genetics, biophysics, pathology, electrophysiology, interventional cardiology and cardiac surgery.

References

1. Maron BJ, Ommen SR, Semsarian C, Spirito P, Olivotto I, Maron MS. Hypertrophic cardiomyopathy: present and future, with translation into contemporary cardiovascular medicine. J Am Coll Cardiol 2014;64(1):83-99.
2. Vulpian A. Contribution à l'étude des rétrécissements de l'orifice ventriculo-aortique. Arch Pathol. 1868;3:456–7.
3. Liouville H. Rétrécissement cardiaque sous aortique. Gazette Med Paris. 1869;24:161–3.
4. Hallopeau M. Rétrécissement ventriculo-aortique. Gazette Med Paris. 1869;24:683–4.
5. Schmincke A. Ueber linkseitige muskulose conustenosen. Dtsch Med Wochenschr. 1907;33:2082–5.
6. Whittle CH. "Idiopathic" hypertrophy of the heart in a young man. Lancet. 1929;216:1354–5.
7. Levy RL, von Glahn WC. Cardiac hypertrophy of unknown cause. A study of the clinical and pathologic features in ten adults. Am Heart J. 1944;28:714–41.
8. Evans W. Familial cardiomegaly. Br Heart J. 1949;11:68–82.
9. Teare D. Asymmetrical hypertrophy of the heart in young adults. Br Heart J. 1958;20(1):1–8.
10. Braunwald E. Hypertrophic cardiomyopathy: the early years. J Cardiovasc Transl Res. 2009;2(4):341–8.
11. Brock R. Control mechanisms in the outflow tract of the right ventricle in health and disease. Guys Hosp Rep. 1955;104:356–7.

12. Brock R. Functional obstruction of the left ventricle (acquired aortic subvalvar stenosis). Guys Hosp Rep. 1957;106:221–38.
13. Morrow AG, Braunwald E. Functional aortic stenosis. A malformation characterized by resistance to left ventricular outflow without anatomic obstruction. Circulation. 1959;20(2):181–9.
14. Brock R. Functional obstruction of the left ventricle (acquired aortic subvalvar stenosis). Guys Hosp Rep. 1959;108:126–43.
15. Braunwald E, Lambrew CT, Rockoff SD, Ross Jr J, Morrow AG. Idiopathic hypertrophic subaortic stenosis: I. A description of the disease based upon an analysis of 64 patients. Circulation. 1964;30 Suppl 4:3–119.
16. Braunwald E, Ebert PA. Hemodynamic alterations in idiopathic subaortic stenosis induced by sympathomimetic drugs. Am J Cardiol. 1962;10:489–95.
17. Braunwald E, Brockenbrough EC, Morrow AG. Hypertrophic subaortic stenosis – a broadened concept. Circulation. 1962;26:161–5. Editorial.
18. Braunwald E, Aygen MM. Idiopathic myocardial hypertrophy without congestive heart failure or obstruction to blood flow: clinical, hemodynamic and angiocardiographic studies in fourteen patients. Am J Med. 1963;35:7–19.
19. Braunwald E, Morrow AG, Cornell WP, Aygen MM, Hilbish TF. Idiopathic hypertrophic subaortic stenosis: clinical, hemodynamic and angiographic manifestations. Am J Med. 1960;29:924–45.
20. Stewart S, Mason DT, Braunwald E. Impaired rate of left ventricular filling in idiopathic hypertrophic subaortic stenosis and valvular aortic stenosis. Circ Res. 1968;22(2):213–9.
21. Goodwin JF, Gordon H, Hollman AB. Clinical aspects of cardiomyopathy. BMJ. 1961;1:69–79.
22. Frank S, Braunwald E. Idiopathic hypertrophic subaortic stenosis. Clinical analysis of 126 patients with emphasis on the natural history. Circulation. 1968;37(5):759–88.
23. Maron BJ, Rowlin EJ, Casey SA, Haas TS, Chan RHM, Udelson JE, Garberich RF, Lesser JR, Appelbaum E, Manning WJ, Maron MS. Risk stratification and outcome of patients with hypertrophic cardiomyopathy ≥60 years of age. Circulation. 2013;127(5):585–93.
24. Spirito P, Autore C, Rapezzi C, Bernabò P, Badagliacca R, Maron MS, Bongioanni S, Coccolo F, Estes NA, Barillà CS, Biagini E, Quarta G, Conte MR, Bruzzi P, Maron BJ. Syncope and risk of sudden death in hypertrophic cardiomyopathy. Circulation. 2009;119(13):1703–10.
25. Harris KM, Spirito P, Maron MS, Zenovich AG, Formisano F, Lesser JR, Mackey-Bojack S, Manning WJ, Udelson JE, Maron BJ. Prevalence, clinical profile, and significance of left ventricular remodeling in the end-stage phase of hypertrophic cardiomyopathy. Circulation. 2006;114(3):216–25.
26. Melacini P, Basso C, Angelini A, Calore C, Bobbo F, Tokajuk B, Bellini N, Smaniotto G, Zuchetto M, Iliceto S, Thiene G, Maron BJ. Clinicopathological profiles of progressive heart failure in hypertrophic cardiomyopathy. Eur Heart J. 2010;31(17):2111–23.
27. Moreyra R, Klein JJ, Shimada H, Segal BL. Idiopathic hypertrophic subaortic stenosis diagnosed by reflected ultrasound. Am J Cardiol. 1969;23(1):32–7.
28. Henry WL, Clark CE, Epstein SE. Asymmetric septal hypertrophy. Echocardiographic identification of the pathognomonic anatomic abnormality of IHSS. Circulation. 1973;47(2):225–33.
29. Shah PM, Gramiak R, Kramer DH. Ultrasound localization of left ventricular outflow obstruction in hypertrophic obstructive cardiomyopathy. Circulation. 1969;40(1):3–11.
30. Weyman AE, Feigenbaum H, Hurwitz RA, Girod DA, Dillon JC, Chang S. Localization of left ventricular outflow obstruction by cross-sectional echocardiography. Am J Med. 1976;60(1):33–8.
31. Olivotto I, Cecci F, Poggesi C, Yacoub M. Patterns of disease progression in hypertrophic cardiomyopathy. Circ Heart Fail. 2012;5:535–46.
32. Schwammenthal E, Schwartzkopff B, Block M, Johns J, Lösse B, Engberding R, Borggrefe M, Breithardt G. Doppler echocardiographic assessment of the pressure gradient during bicycle ergometry in hypertrophic cardiomyopathy. Am J Cardiol. 1992;69(19):1623–8.
33. Maron BJ, Spirito P, Green KJ, Wesley YE, Bonow RO, Arce J. Noninvasive assessment of left ventricular diastolic function by pulsed Doppler echocardiography in patient with hypertrophic cardiomyopathy. J Am Coll Cardiol. 1987;10(4):733–42.
34. Maron MS. Clinical utility of cardiovascular magnetic resonance in hypertrophic cardiomyopathy. J Cardiovasc Magn Reson. 2012;14:13.
35. Rowin EJ, Maron MS, Lesser JR, Maron BJ. CMR with late gadolinium enhancement in genotype positive-phenotype negative hypertrophic cardiomyopathy. JACC Cardiovasc Imaging. 2012;5(1):119–22.
36. Harrison DC, Braunwald E, Glick G, Mason DT, Chidsey CA, Ross Jr J. Effects of beta-adrenergic blockade on the circulation with particular reference to observations in patients with hypertrophic subaortic stenosis. Circulation. 1964;29:84–98.
37. Cohen LS, Braunwald E. Amelioration of angina pectoris in idiopathic hypertrophic subaortic stenosis with beta-adrenergic blockade. Circulation. 1967;35:47–851.
38. Nistri S, Ollivotto I, Maron MS, Ferrantini C, Coppini R, Grifoni C, Baldini K, Sgalambro A, Cecchi F, Maron BJ. β blockers for prevention of exercise-induced left ventricular outflow tract obstruction in patients with hypertrophic cardiomyopathy. Am J Cardiol. 2012;110(5):715–9.
39. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naidu SS, Nishimura RA, Ommen SR, Rakowski H, Seidman CE, Towbin JA, Udelson JE, Yancy CW. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy. J Thorac Cardiovasc Surg. 2011;142(6):e153–203.
40. Spoladore R, Maron MS, D'Amato R, Camici PG, Olivotto I. Pharmacological treatment options for hypertrophic cardiomyopathy: high time for evidence. Eur Heart J. 2012;33(14):1724–33.
41. Sherrid MV, Shetty A, Winson G, Kim B, Musat D, Alviar CL, Homel P, Balaram SK, Swistel DG. Treatment of obstructive hypertrophic cardiomyopathy symptoms and gradient resistant to first-line therapy with β blockade or verapamil. Circ Heart Fail. 2013;6(4):694–702.
42. Maron MS, Olivotto I, Zenovich AC, Link MS, Pandian NG, Kuvin JT, Nistri S, Cecchi F, Udelson JE, Maron BJ. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. Circulation. 2006;114(21):2232–9.
43. Maron BJ, Maron MS, Wigle ED, Braunwald E. The 50-year history, controversy, and clinical implications of left ventricular outflow tract obstruction in hypertrophic cardiomyopathy: from idiopathic hypertrophic subaortic stenosis to hypertrophic cardiomyopathy. J Am Coll Cardiol. 2009;54(3):191–200.
44. Morrow AG, Brockenbrough EC. Surgical treatment of idiopathic hypertrophic subaortic stenosis. Technic and hemodynamic results of subaortic ventriculomyotomy. Ann Surg. 1961;154:181–9.
45. Kirklin JW, Ellis FH. Surgical relief of diffuse subvalvular aortic stenosis. Circulation. 1961;24:739–42.
46. Braunwald E. Obstruction in hypertrophic cardiomyopathy. How often does it occur? Should it be treated? If so, how? Circulation. 2012;126(20):2369–70.
47. Desai MY, Bhonsale A, Smedira NG, Naji P, Thamilarasan M, Lytle BW, Lever HM. Predictors of long-term outcomes in symptomatic hypertrophic obstructive cardiomyopathy patients undergoing surgical relief of left ventricular outflow tract obstruction. Circulation. 2013;128(3):209–16.
48. Williams L, Rakowski H. Surgical myectomy for hypertrophic obstructive cardiomyopathy: the cut that heals. Circulation. 2013;128(3):193–7.

49. Sigwart U. Non-surgical myocardial reduction for hypertrophic obstructive cardiomyopathy. Lancet. 1995;346(8969):211–4.
50. Braunwald E. Hypertrophic cardiomyopathy: the benefits of a multidisciplinary approach. N Engl J Med. 2002;347(17):1306–7.
51. Nagueh SF, Groves BM, Schwartz L, Smith KM, Wang A, Bach RG, Nielsen C, Leya F, Buergler JM, Rowe SK, Woo A, Maldonado YM, Spencer 3rd WH. Alcohol septal ablation for the treatment of hypertrophic obstructive cardiomyopathy: a multicenter North American registry. J Am Coll Cardiol. 2011;58:2322–8.
52. Noseworthy PA, Rosenberg MA, Fifer MA, Palacios IF, Lowry PA, Ruskin JN, Sanborn DM, Picard MH, Vlahakes GJ, Mela T, Das S. Ventricular arrhythmia following alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Am J Cardiol. 2009;104(1):128–32.
53. ten Cate FJ, Soliman OII, Michels M, Theuns DAMJ, de Jong PL, Geleijnse ML, Serruys PW. Long-term outcome of alcohol septal ablation in patients with obstructive hypertrophic cardiomyopathy. Circ Heart Fail. 2010;3:362–9.
54. Sorajja P, Ommen SR, Holmes DR, Dearani JA, Rihal CS, Gersh BJ, Lennon RJ, Nishimura RA. Survival after alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Circulation. 2012;126:2374–80.
55. Topilsky Y, Pereira NL, Shah DK, Boilson B, Schirger JA, Kushwaha SS, Joyce LD, Park SJ. Left ventricular assist device therapy in patients with restrictive and hypertrophic cardiomyopathy. Circ Heart Fail. 2011;4:266–75.
56. Mirowski M, Reid PR, Mower MM, Watkins L, Gott VL, Schauble JF, Langer A, Heilman MS, Kolenik SA, Fischell RE, Weisfeldt ML. Termination of malignant ventricular arrhythmias with an implanted automatic defibrillator in human beings. N Engl J Med. 1980;303(6):322–4.
57. Maron BJ, Shen W-K, Link MS, Epstein AE, Almquist AK, Daubert JP, Bardy GH, Favale S, Rea RF, Boriani G, Estes III MNAM, Spirito P. Efficacy of implantable cardioverter-defibrillators for the prevention of sudden death in patients with hypertrophic cardiomyopathy. N Engl J Med. 2000;342(6):365–73.
58. Pare JAP, Fraser RG, Pirozynski WJ, Shanks JA, Stubington D. Hereditary cardiovascular dysplasia: a form of familial cardiomyopathy. Am J Med. 1961;31:37–62.
59. Seidman CE, Seidman JG. Identifying sarcomere gene mutations in hypertrophic cardiomyopathy: a personal history. Circ Res. 2011;108:732–50.
60. Geisterfer-Lowrance AA, Kass S, Tanigawa G, Vosberg HP, McKenna W, Seidman CE, Seidman JG. A molecular basis for familial hypertrophic cardiomyopathy: a beta cardiac myosin heavy chain gene missense mutation. Cell. 1990;62(5):999–1006.
61. Ho CY. Is genotype clinically useful in predicting prognosis in hypertrophic cardiomyopathy? Circulation. 2010;122(23):2430–40.
62. Maron BJ, Maron MS, Semsarian C. Genetics of hypertrophic cardiomyopathy after 20 years. Clinical perspectives. J Am Coll Cardiol. 2012;60:705–15.
63. Teekakirikul P, Padera RF, Seidman JG, Seidman CE. Hypertrophic cardiomyopathy: translating cellular cross talk into therapeutics. J Cell Biol. 2012;199(3):417–21.
64. Landstrom AP, Ackerman MJ. Mutation type is not clinically useful in predicting prognosis in hypertrophic cardiomyopathy. Circulation. 2010;122:2441–9.
65. Olivotto I, Girolami F, Ackerman MJ, Nistri S, Bos JM, Zachara E, Ommen SR, Theis JL, Vaubel RA, Re F, Armentano C, Poggesi C, Torricelli F, Cecchi F. Myofilament protein gene mutation screening and outcome of patients with hypertrophic cardiomyopathy. Mayo Clin Proc. 2008;83(6):630–8.
66. Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H, Camm AJ, Ellinor PT, Gollob M, Hamilton R, Hershenberger RE, Judge DP, Le Marec H, McKenna WJ, Schulze-Bahr E, Semsarian C, Towbin JA, Watkins H, Wilde A, Wolpert C, Zipes DP. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. Europace. 2011;13:1077–109.
67. Maron BJ, Yeates L, Semsarian C. Clinical challenges of genotype positive (+)-phenotype negative (−) family members in hypertrophic cardiomyopathy. Am J Cardiol. 2011;107(4):604–8.
68. Lakdawala NK, Thune JJ, Colan SD, Cirino AL, Farrohi F, Rivero J, McDonough B, Sparks E, Orav EJ, Seidman JG, Seidman CE, Ho CY. Subtle abnormalities in contractile function are an early manifestation of sarcomere mutations in dilated cardiomyopathy. Circ Cardiovasc Genet. 2013;5:503–10.

Natural History of Untreated Hypertrophic Cardiomyopathy

2

Qin Li, Lynne Williams, and Harry Rakowski

Abstract

Hypertrophic cardiomyopathy (HCM) is a primary disorder of the myocardium with a wide range of anatomic and physiologic forms. Up to 70 % of all HCM patients have either resting or provocable left ventricular outflow tract (LVOT) obstruction while others have predominantly non-obstructive forms. A small proportion of patients have apical hypertrophy which can lead to apical aneurysms. This condition affects people of all ages including the pediatric and adolescent population, as well as adults and the elderly. Although the majority of HCM patients have a relatively benign outcome, it is still the most common cause of death in young people, likely due to ventricular arrhythmias. Untreated HCM can lead to progressive symptoms due to diastolic dysfunction, LVOT obstruction, microvascular ischemia, and mitral regurgitation. A small percentage of HCM patients may develop end stage heart failure with impaired left ventricular systolic function. Stroke is another devastating outcome due to atrial fibrillation or thrombus formation in the setting of an apical aneurysm.

Keywords

Hypertrophic cardiomyopathy • Heart failure • Sudden cardiac death • Arrhythmias • Natural history • Outcomes • Mortality

Key Points

- HCM is a primary disorder of the myocardium with a wide range of anatomic and physiologic forms
- Up to 70 % of patients have either resting or provocable left ventricular outflow tract obstruction
- Although the majority of HCM patients have a relatively benign outcome, it is still the most common cause of sudden cardiac death in young people
- Untreated HCM can lead to progressive symptoms due to diastolic dysfunction, obstruction, and mitral regurgitation
- A small percentage of HCM patients may develop end stage heart failure with impaired left ventricular systolic function
- Three distinctive modes of death account for HCM-related mortality, namely sudden unexpected death, progressive heart failure, and ischemic stroke due to atrial fibrillation or ventricular aneurysm with thrombus.

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Introduction

Hypertrophic cardiomyopathy (HCM) is defined clinically by the presence of a hypertrophied, non-dilated left ventricle in the absence of abnormal loading conditions or another cardiac or systemic disease capable of producing the detected degree of wall thickening. It is a primary genetic disorder of the myocardium with unique clinical, echocardiographic, and hemodynamic features. On a macroscopic level it is characterized by the presence of left ventricular hypertrophy, while histopathologically the cardinal features are those of myocyte hypertrophy, fiber disarray, interstitial fibrosis, and abnormalities of the coronary microvasculature. It represents the most common inherited cardiovascular disorder, affecting approximately 1 in 500 of the general population.

Anatomic and Physiologic Forms of HCM

HCM is typically defined by the presence of hypertrophy and a maximal wall thickness of ≥15 mm. Hypertrophy is most commonly asymmetric, affecting predominantly the interventricular septum [1]. The demonstration of a septal-to-posterior wall thickness ratio exceeding 1.3:1 in normotensive and 1.5:1 in hypertensive patients is strongly suggestive of the diagnosis [2, 3]. In the pediatric population the diagnosis of HCM is made when wall thickness is ≥2 standard deviations above the mean (Z-score) after correction for age and body surface area. The pattern and distribution of hypertrophy can be highly variable, and can be broadly subdivided into the following morphologic patterns: (1) reverse curvature, (2) neutral, (3) apical, and (4) sigmoid. The typical features and examples of each are demonstrated in Fig. 2.1.

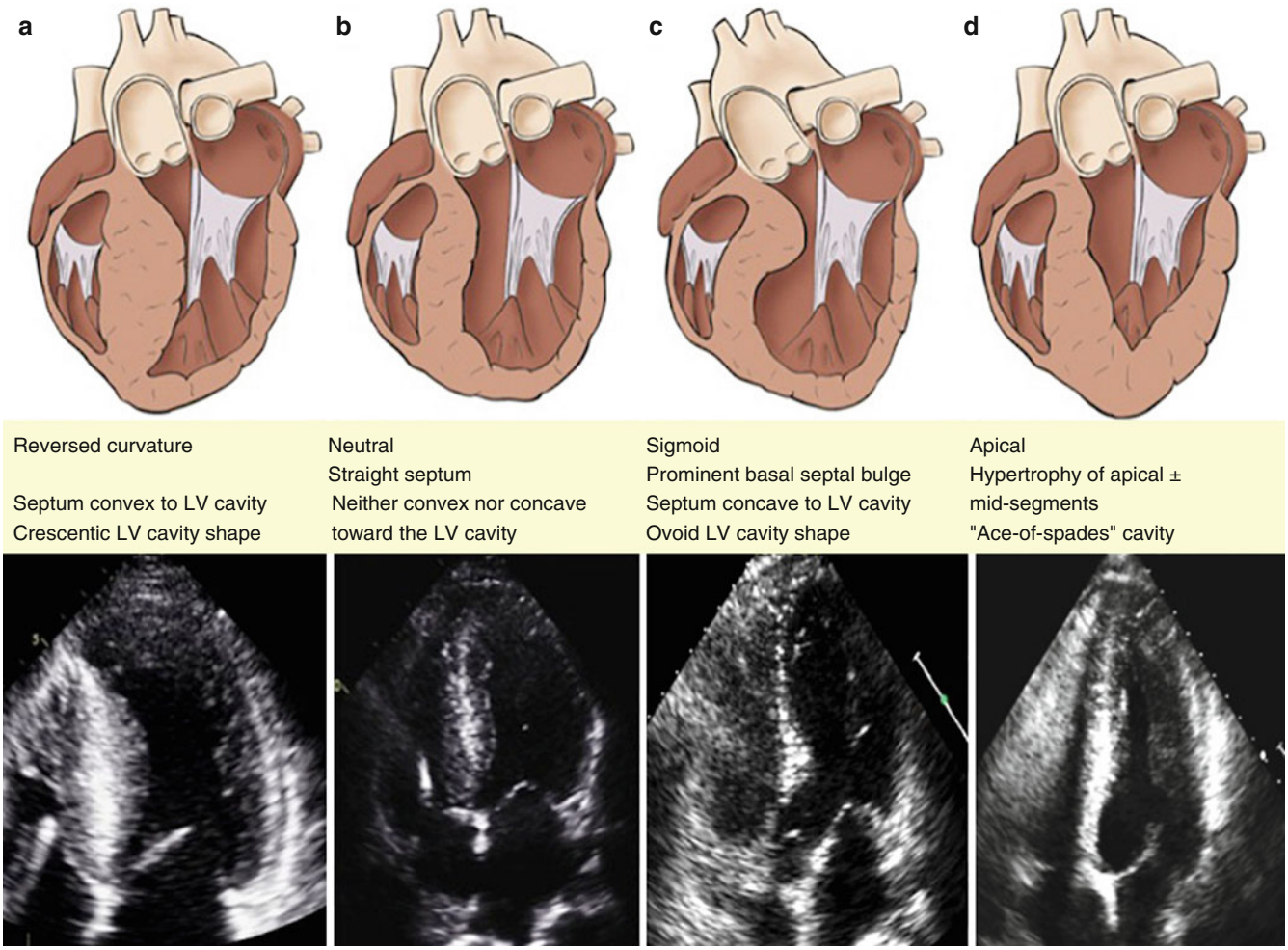

Fig. 2.1 The spectrum of morphologic subtypes seen in hypertrophic cardiomyopathy. Panel (**a**) demonstrates asymmetric septal hypertrophy with a reverse curvature pattern leading to a crescentic shape to the left ventricular cavity. Panel (**b**) demonstrates asymmetric septal hypertrophy with a neutral septal morphology that is neither convex nor concave to the left ventricular cavity. Panel (**c**) demonstrates a sigmoid septum with hypertrophy confined to the basal septum. Panel (**d**) demonstrates apical hypertrophy with hypertrophy confined to the apex and normal wall thicknesses in the basal segments

Identification of these subtypes may have implications with respect to the clinical application of genetic testing. In recent studies from both the Mayo Clinic and Toronto, 53–79 % of patients with a reverse septal curvature and 41–48 % of patients with a neutral septal subtype were found to have an identifiable HCM-causing mutation, in contrast to only 8–23 % of patients with a sigmoid septum, and only 11–30 % of patients with apical hypertrophy [4, 5]. In light of this data, echocardiography may guide the decision to perform cost effective genetic testing.

Independent of the degree and pattern of hypertrophy, marked variation in the hemodynamic consequences of the disease exists, ranging from a nonobstructive phenotype, to obstruction at the level of the left ventricular outflow tract, mid-cavity, or more rarely the right ventricular outflow tract (Fig. 2.2). Three distinct hemodynamic subgroups of patients exist: (1) those with resting outflow tract obstruction; (2) those with provocable gradients but no obstruction at rest (latent obstruction); and (3) those with no gradient either at rest or with provocation.

Non-obstructive HCM

By definition, the nonobstructive form of HCM is defined by the absence of left ventricular outflow tract obstruction (LVOT gradient <30 mmHg) under both resting and provocable conditions. While obstruction (LVOT gradient ≥30 mmHg) is present in resting conditions in only 25–30 % of patients, with exercise provocation LVOT gradients are present in up to 70 % of patients with HCM [6]. Whilst the nonobstructive subgroup may form only a third of all HCM patients, symptoms in this form of the disease may be severe and particularly difficult to treat, given the lack of obstruction as a treatment target. In these patients, symptoms often result from diastolic dysfunction and microvascular ischemia.

Left Ventricular Outflow Tract Obstruction in HCM

Dynamic LVOT obstruction (LVOTO) is an important manifestation of the disease spectrum and a major cause of symptoms of breathlessness, chest pain, presyncope and syncope. A multitude of hemodynamic and morphological features are responsible for the development of LVOTO, as shown in Table 2.1. Hypertrophy of the basal septum, anterior displacement or elongation/redundancy of the mitral valve apparatus, and anterior displacement and/or hypertrophy of the papillary muscles all contribute to a reduction in the cross-sectional area of the LVOT, and have been shown to be directly related to the presence and degree of LVOT obstruction. The mitral valve itself is frequently abnormal, with elongated leaflets [7], and coaptation occurring at the body of the leaflets as opposed to the leaflet tips [8]. Chordal slack, as a result of both anterior displacement of the papillary muscles and a reduction in the distance between the papillary muscle heads and the mitral leaflets, favors the development of systolic anterior motion (SAM) of the mitral valve. Rapid left ventricular ejection, which combined with the structural abnormalities of the mitral valve, results in SAM via Venturi and drag forces which act on the anterior leaflet distal to the point of coaptation. The subsequent sharp anterior angulation of the tip of the anterior leaflet, which comes into contact with the septum in mid-systole, results not only in SAM but also the characteristic posteriorly-directed jet of mitral regurgitation seen in patients with LVOT obstruction.

Outflow tract obstruction is by nature highly dynamic, and affected by multiple hemodynamic changes that occur during daily life. In patients with HCM, it is important to determine whether symptoms are as a result of obstruction, diastolic dysfunction, myocardial ischemia, or arrhythmias, in order to institute appropriate therapy and guide decision making.

The importance of identifying LVOT obstruction lies in its adverse impact on outcomes. The presence of resting LVOT obstruction is associated not only with a higher likelihood of HCM-related mortality, but also with progression to advanced symptoms (NYHA class III and IV) or death as a result of heart failure or stroke [9]. It is well-documented that the prognosis for patients with obstruction

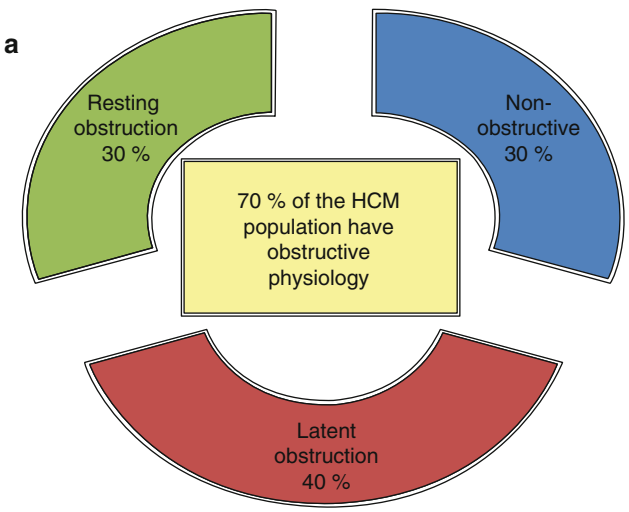

Fig. 2.2 ***Obstructive HCM***. As demonstrated in panel (**a**), patients with HCM can be grouped into three distinct hemodynamic categories based on the presence or absence of obstruction. Panel (**b**) (*upper*): Color Doppler and pulse wave Doppler demonstrating intracavitary obstruction. Panel (**b**) (*lower*): Color Doppler and continuous wave Doppler demonstrating left ventricular outflow tract obstruction and posteriorly directed mitral regurgitation

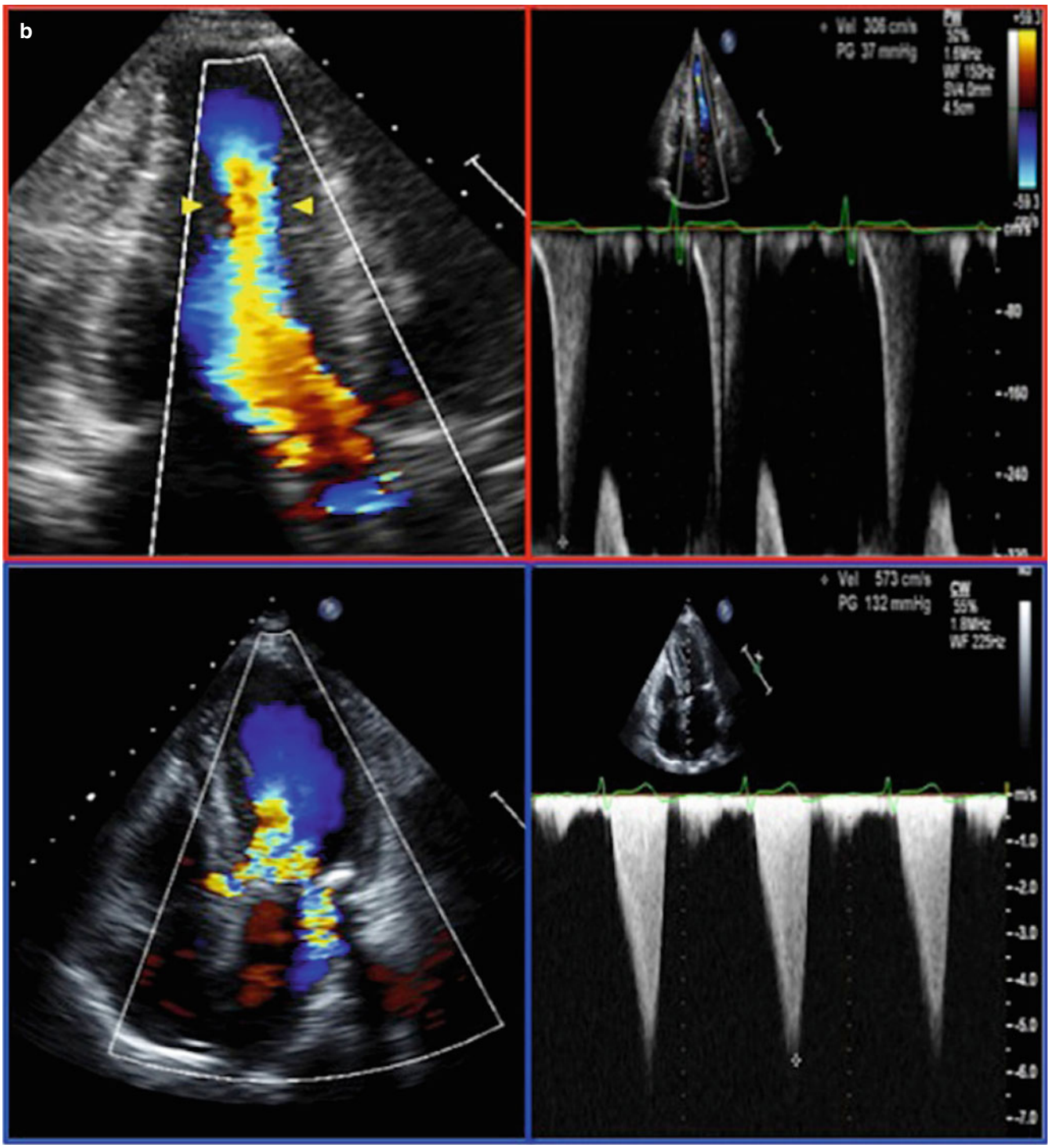

Fig. 2.2 (continued)

is worse, especially in the presence of severe symptoms. Disease consequences of chronic increases in LV intracavitary pressures such as increased wall stress, myocardial ischemia, and eventual cell death and replacement fibrosis, justify the consideration of interventions to relieve obstruction in those patients who remain markedly symptomatic despite optimal medical therapy. While LVOT obstruction is an important feature of the disease in children with HCM, in contrast to data derived from adult populations, the presence of obstructive physiology later in childhood does not appear to be related to a worse prognosis, or the risk of death or transplantation [10, 11].

Table 2.1 Factors contributing to left ventricular outflow tract obstruction

Anatomical (reduced cross-sectional area of the LVOT)
Basal septal hypertrophy
Anterior displacement of the mitral valve apparatus
Anterior malposition, abnormal hypertrophy, or abnormal insertion of the papillary muscles
Elongated mitral valve leaflets and chordae
Abnormal coaptation of the mitral valve leaflets in the body of the leaflet as opposed to the leaflet tips
Relative chordal slack due to anterior displacement of the papillary muscles and elongation of the mitral valve leaflets
Hemodynamic
Rapid early left ventricular ejection
Venturi or drag forces acting on the anterior mitral valve leaflet distal to the coaptation point

Midventricular Obstruction (MVO) in HCM

The midventricular form of obstructive HCM, first described in 1976 [12], is an uncommon variant occurring in less than 10 % of cases. Phenotypic features include an "hourglass" shaped left ventricular cavity with a distinct apical chamber, systolic mid-cavity obliteration with turbulence at the mid-ventricle on color Doppler imaging, and the presence of a late-peaking systolic pressure gradient originating at the midventricular level. This impedance to intracavitary flow, unrelated to SAM of the mitral valve, appears to arise as a result of marked mid-septal hypertrophy coming into contact with a hyperdynamic left ventricular free wall, often aggravated by the interposition of a hypertrophied papillary muscle [12]. MVO has been shown to be associated with a greater symptom burden [13, 14], as well as a predictor of progression to end-stage ("burnt-out") HCM and heart failure-related deaths [13]. In addition, MVO strongly predicts HCM-related death, particularly sudden death and potentially lethal arrhythmias [13, 14]. Apical aneurysm formation occurs in more than one-fourth of patients [13, 14], and is associated with a higher likelihood of stroke and progression to end-stage HCM [13]. In those patients with an apical aneurysm the risk of sudden death or potentially lethal arrhythmia appears to be even greater [14].

Apical HCM

Apical HCM is a relatively rare phenotypic variant of the disease in the United States, but comprises a sizable minority in Asian populations. In apical HCM, hypertrophy involves predominantly the apex of the left ventricle, resulting in the characteristic "ace of spades" configuration of the left ventricle at end-diastole [15]. Associated electrocardiographic features include the presence of giant negative T-waves (>10 mm) in the precordial leads [16]. The majority of patients with apical HCM have a favourable outcome, with annual mortality rates of 0.1 % [17]. However, some patients have severe symptoms of diastolic dysfunction, including that due to marked reduction in the effective left ventricular chamber size from apical cavity obliteration. Several predictors of adverse events have been identified in these patients, including young age at diagnosis [17], NYHA class II or greater symptoms at baseline [17], and an increased left atrial volume index [17, 18]. In a subset of around 10 % patients apical infarction may occur (in the absence of epicardial coronary artery disease) [17], and this may subsequently result in apical aneurysm formation [19]. While apical HCM itself carries a relatively benign prognosis, the presence of apical aneurysm formation has been shown to be associated with adverse outcomes and an annual event rate of 10.5 %, including sudden death, appropriate AICD discharges, thromboembolic events, and progressive heart failure [19].

Table 2.2 Differential diagnosis of HCM in childhood

Syndromic
Noonan's syndrome
LEOPARD syndrome
Friedrich's Ataxia
Metabolic
Glycogen storage disease
Mucopolysaccharide storage disease
Disproportionate ventricular septal hypertrophy
d-Transposition of the great arteries
Right ventricular hypertrophy
Other causes of LVH
Supravalvar or subvalvar aortic stenosis

Disease Presentation

With greater understanding of the disease over numerous decades, it is now clear that LVH is not a static manifestation associated with the presence of a disease-causing mutation, but rather a feature of the disease that can appear and progress at virtually any age. After more than five decades of studying HCM, the risk of eventually expressing disease (if at all), and the age at which this will occur, still remain largely unknown; marked variability, even within a given family, has been seen.

In childhood, HCM is characterized by a diverse spectrum of aetiologies, with a peak incidence in the first year of life [20]. However, in a significant proportion of these cases a syndromal malformation, metabolic or mitochondrial disease may be responsible for the phenotypic LVH [20, 21] (Table 2.2). Hypertrophy may be present at birth, or develop at any period during childhood or early adolescence. In those children with evidence of HCM, progression of LVH has been demonstrated, with substantial increases in both

magnitude and overall distribution of hypertrophy [22]. This progression has been shown to occur even in the absence of LVOT obstruction or clinical deterioration [22], and is postulated to be related to growth factors responsible for the normal adolescent growth spurt.

LVOT obstruction is an important feature of the disease in pediatric populations, occurring in up to 50 % of patients [10, 11]. Children with obstruction have been shown to have greater degrees of hypertrophy, smaller left ventricular cavities, and a greater degree of left atrial dilatation [10]. The onset of obstruction in the pediatric population appears to develop during two distinct periods; an early period within the first 3 years of life (likely representing an aggressive obstructive phenotype), and a later period around early adolescence [10].

While the majority of patients carrying a sarcomere mutation for HCM demonstrate disease penetrance in childhood and adolescence, with increases in LV wall thickness usually complete upon achieving physical maturity [22], HCM phenotypic conversion can occur at any age with disease expression delayed until the third and fourth decades of life and beyond. A recent longitudinal study following at-risk HCM patients (i.e. genotype positive), has suggested that the incidence of HCM phenotypic expression during childhood and adolescence may be lower than previously believed [23]. In addition, a large study of patients carrying a mutation in the cardiac troponin T gene (TNNT2) demonstrated a low disease penetrance in children [24]. Studies attempting to elucidate genotype-phenotype correlations in HCM have all demonstrated marked heterogeneity in relation to phenotypic expression, with age at diagnosis ranging from the first to the eighth decades of life in patients carrying mutations in the cardiac myosin-binding protein-C [25, 26], beta-myosin heavy chain [26], and cardiac troponin I gene (TNNI3) [27].

Natural History and Prognosis

Pediatric HCM

While previous studies have suggested a high mortality for HCM diagnosed during infancy and childhood [28–30], more recent studies from the Australian and North American Pediatric Cardiomyopathy Registries have demonstrated annual mortality rates of around 1–1.5 % for patients diagnosed after the first year of life [11, 21]. The outcome of childhood HCM depends greatly on the underlying cause and age at diagnosis. While LVOT obstruction is an important feature of the disease in children with HCM, in contrast to data derived from adult populations, the presence of obstructive physiology later in childhood does not appear to be related to a worse prognosis, or the risk of death or transplantation [10, 11].

Patients presenting in the first 12 months of life have a more diverse aetiology and the poorest outcomes, whereas those children who survive beyond the first year of life have an annual mortality rate comparable to that described in population-based studies in adults [21]. However, a more recent study has demonstrated not only a higher annual mortality than previous registry studies, but also a variation in the risk of sudden death over time [31]. Those children in the age range of 8–16 years have a higher risk than young adults aged 17–30 years, with a peak risk between 9 and 12 years of age [31]. The North America Registry data also demonstrated a clear clustering of deaths between the ages of 12 and 16 years, with no deaths occurring in the 4–8 year age range [21]. It would therefore seem that calculating a flat annual mortality rate over a wide age range may be misleading in the pediatric population.

HCM in Adolescents and Adults

While HCM was initially thought to be a rare disease with poor prognosis, current knowledge suggests that the natural history of the HCM population as a whole is relatively benign, provided that those at risk of sudden cardiac death and other complications are identified and treated appropriately. Published survival rates for patients with HCM have improved over the last five decades, with a reduction in all-cause mortality from 5 % or greater to less than 3 %, and a fall in annual sudden death mortality from 3 to 1 % [32–41] (see Fig. 2.3). Historical misconceptions regarding the prognosis of patients with HCM arise from an era in which a skewed referral bias towards selected tertiary centers existed, with clinically-stable low-risk patients under-represented in the cohorts from which this mortality data arose. The narrow range of mortality rates reported over the past decades suggests that referral bias no longer plays a major role in the historical discrepancies in annual mortality rates, as the introduction of common management protocols and published guidelines are applicable to patients irrespective of the clinical setting in which care is provided.

HCM in Older Adults

While the natural history and prognosis of older patients with HCM has remained incompletely defined, previous studies have suggested it to be favorable [42]. Recent data form a large cohort of patients presenting at ≥60 years of age has demonstrated a low-risk for HCM-related morbidity and mortality in those patients surviving into their seventh decade, regardless of the coexistence of traditional risk factors for sudden cardiac death [43].

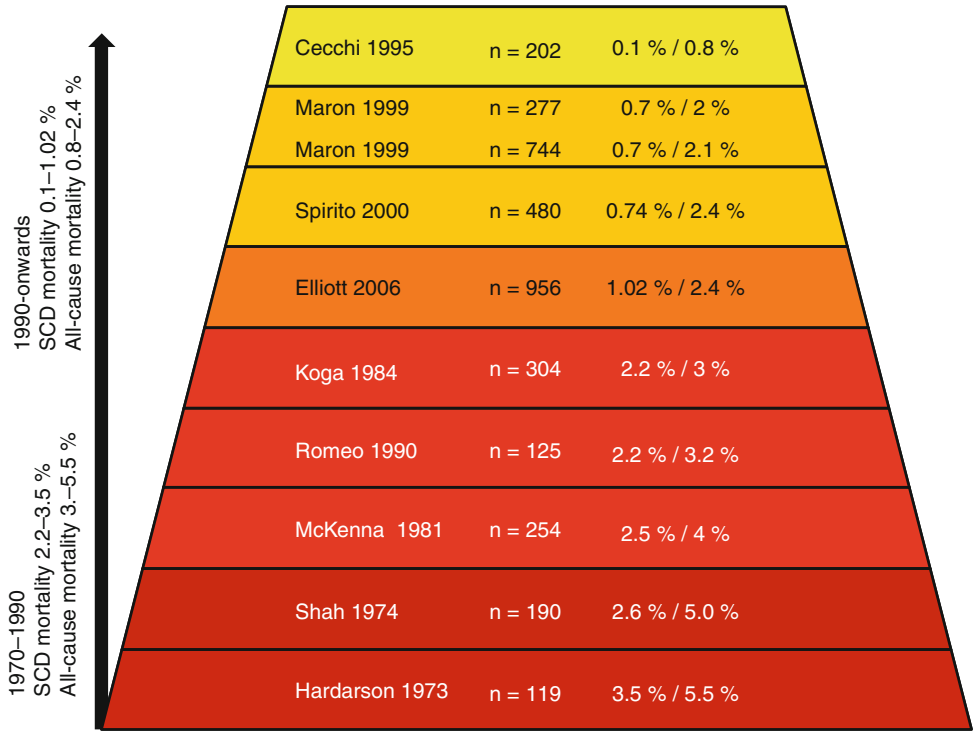

Fig. 2.3 Historical trends in sudden cardiac death and all-cause mortality in selected studies of patients with HCM over the past five decades

Causes of Mortality

Patients experience a diverse range of outcomes, ranging from a benign and stable clinical course over decades to progressive congestive heart failure symptoms or sudden and unexpected cardiac death. Natural history data has historically been derived from a small number of large tertiary referral centers caring for high-risk patients, and has largely focused on sudden premature cardiac death as the most devastating manifestation of the disease. However a study of a largely unselected cohort of 744 patients has addressed the epidemiology and clinical profile of HCM-related mortality, demonstrating annual mortality rates of <1 %/year [37]. In this study three distinctive modes of death were identified: (1) sudden and unexpected, (2) progressive heart failure, and (3) HCM-related ischemic stroke associated with atrial fibrillation or mural thrombus.

Up to half of all HCM-related deaths have been shown to be sudden (see Fig. 2.4) [32, 33, 35–37, 39, 44], occurring over a wide range of age ranges, but with a trend towards a greater frequency of episodes in younger patients [37]. This is in contrast to previous reports suggesting that sudden cardiac death occurred predominantly in adolescents and adults below 35 years of age [45, 46]. Over two-thirds of patients experiencing a sudden cardiac death were asymptomatic or only mildly symptomatic [37]. This and other studies have shown that up to two-thirds of sudden cardiac deaths are unrelated to physical activity [45, 47]. Whether this phenomenon is related to the widespread counselling of young HCM patients regarding the risk of participation in moderate-to-strenuous physical activity is undetermined. Exercise-related sudden death appears to occur more commonly in younger patients compared to exercise-unrelated deaths [47]. Heart-failure and HCM-related stroke accounted for 31 and 13 % of deaths respectively, and tended to occur in midlife and beyond, with stroke-related deaths occurring disproportionately in the elderly [37]. In pediatric HCM a greater proportion of HCM-related mortality is accounted for by non-sudden cardiac deaths [48]. In children dying within the first year of life, congestive heart failure accounts for a disproportionate number of deaths [21].

Diastolic Dysfunction

Diastolic dysfunction is a well-recognized complication of HCM and occurs in obstructive, nonobstructive, and genotype-positive patients in the absence of LVH [49]. Histologically, myocardial disarray and fibrosis are cardinal features of this condition. Echocardiographic diastolic parameters such as Ea velocities and E/Ea ratio are significantly different in patients harbouring pathogenic HCM mutations without evidence of LVH compared to controls [50]. HCM patients with preserved ejection fraction were shown to have abnormal diastolic myocardial mechanics evidenced by decreased ratio of peak early diastolic to peak

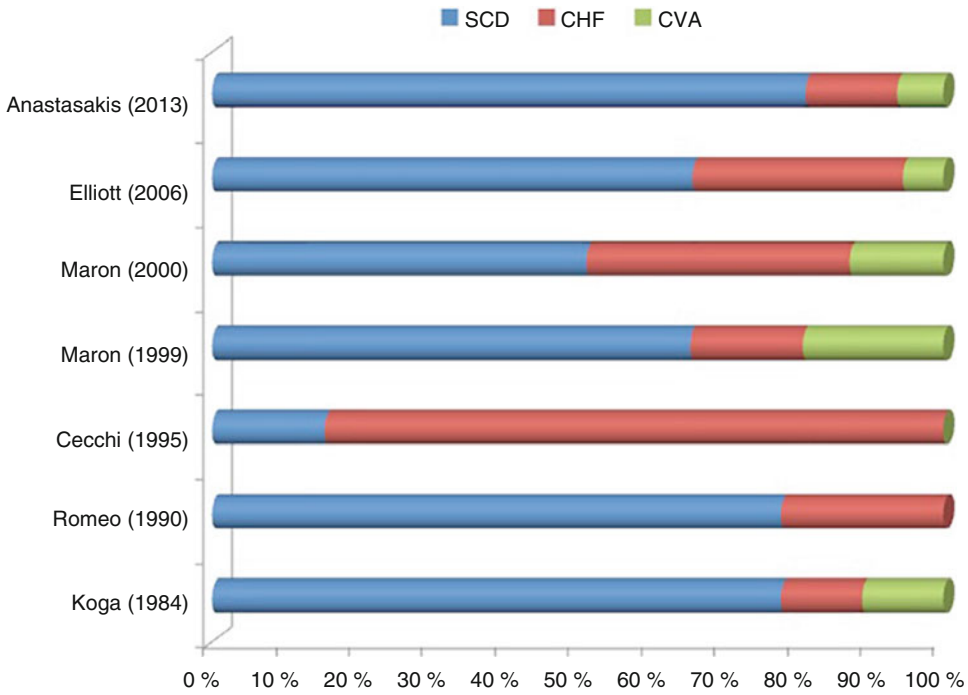

Fig. 2.4 Epidemiology of HCM-related death in selected studies of patients with HCM. Multiple studies have consistently shown that sudden cardiac death accounts for >50 % of all HCM-related mortality. *SCD* sudden cardiac death, *CHF* heart-failure related death, *CVA* stroke-related death

systolic strain rate, prolonged time for LV untwisting, and lower apical reverse rotation fraction. Many of these parameters correlated with the severity of symptoms [51]. The cause of diastolic dysfunction could be explained by the fact that patients with HCM have abnormal intracellular calcium handling and compromised cardiomyocyte energetic balance which can lead to the development of myocardial disarray and fibrosis [52]. Pathways involved in fibrosis and collagen deposition responsible for diastolic dysfunction are activated before the onset of LVH: elevated levels of myocardial type I collagen synthesis and extracellular volume expansion based on T1 measurements on cardiac MRI were evident in genotype positive patients before the onset of hypertrophy [53, 54]. Clinically, diastolic dysfunction is a major cause of exertional symptoms and predisposes patients to developing atrial fibrillation and atrial flutter due to elevated filling pressures and progressive left atrial enlargement and remodelling [55]. Consequently, chamber remodelling has been associated with higher levels of NT-proBNP, which has been shown to be an independent predictor of heart failure outcomes and transplantation in HCM patients with preserved ejection fraction [56]. Diastolic dysfunction also occurs on a macroscopic level, with hypertrophy markedly reducing the left ventricular cavity available for diastolic filling. Patients with massive hypertrophy and those with apical variants, in particular, often have both macroscopic (reduced chamber size) and microscopic (myocardial diastology) components of diastolic dysfunction at play, each contributing to symptoms of heart failure.

Systolic Dysfunction, Heart Failure and Transplantation

While HCM patients may initially present with preserved ejection fraction or even hyperdynamic left ventricles, a small proportion of patients can develop systolic impairment, defined as a left ventricular ejection fraction of <50 %, often in association with heart failure symptoms, the loss of obstructive physiology, and advanced NYHA Class. The estimated prevalence of systolic impairment varies between 2.4 and 15 % [57, 58]. Strain analysis is an excellent method for detection of early systolic impairment by demonstrating reductions in both longitudinal strain and strain rates in patients with apparently normal LV ejection fraction [59, 60] The adverse left ventricular remodelling is also evident on cardiac MRI, where the degree of late gadolinium enhancement (LGE) has an inverse relationship with the extent of LV systolic dysfunction (see Fig. 2.5) [61]. HCM patients with end-stage heart failure show extensive areas of LGE (often >15 %) which are frequently transmural and distributed diffusely throughout the septum and LV free wall [57].

The link between progressive systolic impairment and a patient's genotype status has sparked tremendous interest in the field of HCM. Earlier studies have shown that mutations in myosin binding protein C 3 (MYBPC3) were associated with late-onset disease and the tendency for developing systolic dysfunction, possibly due to its role in causing truncated protein products and haploinsufficiency. Consequently, the collapse of sarcomere stability and the compensatory

process by residual MYBPC3 proteins in heterozygous patients can lead to fibrosis and ventricular dysfunction [62, 63]. Similarly, mutations in other sarcomere genes have been implicated, including those in β myosin heavy chain (MYH7), cardiac troponin T (TNNT2), troponin I (TNNI3), regulatory light chain (MYL2), and alpha-tropomyosin (TPM1) [64, 65]. Interestingly, there is evidence that having any pathogenic sarcomere mutations predisposes patients to worse cardiovascular outcomes including death, ischemic stroke, and progression to advanced NYHA class [65]. Furthermore, the presence of double or triple pathogenic sarcomere gene mutations confers increased risk of progression

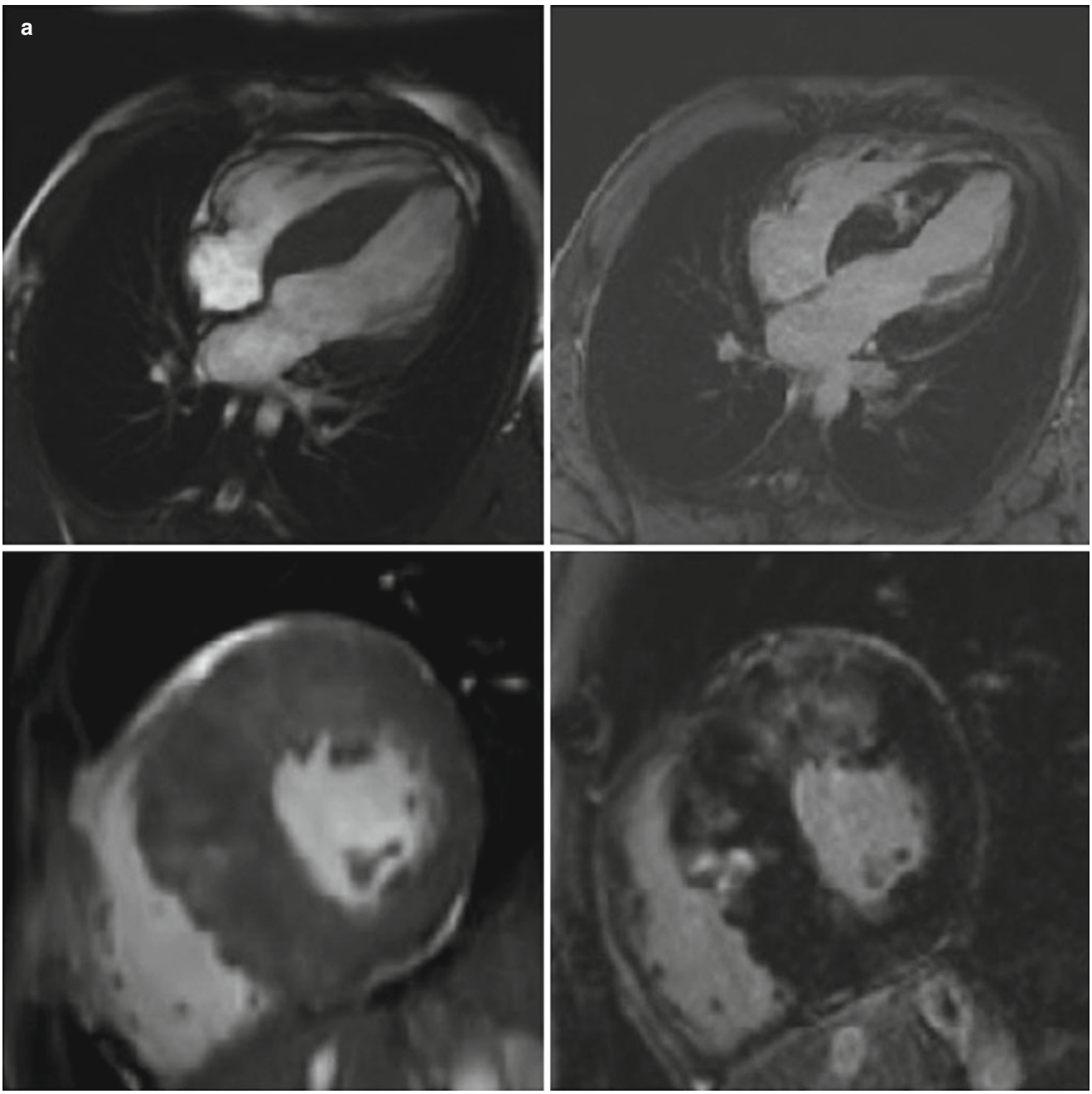

Fig. 2.5 Typical patterns of late gadolinium enhancement (LGE) on cardiac MRI in patients with HCM. Panel (**a**) (*upper*): Horizontal long-axis view in a patient with septal hypertrophy and nodular LGE in the septum. Panel (**a**) (*lower*): Short-axis view in the same patient showing LGE in the hypertrophied septum with extension to the anterior wall. Panel (**b**) (*upper*): Horizontal long-axis view in a patient with apical HCM and apical aneurysm, showing transmural LGE in the apex. Panel (**b**) (*lower*): Short-axis view in the same patient showing the extent of fibrosis in the apex

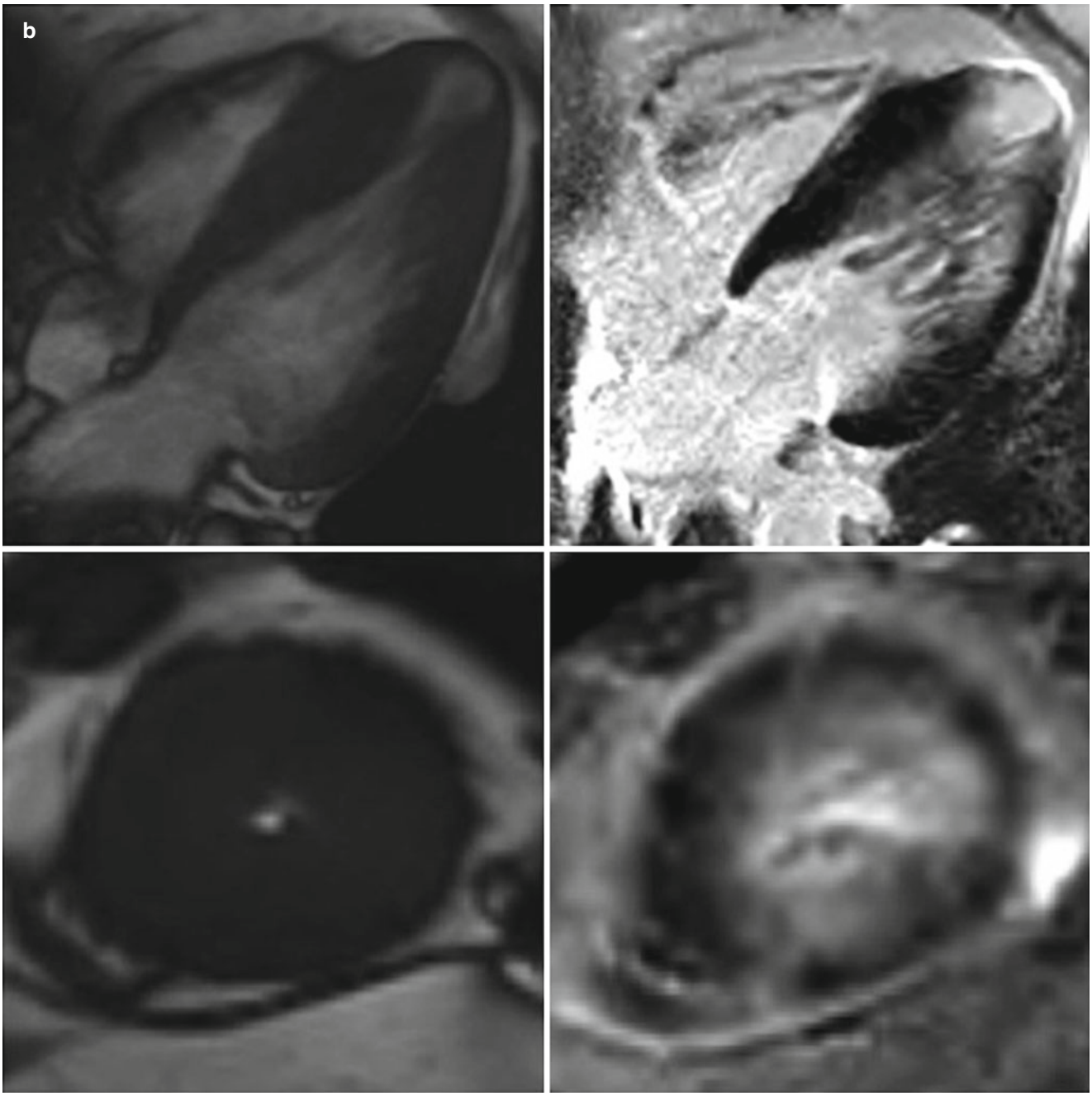

Fig. 2.5 (continued)

to end-stage disease (characterized by restrictive physiology and chamber dilatation) as well as a heightened risk of sudden cardiac death [65, 66]. In addition to genetic predisposition, female gender, the presence of coronary artery disease, and young age at disease onset have all been associated with the development of "end-stage" or "burned-out" HCM [67]. Similar to other causes of LV dysfunction, the left ventricle in "end-stage" HCM shows progressive wall thinning and chamber dilatation. Histopathologically, there are patchy areas of scarring characterized by myocyte disarray, increased interstitial fibrosis, abnormal intramural arterioles, and silent myocardial ischemia [58].

Based on a large cohort study in HCM, the interval from identification of "end-stage" disease to death or transplantation is approximately 2.7 ± 2 years [57]. The rate of cardiac transplantation in HCM patients varies between 1 and 2 % [58]. Cardiac transplant recipients with a primary diagnosis of HCM comprised 1 % of the 26,706 patients who had undergone cardiac transplantation over a 15-year period, based on the United Network of Organ Sharing (UNOS)

Registry [68]. The 10-year survival rate of HCM patients after cardiac transplantation is >60 % which is comparable to patients whose primary diagnosis was non-ischemic cardiomyopathy [68]. Of note, endomyocardial biopsies performed in a large group of post-transplant HCM patients have shown no evidence of recurrence of HCM [69].

Incidence of Arrythmias

Atrial Fibrillation

Atrial fibrillation (AF) is by far the most common sustained arrhythmia encountered in HCM, occurring in approximately 20 % of patients with an annual incidence of up to 2 %/year [55]. In these patients susceptibility to AF is linked to factors such as aging and substantial left atrial dilatation [70, 71]. Although clinical studies have shown that AF is well-tolerated and compatible with a benign outcome in around one-third of patients [55], paroxysmal and chronic AF episodes may results in acute clinical deterioration and either syncope or heart failure. A hypertrophied left ventricle with pre-existing impaired relaxation and compliance is exquisitely sensitive to reduced diastolic filling and cardiac output as a consequence of increased ventricular rates and loss of atrial contraction (and its contribution to left ventricular filling). The occurrence of AF has been shown to be related to an increased risk of heart failure progression and embolic stroke (with a prevalence of 6 % and incidence of 0.8 %/year) in patients with HCM [55, 72], which is most substantial in those patients with obstructive physiology.

Ventricular Arrhythmias

Non-sustained ventricular tachycardia (NSVT) during ambulatory ECG monitoring is common in HCM, with a low prevalence in children and adolescence, but occurring in around 25 % of patients over the age of 40 years [73–75]. While usually asymptomatic (occurring during periods of heightened vagal tone), its presence has been shown to be related to a 2–2.5 fold increased risk of sudden cardiac death, particularly in adults and young children with the disease [73–76]. There is very little evidence to suggest that the rate, duration or frequency of runs of NSVT influences its prognostic significance.

Sustained ventricular tachycardia, in contrast, is uncommon in the HCM population as a whole. However, in high-risk patients undergoing implantation of an ICD for primary prevention of sudden cardiac death, sustained monomorphic VT is seen more frequently on device interrogation [77, 78], particularly during sedentary or non-competitive activity. Sustained monomorphic VT may arise from a distal apical aneurysm in patients with mid-cavity obstruction, or in those patients with apical HCM with scarring at the LV apex [79].

Exercise-induced ventricular arrhythmias have been shown to be markedly rare in a large series of patients with HCM undergoing exercise testing [80], occurring in only 2 % of a total of 1,380 patients studied. While rare, the presence of NSVT or ventricular fibrillation on exercise was associated with a significantly increased risk of sudden death or ICD discharge [80].

Summary

With the passage of time and advances in knowledge, the historical misconceptions regarding HCM as a rare disease with poor prognosis have been dispelled to a large degree. Current understanding of this common disease suggests that the natural history is indeed benign for the HCM patient population as a whole, with annual sudden death mortality rates of <1 %. However, a subgroup of high-risk patients and those with obstructive physiology remain at risk for complications such as heart failure progression, advanced symptoms, atrial fibrillation, and stroke.

Clinical Pearls

- While initially thought to be a rare disease with poor prognosis, current knowledge suggests that the natural history of the HCM population as a whole is relatively benign
- Phenotypic expression can occur at any age, with age at diagnosis ranging from the first to the eighth decades of life
- Identification of LVOT obstruction is essential given the association with HCM-related morbidity and mortality
- Diastolic dysfunction is an almost universal feature of HCM
- A small percentage of HCM patients may develop end stage heart failure with impaired left ventricular systolic function
- While three distinctive modes of cardiac death occur in HCM, sudden unexpected death accounts for up to half of all HCM-related mortality
- Published survival rates have improved over the last five decades, with a reduction in all-cause mortality from 5 to 3 %, and a reduction in annual sudden death mortality from 3 to 1 %

References

1. Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol. 2011;58:e212–60.
2. Doi YL, Deanfield JE, McKenna WJ, Dargie HJ, Oakley CM, Goodwin JF. Echocardiographic differentiation of hypertensive heart disease and hypertrophic cardiomyopathy. Br Heart J. 1980;44:395–400.
3. Henry WL, Clark CE, Epstein SE. Asymmetric septal hypertrophy: echocardiographic identification of the pathognomonic anatomic abnormality of IHSS. Circulation. 1973;47:225–33.
4. Binder J, Ommen SR, Gersh BJ, et al. Echocardiography-guided genetic testing in hypertrophic cardiomyopathy: septal morphological features predict the presence of myofilament mutations. Mayo Clin Proc. 2006;81:459–67.
5. Gruner C, Ivanov J, Care M, et al. Toronto hypertrophic cardiomyopathy genotype score for prediction of a positive genotype in hypertrophic cardiomyopathy. Circ Cardiovasc Genet. 2013;6:19–26.
6. Maron MS, Olivotto I, Zenovich AG, et al. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. Circulation. 2006;2006:2232.
7. Klues HG, Maron BJ, Dollar AL, Roberts WC. Diversity of structural mitral valve alterations in hypertrophic cardiomyopathy. Circulation. 1992;85:1651–60.
8. Grigg LE, Wigle ED, Williams WG, Daniel LB, Rakowski H. Transesophageal Doppler echocardiography in obstructive hypertrophic cardiomyopathy: clarification of pathophysiology and importance in intraoperative decision making. J Am Coll Cardiol. 1992;20:42–52.
9. Maron MS, Olivotto I, Betocchi S, et al. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. N Engl J Med. 2003;348:295–303.
10. Hickey EJ, McCrindle BW, Larsen SH, et al. Hypertrophic cardiomyopathy in childhood: disease natural history, impact of obstruction, and its influence on survival. Ann Thorac Surg. 2012;93:840–8.
11. Nugent AW, Daubeney PEF, Chondros P, et al. Clinical features and outcomes of childhood hypertrophic cardiomyopathy: results from a national population-based study. Circulation. 2005;112:1332–8.
12. Falicov RE, Resnekov L. Mid ventricular obstruction in hypertrophic obstructive cardiomyopathy. New diagnostic and therapeutic challenge. Br Heart J. 1977;39:701–5.
13. Efthimiadis GK, Pagourelias ED, Parcharidou D, et al. Clinical characteristics and natural history of hypertrophic cardiomyopathy with midventricular obstruction. Circ J. 2013;77:2366–74.
14. Minami Y, Kajimoto K, Terajima Y, et al. Clinical implications of midventricular obstruction in patients with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2011;57:2346–55.
15. Yamaguchi H, Ishimura T, Nishiyama S, et al. Hypertrophic nonobstructive cardiomyopathy with giant negative T waves (apical hypertrophy): ventriculographic and echocardiographic features in 30 patients. Am J Cardiol. 1979;44:401–12.
16. Sakamoto T, Tei C, Murayama M, Ichiyasu H, Hada Y. Giant T wave inversion as a manifestation of asymmetrical apical hypertrophy (AAH) of the left ventricle: echocardiographic and ultrasonocardiotomographic study. Jpn Heart J. 1976;17:611–29.
17. Eriksson MJ, Sonnenberg B, Woo A, et al. Long-term outcome in patients with apical hypertrophic cardiomyopathy. J Am Coll Cardiol. 2002;39:638–45.
18. Moon J, Shim CY, Ha JW, et al. Clinical and echocardiographic predictors of outcomes in patients with apical hypertrophic cardiomyopathy. Am J Cardiol. 2011;108:1614–9.
19. Maron MS, Finley JJ, Bos JM, et al. Prevalence, clinical significance, and natural history of left ventricular apical aneurysms in hypertrophic cardiomyopathy. Circulation. 2008;118:1541–9.
20. Nugent AW, Daubeney PEF, Chondros P, et al. The epidemiology of childhood cardiomyopathy in Australia. N Engl J Med. 2003;348:1639–46.
21. Colan SD, Lipschultz SE, Lowe AM, et al. Epidemiology and cause-specific outcome of hypertrophic cardiomyopathy in children: findings from the pediatric cardiomyopathy registry. Circulation. 2007;115:773–81.
22. Maron BJ, Spirito P, Wesley Y, Arce J. Development and progression of left ventricular hypertrophy in children with hypertrophic cardiomyopathy. N Engl J Med. 1986;315:610–4.
23. Jensen MK, Havndrup O, Christiansen M, et al. Penetrance of hypertrophic cardiomyopathy in children and adolescents: a 12-year follow-up study of clinical screening and predictive genetic testing. Circulation. 2013;127:48–54.
24. Pasquale F, Syrris P, Kaski JP, Mogensen J, McKenna WJ, Elliott PM. Long-term outcomes in hypertrophic cardiomyopathy caused by mutations in the cardiac troponin T gene. Circ Cardiovasc Genet. 2012;5:10–7.
25. Page SP, Kounas S, Syrris P, et al. Cardiac myosin binding protein-C mutations in families with hypertrophic cardiomyopathy. Disease expression in relation to age, gender, and long term outcome. Circ Cardiovasc Genet. 2012;5:156–66.
26. Van Driest SL, Vasile VC, Ommen SR, et al. Myosin binding protein C mutations and compound heterozygosity in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2004;44:1903–10.
27. Mogensen J, Murphy RT, Kubo T, et al. Frequency and clinical expression of cardiac troponin I mutations in 748 consecutive families with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2004;44:2315–25.
28. Maron BJ, Tajik AJ, Ruttenberg HD, et al. Hypertrophic cardiomyopathy in infants: clinical features and natural history. Circulation. 1982;65:7–17.
29. McKenna W, Deanfield J, Faruqui A, England D, Oakley C, Goodwin J. Prognosis in hypertrophic cardiomyopathy: role of age and clinical, electrocardiographic and hemodynamic features. Am J Cardiol. 1981;47:532–8.
30. Suda K, Kohl T, Kovalchin JP, Silverman NH. Echocardiographic predictors of poor outcome in infants with hypertrophic cardiomyopathy. Am J Cardiol. 1997;80:595–600.
31. Ostman-Smith I, Wettrell G, Keeton B, et al. Age- and gender-specific mortality rates in childhood hypertrophic cardiomyopathy. Eur Heart J. 2008;29:1160–7.
32. Cecchi F, Olivotto I, Montereggi A, Santoro G, Dolara A, Maron BJ. Hypertrophic cardiomyopathy in Tuscany: clinical course and outcome in an unselected regional population. J Am Coll Cardiol. 1995;26:1529–36.
33. Elliott PM, Gimeno JR, Thaman R, et al. Historical trends in reported survival rates in patients with hypertrophic cardiomyopathy. Heart. 2006;92:785–91.
34. Hardarson T, De la Calzada CS, Curiel R, Goodwin JF. Prognosis and mortality of hypertrophic obstructive cardiomyopathy. Lancet. 1973;2:1462–7.
35. Koga Y, Itaya K, Toshima H. Prognosis in hypertrophic cardiomyopathy. Am Heart J. 1984;108:351–9.
36. Maron BJ, Casey SA, Poliac LG, Gohman TE, Almquist AK, Aeppli DM. Clinical course of hypertrophic cardiomyopathy in a regional United States cohort. JAMA. 1999;281:650–5.
37. Maron BJ, Olivotto I, Spirito P, et al. Epidemiology of hypertrophic cardiomyopathy-related death: revisited in a large non-referral based patient population. Circulation. 2000;102:858–64.
38. McKenna WJ, Goodwin JF. The natural history of hypertrophic cardiomyopathy. Curr Probl Cardiol. 1981;6:1–26.

39. Romeo F, Pelliccia F, Cristofani R, Martuscelli E, Reale A. Hypertrophic cardiomyopathy: is a left ventricular outflow tract gradient a major prognostic determinant? Eur Heart J. 1990;11:233–40.
40. Shah PM, Adelman AG, Wigle ED, et al. The natural (and unnatural) history of hypertrophic obstructive hypertrophic cardiomyopathy. Circ Res. 1974;35:179–95.
41. Spirito P, Bellone P, Harris KM, Bernabo P, Bruzzi P, Maron BJ. Magnitude of left ventricular hypertrophy and risk of sudden death in hypertrophic cardiomyopathy. N Engl J Med. 2000;342:1778–85.
42. Fay WP, Taliercio CP, Ilstrup DM, Tajik AJ, Gersh BJ. Natural history of hypertrophic cardiomyopathy in the elderly. J Am Coll Cardiol. 1990;16:821–6.
43. Maron BJ, Rowin EJ, Casey SA, et al. Risk stratification and outcome of patients with hypertrophic cardiomyopathy >=60 years of age. Circulation. 2013;127:585–93.
44. Anastasakis A, Theopistou A, Rigopoulos A, et al. Sudden cardiac death: investigation of the classical risk factors in a community-based hypertrophic cardiomyopathy cohort. Hellenic J Cardiol. 2013;54:281–8.
45. Maron BJ, Roberts WC, Epstein SE. Sudden death in hypertrophic cardiomyopathy: a profile of 78 patients. Circulation. 1982;65: 1388–94.
46. Swan DA, Bell B, Oakley CM, Goodwin J. Analysis of symptomatic course and prognosis and treatment of hypertrophic obstructive cardiomyopathy. Br Heart J. 1971;33:671–85.
47. Maki S, Ikeda H, Muro A, et al. Predictors of sudden cardiac death in hypertrophic cardiomyopathy. Am J Cardiol. 1998;82:774–8.
48. Decker JA, Rossano JW, O'Brian Smith E, et al. Risk factors and mode of death in isolated hypertrophic cardiomyopathy in children. J Am Coll Cardiol. 2009;54:250–4.
49. Ho CY, Sweitzer NK, McDonough B, et al. Assessment of diastolic function with Doppler tissue imaging to predict genotype in preclinical hypertrophic cardiomyopathy. Circulation. 2002;105: 2992–7.
50. Nagueh SF, Bachinski LL, Meyer D, et al. Tissue Doppler imaging consistently detects myocardial abnormalities in patients with hypertrophic cardiomyopathy and provides a novel means for an early diagnosis before and independently of hypertrophy. Circulation. 2001;104:128–30.
51. Carasso S, Yang H, Woo A, Jamorski M, Wigle ED, Rakowski H. Diastolic myocardial mechanics in hypertrophic cardiomyopathy. J Am Soc Echocardiogr. 2010;23:164–71.
52. Bers DM. Calcium cycling and signaling in cardiac myocytes. Annu Rev Physiol. 2008;70:23–49.
53. Ho CY, Lopez B, Coelho-Filho OR, et al. Myocardial fibrosis as an early manifestation of hypertrophic cardiomyopathy. N Engl J Med. 2010;363:552–63.
54. Ho CY, Abbasi SA, Neilan TG, et al. T1 measurements identify extracellular volume expansion in hypertrophic cardiomyopathy sarcomere mutation carriers with and without left ventricular hypertrophy. Circ Cardiovasc Imaging. 2013;6:415–22.
55. Olivotto I, Cecchi F, Casey SA, Dolara A, Traverse JH, Maron BJ. Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. Circulation. 2001;104:2517–24.
56. Coats CJ, Gallagher MJ, Foley M, et al. Relation between serum N-terminal pro-brain natriuretic peptide and prognosis in patients with hypertrophic cardiomyopathy. Eur Heart J. 2013;34:2529–37.
57. Harris KM, Spirito P, Maron MS, et al. Prevalence, clinical profile, and significance of left ventricular remodelling in the end-stage phase of hypertrophic cardiomyopathy. Circulation. 2006;114: 216–25.
58. Melacini P, Basso C, Angelini A, et al. Clinicopathological profiles of progressive heart failure in hypertrophic cardiomyopathy. Eur Heart J. 2010;31:2111–23.
59. Ho CY, Carlsen C, Thune JJ, et al. Echocardiographic strain imaging to assess early and late consequences of sarcomere mutations in hypertrophic cardiomyopathy. Circ Cardiovasc Genet. 2009;2: 314–21.
60. Carasso S, Yang H, Woo A, et al. Systolic myocardial mechanics in hypertrophic cardiomyopathy: novel concepts and implications for clinical status. J Am Soc Echocardiogr. 2008;21:75–83.
61. Maron MS, Appelbaum E, Harrigan CJ, et al. Clinical profile and significance of delayed enhancement in hypertrophic cardiomyopathy. Circ Heart Fail. 2008;1:184–91.
62. Kubo T, Kitaoka H, Okawa M, et al. Lifelong left ventricular remodelling of hypertrophic cardiomyopathy caused by a founder frameshift deletion mutation in the Myosin-binding protein C gene among Japanese. J Am Coll Cardiol. 2005;46:1737–43.
63. Oliva-Sandoval MJ, Ruiz-Espejo F, Monserrat L, et al. Insights into genotype-phenotype correlation in hypertrophic cardiomyopathy. Findings from 18 Spanish families with a single mutation in MYBPC3. Heart. 2010;96:1980–4.
64. Garcia-Pavia P, Vazquez ME, Segovia J, et al. Genetic basis of end-stage hypertrophic cardiomyopathy. Eur J Heart Fail. 2011;13: 1193–201.
65. Olivotto I, Girolami F, Ackerman MJ, et al. Myofilament protein gene mutation screening and outcome of patients with hypertrophic cardiomyopathy. Mayo Clin Proc. 2008;83:630–8.
66. Girolami F, Ho CY, Semsarian C, et al. Clinical features and outcome of hypertrophic cardiomyopathy associated with triple sarcomere protein gene mutations. J Am Coll Cardiol. 2010;55: 1444–53.
67. Yacoub MH, Olivotto I, Cecchi F. 'End-stage' hypertrophic cardiomyopathy: from mystery to model. Nat Clin Pract Cardiovasc Med. 2007;4:232–3.
68. Maron MS, Kalsmith BM, Udelson JE, Li W, DeNofrio D. Survival after cardiac transplantation in patients with hypertrophic cardiomyopathy. Circ Heart Fail. 2010;3:574–9.
69. Kato TS, Takayama H, Yoshizawa S, et al. Cardiac transplantation in patients with hypertrophic cardiomyopathy. Am J Cardiol. 2012;110:568–74.
70. Nistri S, Olivotto I, Betocchi S, et al. Prognostic significance of left atrial size in patients with hypertrophic cardiomyopathy (from the Italian registry for hypertrophic cardiomyopathy). Am J Cardiol. 2006;98:960–5.
71. Yang W, Shim CY, Kim YJ, et al. Left atrial volume index: a predictor of adverse outcome in patients with hypertrophic cardiomyopathy. J Am Soc Echocardiogr. 2009;22:1338–43.
72. Maron BJ, Olivotto I, Bellone P, et al. Clinical profile of stroke in 900 patients with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2002;39:301–7.
73. Maron BJ, Savage DD, Wolfson JK, Epstein SE. Prognostic significance of 24-h ambulatory electrocardiographic monitoring in patients with hypertrophic cardiomyopathy: a prospective study. Am J Cardiol. 1981;48:252–7.
74. Monserrat L, Elliott PM, Gimeno JR, Sharma S, Penas-Lado M, McKenna WJ. Non-sustained ventricular tachycardia in hypertrophic cardiomyopathy: an independent marker of sudden death risk in young patients. J Am Coll Cardiol. 2003;42:873–9.
75. Spirito P, Rapezzi C, Autore C, et al. Prognosis of asymptomatic patients with hypertrophic cardiomyopathy and non-sustained ventricular tachycardia. Circulation. 1994;90:2743–7.
76. Elliott PM, McKennna WJ. Hypertrophic cardiomyopathy. Lancet. 2004;363:1881–91.
77. Begley DA, Mohiddin SA, Tripodi D, Winkler JB, Fananapazir L. Efficacy of implantable cardioverter defibrillator therapy for primary and secondary prevention of sudden cardiac death in hypertrophic cardiomyopathy. Pacing Clin Electrophysiol. 2003;26: 1887–96.

78. Cha YM, Gersh BJ, Maron BJ, et al. Electrophysiologic manifestations of ventricular tachyarrhythmias provoking appropriate defibrillator interventions in high-risk patients with hypertrophic cardiomyopathy. J Cardiovasc Electrophysiol. 2007;18:483–7.
79. Alfonso F, Frenneaux MP, McKenna WJ. Clinical sustained uniform ventricular tachycardia in hypertrophic cardiomyopathy: association with left ventricular apical aneurysm. Br Heart J. 1989;61:178–81.
80. Gimeno JR, Tome-Esteban M, Lofiego C, et al. Exercise-induced ventricular arrhythmias and risk of sudden cardiac death in patients with hypertrophic cardiomyopathy. Eur Heart J. 2009;30: 2599–605.

Pathology and Pathophysiology

3

Kazuyuki Yahagi, Elena Ladich, and Renu Virmani

Abstract

Hypertrophic cardiomyopathy (HCM) is a primary and usually familial cardiac disorder with heterogeneous expression, unique pathophysiology, and a diverse clinical course. Clinically HCM requires a hypertrophied non-dilated left ventricle without evidence of any other cardiac or systemic disease that could produce the extent of hypertrophy observed. In the vast majority of individual adults dying from HCM, there is cardiomegaly typically in the range of twice the normal heart weight. The characteristic histological features in HCM are the presence of marked myocyte hypertrophy, myofiber disarray, left ventricular outflow tract plaque, intramural coronary abnormalities and interstitial fibrosis. The pathophysiology of HCM is complex and consists of multiple interrelated abnormalities, including left ventricular outflow tract obstruction, diastolic dysfunction, mitral regurgitation, myocardial ischemia, and arrhythmia. Sudden death is not an uncommon complication of HCM, and is often precipitated by exercise. The frequency of sudden death in HCM is up to 1 % per year in adults with 2–4 % per year in children and adolescents.

Keywords

Sudden death • Myocyte hypertrophy • Myofiber disarray • Interstitial fibrosis • Intramural coronary abnormalities • Left ventricular outflow tract plaque

Abbreviations

HCM Hypertrophic cardiomyopathy
MRI Magnetic resonance imaging

Key Points

- Diagnosis of HCM is dependent on pathologic findings in the heart along with family history
- HCM must be distinguished from physiologic enlargement of the heart in athletes.
- Conditions that may result in myofiber disarray other than HCM include other causes of ventricular hypertrophy, aortic stenosis and chronic hypertension.
- Risk factors of sudden death include sustained ventricular or supraventricular tachycardia, recurrent syncope in the young, non-sustained ventricular tachycardia, bradycardia, and massive myocardial thickening >3 cm.

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Introduction

In 1958 Teare's first report of asymmetric hypertrophy of the heart in a 14-year-old boy was described as a "localized and diffuse hypertrophy of the interventricular septum in close proximity to the mitral valve with a coarse texture" and microscopically had "bizarre arrangement of bundles of muscle fibers running in diverse directions." He thought it represented a tumor of the heart. In the 1960s investigators from Bethesda, London and Toronto defined the clinical, hemodynamic and pathologic features of hypertrophic cardiomyopathy (HCM) and these investigators emphasized the obstructive nature of the disease [1]. The original definition by the World Health Organization (WHO) of cardiomyopathy in 1980 was "heart muscle disease of unknown etiology". Diseases that involved the myocardium but were of a known cause were considered separately and termed specific heart muscle diseases. The report of the 1995 WHO/International Society and Federation of Cardiology Task Force defined cardiomyopathy as "disease of the myocardium associated with cardiac dysfunction". They classified these into dilated cardiomyopathy, HCM, restrictive cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy and unclassified cardiomyopathies. Much progress has been made in our understanding of the etiology and pathogenesis of heart muscle disease such that the distinction between cardiomyopathy and specific heart muscle disease has become much clearer.

The first modern pathologic description as stated above was provided by Teare [2] and the most important early clinical report was given by Braunwald et al. in 1964 [3]. Using the term asymmetry of the heart in young adults, Teare hypothesized that the condition was likely to be a hamartoma that resulted in outflow tract obstruction. Further pathological characterization of the condition, later referred to as "idiopathic subaortic hypertrophic stenosis", followed [4]. It was gradually accepted that HCM was a result of generalized ventricular dysfunction, and that significant outflow tract obstruction occurred in only 50–70 % of patients [5]. The importance of myofiber disarray and its quantification by morphometric techniques occurred in the late 1970s [1, 6, 7]. Although an autosomal dominant mode of inheritance was described as early as 1960 [8, 9], the genetic basis for many of the inherited forms of the disease was established only in 1990, more than 30 years after the initial morphological description [10].

Epidemiology

HCM is a common genetic cardiovascular disease with a global distribution; epidemiological studies from several parts of the world report a similar prevalence of LV hypertrophy, the quintessential phenotype of HCM, to be 0.2 % in the general population, which is equivalent to at least 600,000 affected individuals in the United States (120,000 in the UK) [11–13]. In a recently published analysis of 1,866 sudden death in young athletes in the United States, HCM was the major underlying cardiovascular disorder in confirmed cardiovascular events (Fig. 3.1) [14]. The variability in this range is probably due to study methodology, as the lower prevalence is based on patients presenting with symptomatic disease and the higher prevalence is based on echocardiographic screening. The disease may occur at any age, although most patients are in their 30's or 40's at the time of diagnosis. In a recent clinical series of 600 patients, the mean age was 45 (range 7–79 years), and 66 % of patients were men [15]. Males were affected one and one-half times as frequently as females in a different multicenter study [16]. The disease is either under-recognized or clinical diagnosis is delayed, more frequently in women and in African-Americans. The mean age at presentation is approximately 45 years, with a bimodal distribution, that peaks in early and later adulthood. The infantile form of the syndrome is probably a heterogeneous entity distinct from the adult disease. However, hereditary forms of the disease have been identified with expression of typical HCM in infancy. Clinically, elderly patients are more likely hypertensive, with greater basal septal bulging, and anterior septal hypertrophy of the left ventricle [17].

Gross Pathology (Figs. 3.2, 3.3, 3.4, 3.5, and 3.6)

HCM is indeed unique because it may present at any age from infancy to old age [18]. Clinically HCM requires a hypertrophied non-dilated left ventricle without evidence of any other cardiac or systemic disease (e.g., systemic hypertension) that could produce the extent of hypertrophy observed. In the vast majority of adults dying from HCM, there is cardiomegaly typically in the range of twice the normal heart weight. The mean heart weight is above 600 g in most autopsy series, and several reports describe heart weights of over 1,000 g [19–21]; however sudden death in HCM may occur in the absence of left ventricular hypertrophy

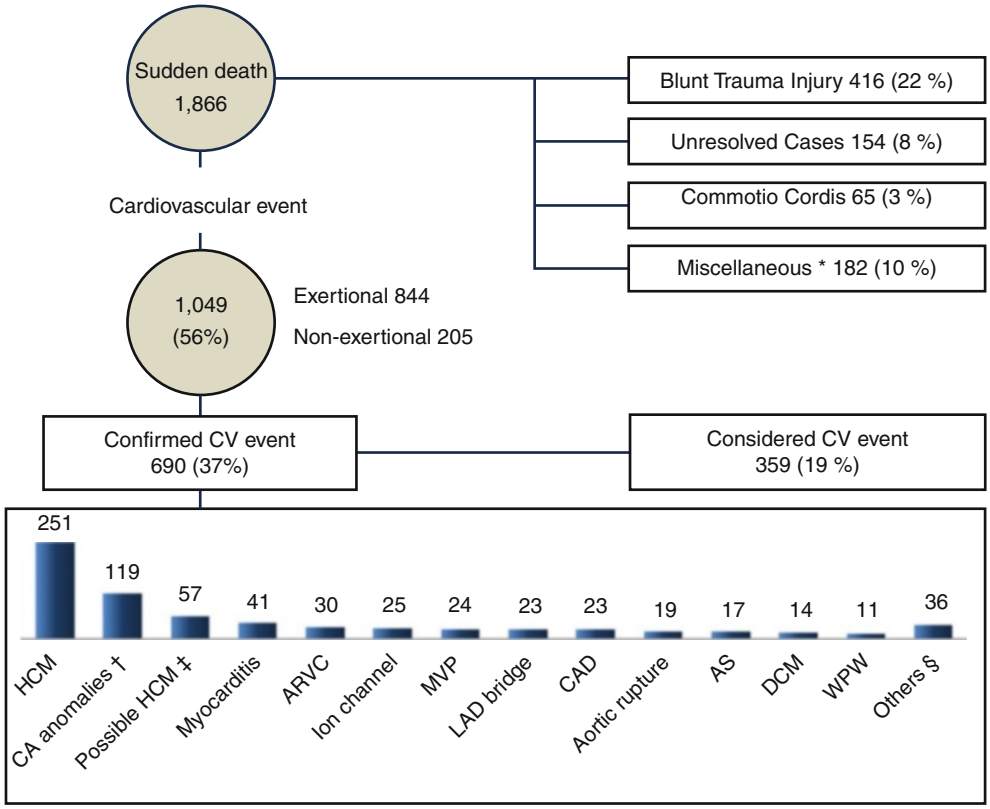

Fig. 3.1 Distribution of sudden death (SD) attributed to underlying cardiovascular disease in young competitive athletes in the USA 1980–2006. Hypertrophic cardiomyopathy (HCM) is the most common primary cardiovascular disease leading to SD in this cohort. *Heat stroke (n = 46), drugs (n = 34), pulmonary disease (n = 35), suicide (n = 22), lightning (n = 12), drowning (n = 10 and 3 during the swimming segment of triathlon events), cerebral aneurysm (n = 9), rhabdomyolysis (n = 8), epilepsy (n = 2), and miscellaneous (n = 4). †Of wrong sinus origin coursing between aorta and pulmonary trunk; most commonly, anomalous left main coronary artery from right (anterior) sinus of Valsalva (n = 65) and anomalous right coronary artery from the left sinus (n = 16). ‡Regarded as possible (not definitive) evidence for hypertrophic cardiomyopathy at autopsy with mildly increased left ventricular wall thickness (18 ± 4 mm) and heart weight (447 ± 76 g). §Congenital heart disease (n = 8), myocardial infarction (n = 6), Kawasaki disease or related conditions (n = 5), sickle cell trait (n = 5), sarcoidosis (n = 4), stroke (n = 3), cardiac tumor (n = 1), conduction system disease (n = 2), miscellaneous (n = 2). *ARVC* arrhythmogenic right ventricular cardiomyopathy, *AS* aortic stenosis, *CA* coronary artery, *CAD* coronary artery disease, *CV* cardiovascular, *DCM* dilated cardiomyopathy, *LAD* left anterior descending coronary artery, *MVP* mitral valve prolapse syndrome, *WPW* Wolff-Parkinson-White syndrome (Modified and reproduced from Maron et al. [14])

(Fig. 3.2). The heart weight should be evaluated in conjunction with body weight, especially in sudden death in young individuals, where marked cardiomegaly may not have yet developed [22]. The latter cases, although rare, have been documented on the basis of family studies and histological findings of myofiber disarray, in which there is loss of the normal parallel configuration of cardiomyocytes [23].

In early stages of the disease, the left ventricular cavity is small, and there is usually left atrial dilatation resulting from decreased left ventricular compliance. In children, there may be relatively rapid accumulation of myocardial mass, with 250 % increases in ventricular thickness occurring over 3–6 years [24]. The gross features of apical HCM differ from other types. The heart weight may be only mildly increased, and the apex of the ventricular septum demonstrates scarring and myofiber disarray which may be grossly visible and involve the right ventricle and left ventricular septum.

In later stages of disease, there may be gradual dilatation of the left ventricle, and areas of hypertrophy may be partly replaced by grossly discernible fibrous tissue. The

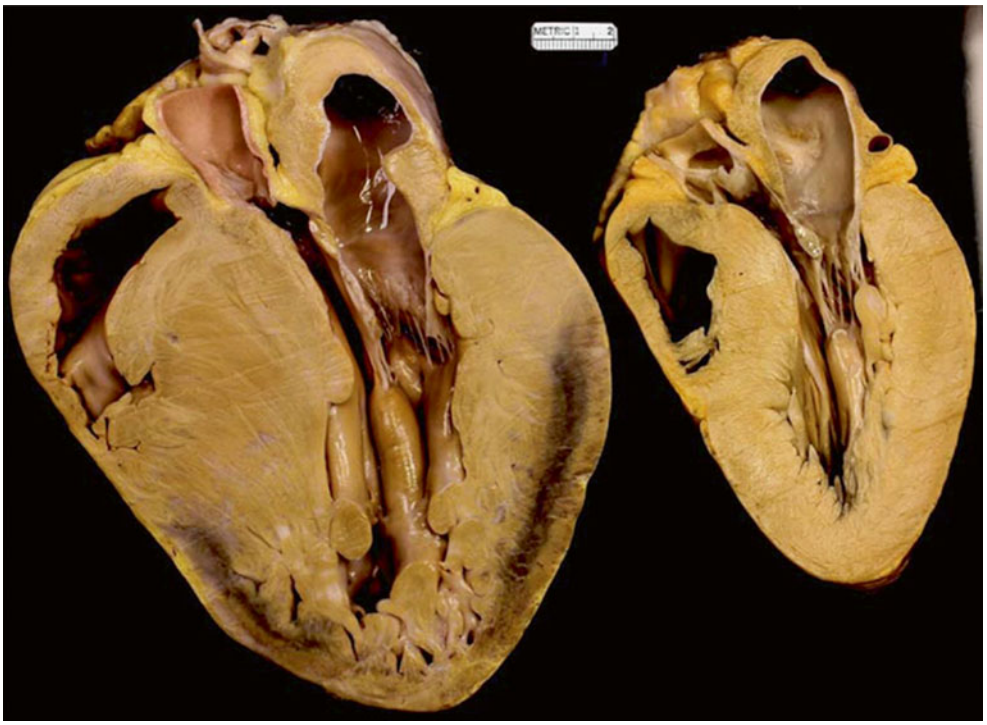

Fig. 3.2 The hearts of two 15-year-old male patients with hypertrophic cardiomyopathy, each of whom died suddenly. The heart on the left weighed 1,415 g, and the ventricular septum was much thicker than the left ventricular free wall. The heart on the right weighed 425 g, and the thicknesses of the ventricular septum and left ventricular free wall were similar (Modified and reproduced from Roberts et al. [73] and Maron et al. [74])

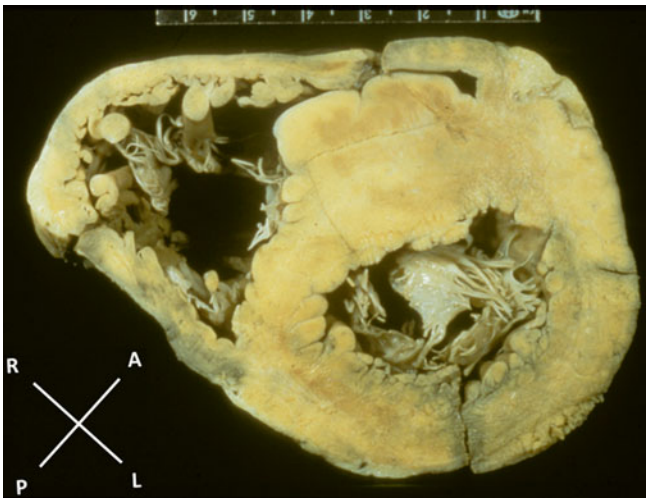

Fig. 3.3 Hypertrophic cardiomyopathy, asymmetric hypertrophy. The anterior portion of the septum is thickened, which is the most common area in the septum to demonstrate hypertrophy (Modified and reproduced from Virmani et al. [75])

replacement of hypertrophied areas by scarring may transform previously hypertrophied areas of ventricular wall to normal or even thin ones [25], and transmural scars may be present in the absence of epicardial coronary occlusions [7]. Occasionally, there may be diffuse gross myocardial scarring in late stages of disease. The evolution of morphologic features must be considered if autopsy findings are compared to cardiac imaging performed years prior to death.

The site of hypertrophy has been classified on the basis of echocardiographic criteria into four types [15]: in type 1, only the anterior ventricular septum is thickened; in type II, the entire septum in thick, with a normal free wall; in type III there is involvement of the free wall as well as the ventricular septum and in type IV, the least common the anterior septum is normal and the hypertrophy is found in other locations of the septum or free wall. In the past M-mode echocardiography was the main methods for confirming the presence of HCM. However, increasingly high resolution

Fig. 3.4 Hypertrophic cardiomyopathy. The predominant area of septal hypertrophy was towards the apex (Modified and reproduced from Burke and Virmani [76])

cardiovascular MRI has assumed an important role in the clinical diagnosis of HCM, especially in individuals with hypertrophy of the anterolateral free wall, apex, or posterior septum [18]. By pathologic examination the location of the hypertrophy can be easily established. In patients with HCM the left ventricular wall thickness ranges widely from mild (13–15 mm) to massive (>50 mm). In 73 % of hearts, asymmetric hypertrophy is accompanied by the presence of a left ventricular outflow tract plaque, which correlates clinically with subaortic stenosis and systolic anterior motion of the anterior leaflet of the mitral valve [19]. Mitral valve thickening and elongation, with increased mass of the valve, is frequently observed.

Apical Hypertrophic Cardiomyopathy

Apical HCM is characterized by hypertrophy of the myocardium, predominantly in the left ventricular apex [26–28]. This relatively rare variant of HCM, first described in Japan, constitutes 13–25 % of all cases of HCM in Japan; however, it is much less often observed in non-Japanese populations. Despite a relatively good prognosis for apical HCM, long-term observations have occasionally included sudden cardiac death, severe arrhythmias, and apical infarctions with apical aneurysms. In the USA, the apical form of the disease is rare accounting for only 1 % of cases pathologically, although this may underestimate the true clinical prevalence given the more benign prognosis.

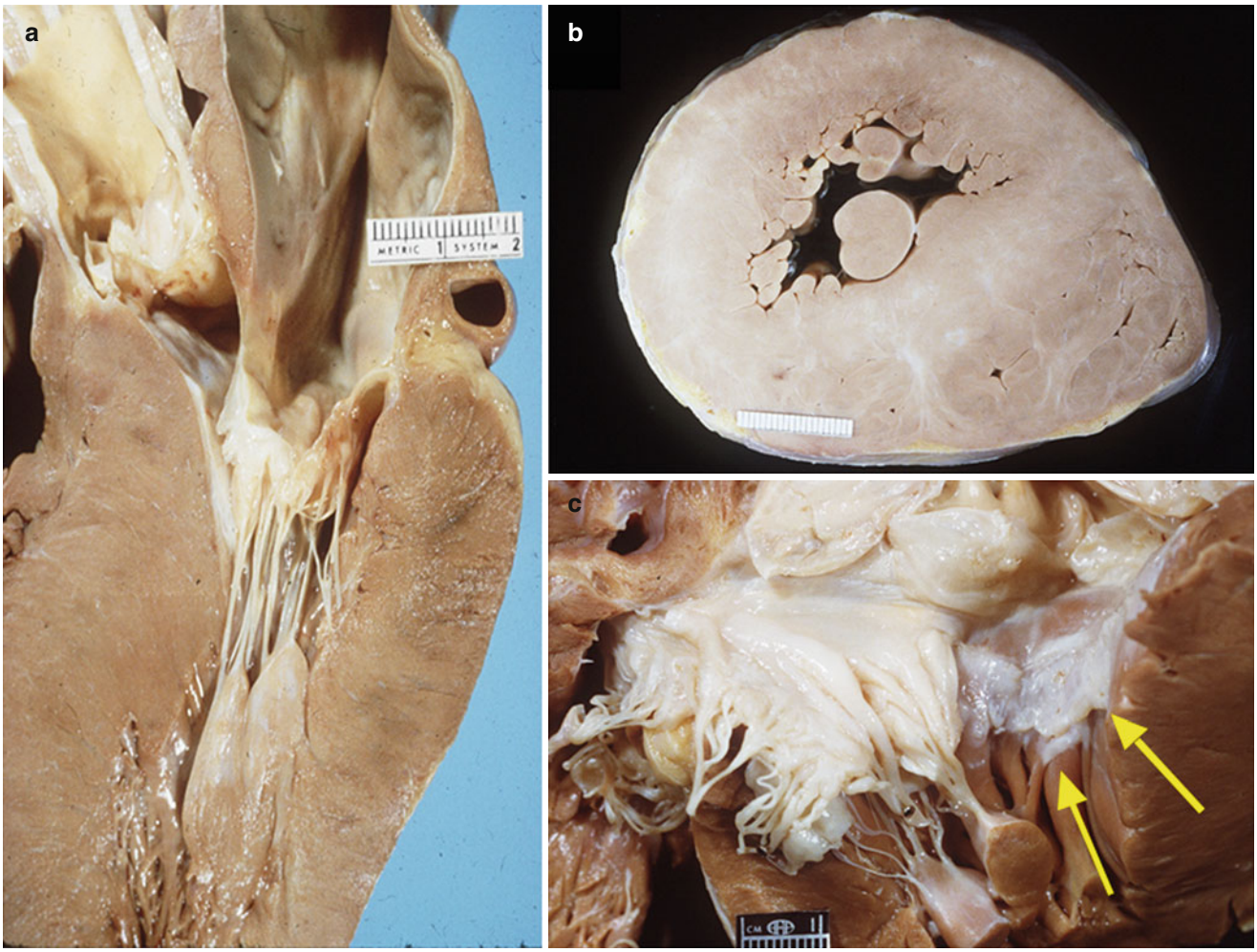

Fig. 3.5 Hypertrophic cardiomyopathy, left ventricular outflow tract plaque. (**a**, **b**) Hypertrophic cardiomyopathy with left ventricular outflow tract plaque. (**c**) A higher magnification of the outflow tract, with the anterior leaflet of the mitral valve lifted back, shows a discrete outflow tract plaque

Endocardial and Valvular Pathology (Figs. 3.5 and 3.6)

As stated above left ventricular outflow tract plaque is observed in up to 73 % of hearts [19]. In contrast to congenital subaortic stenosis, the area of endocardial fibrosis is limited to that opposite the anterior leaflet of the mitral valve. The frequency of a left ventricular outflow tract plaque is 95 % in patients with documented subaortic stenosis by catheterization, and less than 50 % in patients without subaortic stenosis [19]. The area of stenosis may be surgically removed to relieve outflow tract obstruction. Currently, percutaneous ethanol injection into the ventricular septum is performed in lieu of surgical correction (see below) in a significant portion of patients.

Microscopic Pathologic Features (Table 3.1)

The characteristic histological features in HCM are the presence of marked myofiber disarray, (also called myocyte disarray, myocardial disarray (Fig. 3.7) [29], and myocyte disorganization [30]). Myocyte hypertrophy, interstitial fibrosis and intramural coronary abnormalities (thickening with severe narrowing) have all been described. Myocytes show hypertrophy with increase in transverse diameter, and the myocyte nuclei appear hyperchromatic, hypertrophied and assume bizarre shapes. The histologic manifestations of myocyte disarray include oblique alignment of myocytes, producing a whorled, tangled, or pinwheel configuration [31, 32]. In addition, the shape of myocytes is abnormal, with branching fibers common, and lateral attachments are

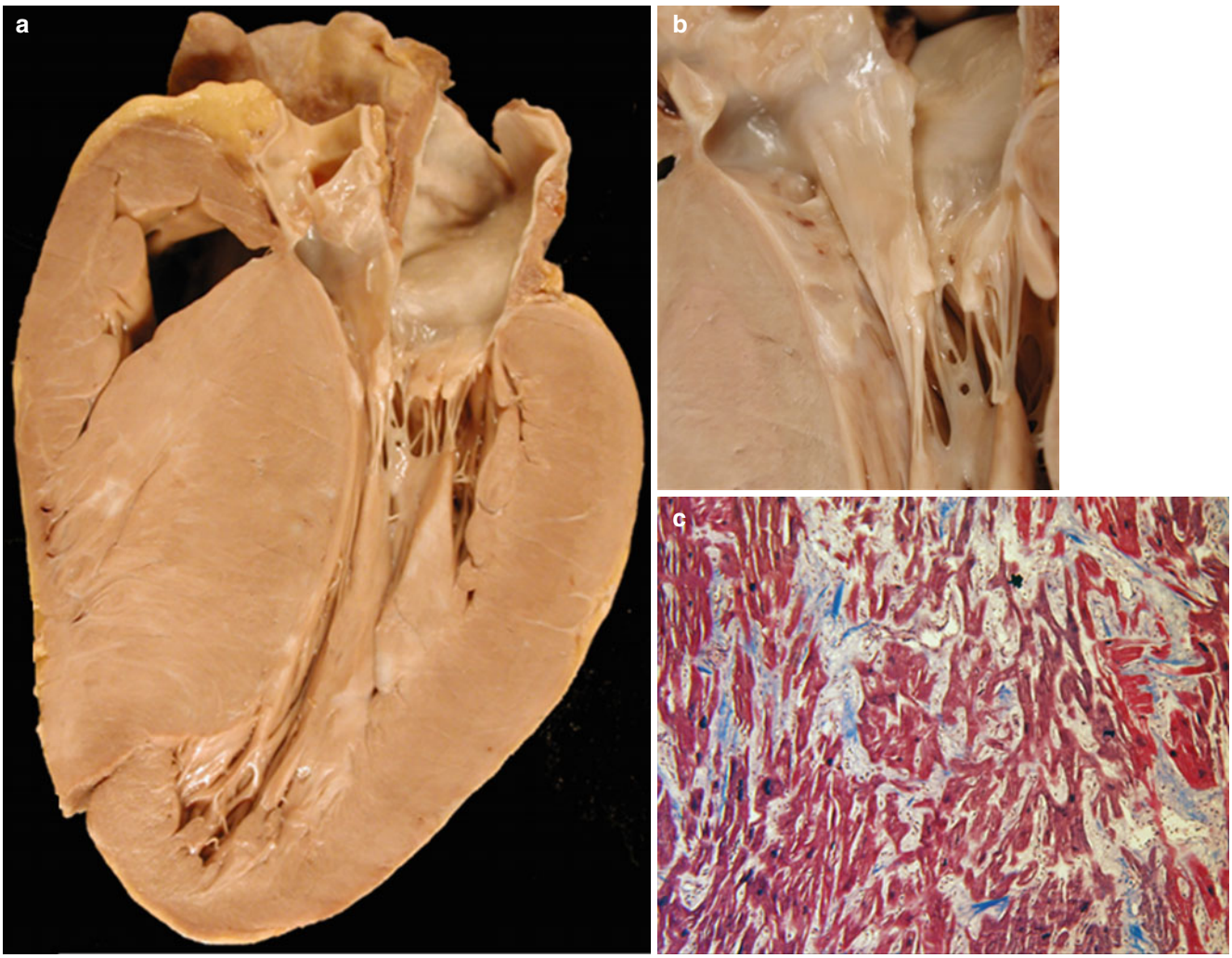

Fig. 3.6 Hypertrophic cardiomyopathy. (**a**) Long-axis echocardiographic view of the right and posterior half of the heart demonstrates asymmetric hypertrophy. (**b**) A higher magnification of the outflow tract, with the anterior leaflet of the mitral valve lifted back, shows a discrete outflow tract plaque. (**c**) Masson trichrome stain demonstrating fibrosis in the area of myofiber disarray (blue-stained interstitial collagen)

Table 3.1 Autopsy pathologic features, hypertrophic cardiomyopathy

Feature	Frequency[a] (%)
Gross	
Cardiomegaly	95
Asymmetric hypertrophy	90
Subendocardial scars	80
Left ventricular outflow tract plaque	60
Mitral valve prolapse	3
Transmural scars	2
Apical septal hypertrophy	1[b]
Histologic	
Myofiber disarray >5 % of ventricular septum	85
Intramural coronary artery thickening	83
Interstitial fibrosis	95

Modified and reproduced from Virmani et al. [75]
[a]These are approximate and may vary by definitions used and phase of illness
[b]Up to 25 % in the Japanese

increased. Some earlier studies have suggested that at least 5 % of the ventricular septal myocytes should show disarray; a diagnostic sensitivity of 86 % and a specificity of 90 % [6]. The histological boundaries of myofiber disarray are not circumscribed, and the evaluation may be somewhat subjective. It must be kept in mind, in addition, that the evaluation of myofiber disarray is only possible if cross-sections (short-axis cuts) are taken for microscopic evaluation. It has been reported that cellular disarray is widely varied, but occupies on an average 33 % and is more extensive in the young patients who die of their disease [33, 34].

Conditions that may result in myofiber disarray other than HCM include other causes of ventricular hypertrophy, including aortic stenosis and chronic hypertension [35]. However, the degree of myofiber disarray in these conditions is generally minimal, and less than 5 %. Normal hearts may demonstrate myofiber disarray at the junction of the free

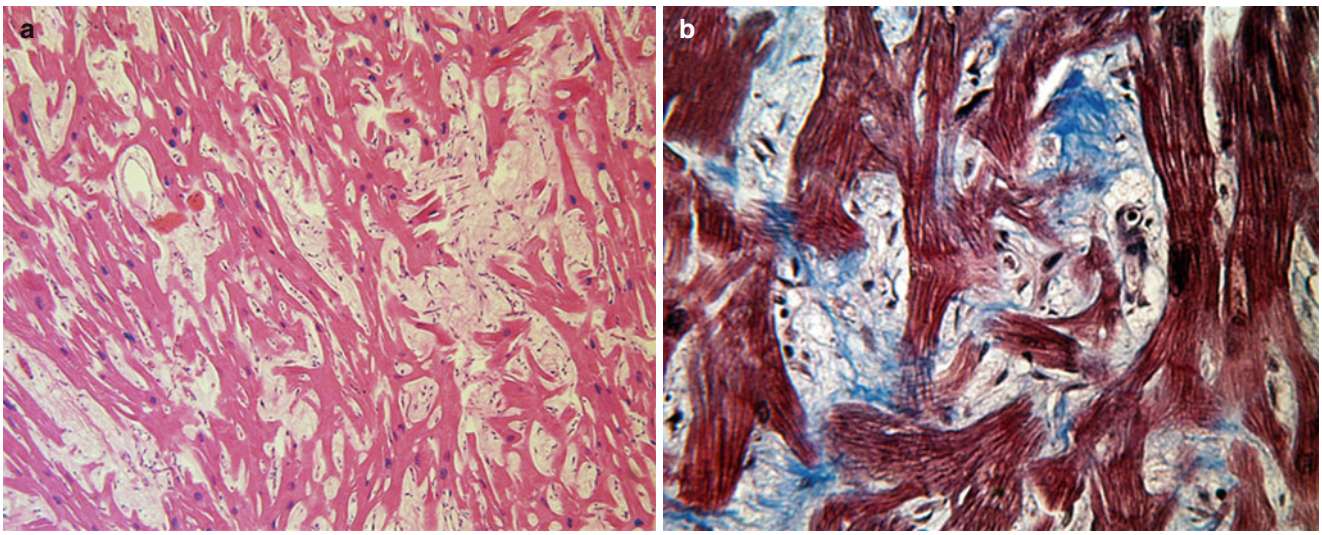

Fig. 3.7 Fibromuscular disarray in hypertrophic cardiomyopathy. (**a**) Hematoxylin-eosin-stained section demonstrating hypertrophied myocytes with abnormal branching forms. (**b**) Masson trichrome stain demonstrating fibrosis in the area of myofiber disarray (blue-stained interstitial collagen)

walls and septum. The myocyte disarray of HCM is characterized by a greater enlargement of myocyte size in the affected region (usually in the middle third of the ventricular septum) than in the subendocardial areas in the same section of myocardium. Myofiber disarray is usually accompanied by increase in fibroblasts and collagen, the former predominating in early stages, and the latter in later stages of the disease [36–38].

Abnormal patterns of desmin immunoreactivity have been described in areas of myofiber disarray. These include a decrease or loss of labeling of intercalated discs and Z bands, longitudinal arrangement of desmin intermediate filaments, and focal intense, granular staining of myocytes [39]. Ultrastructurally, malalignment of sarcomeric myosin filaments has been described in patients with HCM with known genetic mutations [40].

Fibrosis (Fig. 3.8)

The ventricular septum in HCM may also demonstrate interstitial and replacement fibrosis, as well as foci of lymphocytic inflammation. The fibrosis is often most marked in areas of myofiber disarray. In patients with longstanding disease, there may be diffuse scarring throughout the ventricles and the free wall. In such cases, the distinction between HCM and idiopathic restrictive cardiomyopathy may be difficult. It has been suggested that many cases of restrictive cardiomyopathy are, in fact, forms of HCM [41]. In the dilated phase of HCM, extensive scarring may be present, but is predominantly found in the ventricular septum and the right ventricle and has been attributed to intramyocardial small vessel disease [42].

Coronary Artery Abnormalities (Fig. 3.9)

Another important microscopic feature of HCM is intramural coronary abnormalities. Intramural coronary artery thickening is present in the ventricular septum in 83 % of HCM [43], and the location correlates fairly well with areas of myofiber disarray. Intramural coronary artery thickening is more common in hearts with fibrosis than those without significant fibrosis [43–45]. The vessels are dysplastic without a well developed internal elastic lamina and smooth muscle cells are in disarray.

Epicardial coronary arteries are usually normal in HCM. It is debated whether the interstitial and replacement fibrosis are secondary to ischemic insults or are an intrinsic part of the disease. It seems likely, although difficult to prove with certainty, that the majority of fibrosis is not related to ischemia. Also, the presence of a myocardial bridge over a portion of the left anterior descending artery (tunnel) has been associated with an increased risk of sudden death, especially in children [46].

HCM patients have been associated with many different complications (Table 3.2), one of them is thinning of the apex of left ventricle which appears as an aneurysm and can occur secondary to healed infarction in the presence or absence of coronary artery disease (Fig. 3.10).

We have studied 64 hearts from 51 men and 13 women dying with HCM. These patients were divided into four groups: (1) those dying suddenly during exertion (mean age 26 years); (2) those dying at rest (mean age 38 years); (3) those dying from their disease but not suddenly (mean age 34 years); and (4) those dying of other causes (mean age 51 years) (incidental). Those dying during exercise were significantly younger than the other groups (mean age: 26 years vs.

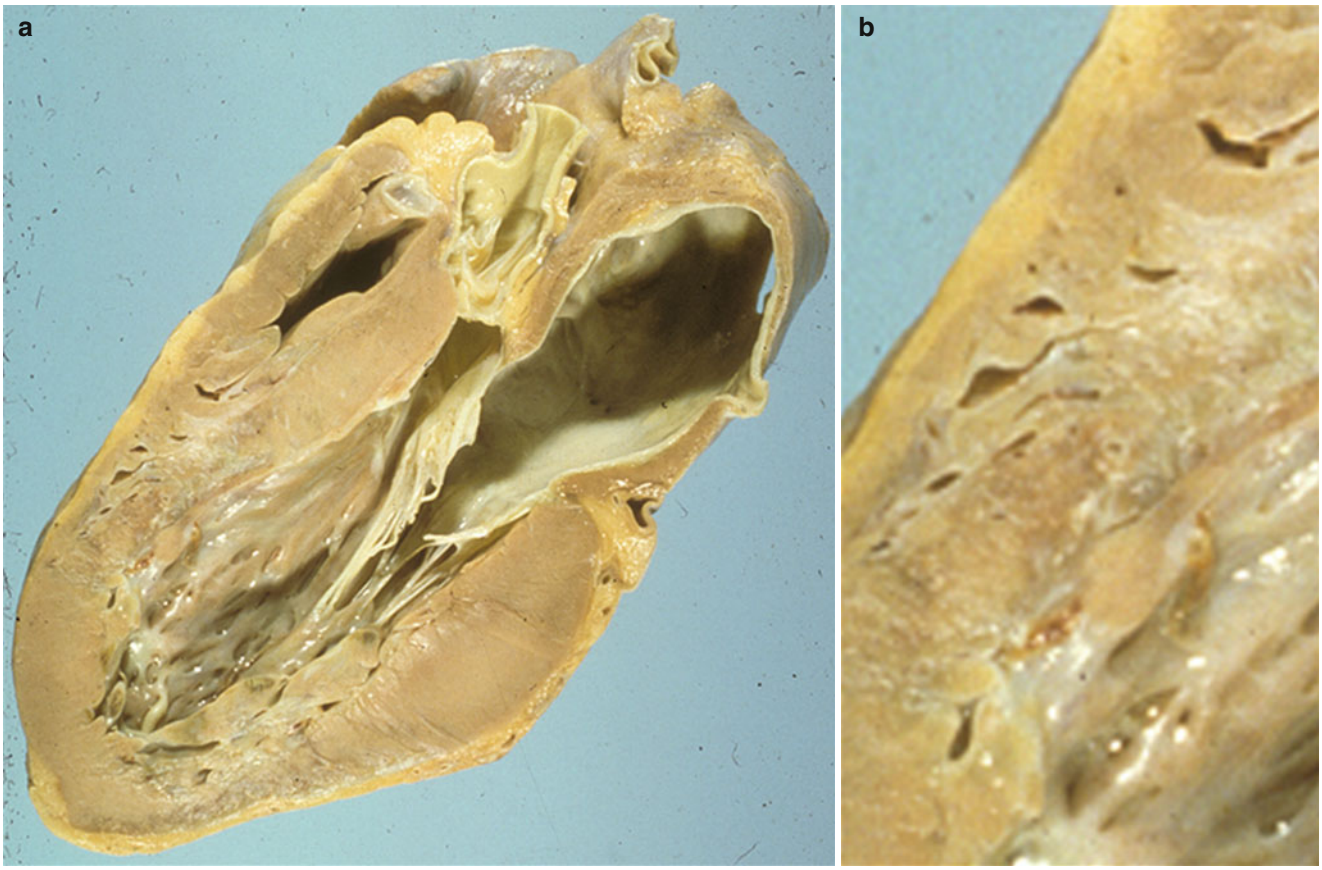

Fig. 3.8 Hypertrophic cardiomyopathy, ventricular scarring. (**a**) The thinned scarred septum located in the apical half of the left ventricle. (**b**) A higher magnification demonstrates grossly visible myocardial scars (Modified and reproduced from Virmani et al. [75])

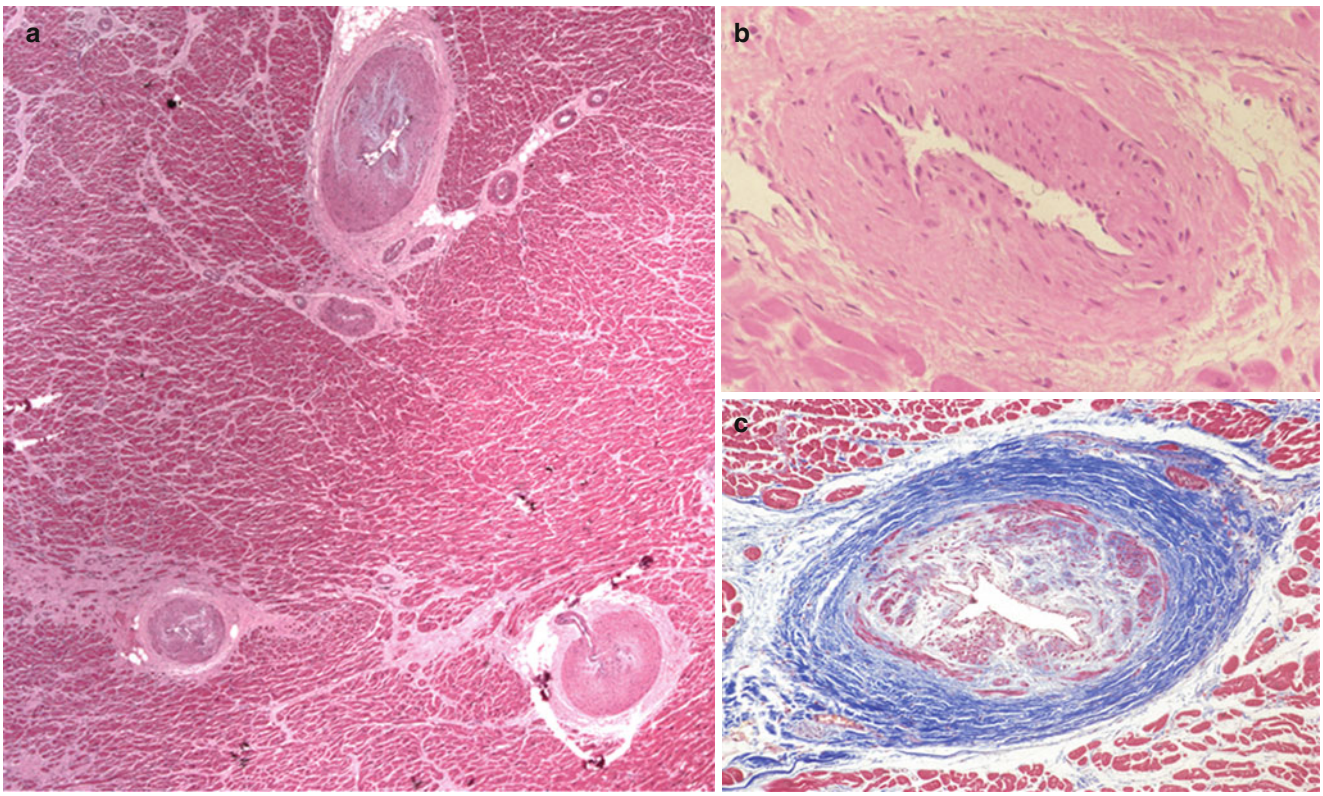

Fig. 3.9 Intramural coronary artery thickening. Intramural coronary artery thickening demonstrated in multiple intramural arteries (**a**). H&E (**b**) and Masson trichrome stain (**c**) showing adventitial scarring with thickening and dysplastic media (Modified and reproduced from Burke and Virmani [76])

Table 3.2 Complications of hypertrophic cardiomyopathy

Death: sudden and non-sudden
Atrial dilatation: atrial fibrillation
Mitral valve disease: mitral regurgitation
Fibrous thickening (anatomic systolic anterior motion)
Insertion, papillary muscle, into leaflet
Rupture of chordae tendineae
Prolapse
Annular calcification
Infective endocarditis
Papillary muscle calcification
Myocardial infarction: left ventricular dilation
Left ventricular apical diverticulum
Pulmonary hypertension
Aneurysm pulmonary arteries
Ossific nodules, lungs
Heart block and bundle branch block

Modified and reproduced from Roberts et al. [73]

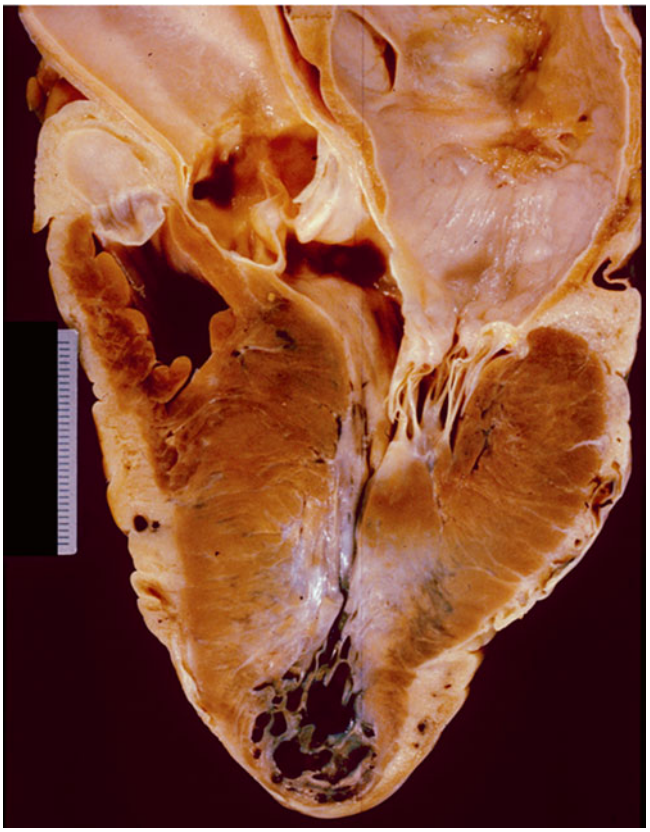

Fig. 3.10 Hypertrophic cardiomyopathy. Long-axis echocardiographic view of the right and posterior half of the heart from a patient with hypertrophic cardiomyopathy. There is marked left atrial dilatation; the patient had long-standing atrial fibrillation. The thinning of the apical left ventricle was secondary to healed infarction secondary to coronary artery disease (Modified and reproduced from Virmani et al. [75])

43 years, P = 0.0009). The mean heart weight was also significantly greater in the incidental group (696 g), than the other groups (range of means 496–622 g, p = 0.02). Asymmetric hypertrophy with an outflow tract plaque was observed more frequently in the exercise group than in the incidental group or those dying of the disease at rest. The degree of intramural coronary artery thickening was also greatest in the exertion group, as compared with non-exertional deaths and incidental cases. These results suggest that there are morphological differences in hearts from patients with HCM dying during exertion, and that there is a higher frequency of left ventricular outflow tract obstruction and intramural coronary artery thickening. Litovsky et al. reported on 55 cases of HCM and showed that asymmetric septal hypertrophy was more prevalent in younger than older subjects. Sudden death was more prevalent in the younger patients and had endocardial outflow tract plaque than elderly patients. Also, myofiber disarray was greater and intramural coronary artery thickening was more frequent in younger patients compared with elderly patients [45]. The largest experience comes from the laboratory of William C. Roberts with examination of over 200 hearts at autopsy (Table 3.3). He has described marked diversity in the anatomic findings and of the ten morphologic characteristics studied not a single heart showed all ten features.

Histologic Findings of Myomectomy Specimens

Patients with >50 mmHg subaortic gradient are often treated surgically with myomectomy and/or myotomy for the relief of outflow tract obstruction. In a study of 89 myomectomy specimens from patients with HCM, myofiber disarray was present in 58 %, generally in the deepest portion of the specimen. In contrast, myofiber disarray is present in a smaller proportion of endomyocardial biopsies, secondary to sampling error [47]. Other histologic features of HCM that may be seen in myomectomy specimens include intramural artery thickening and endocardial fibrous plaque [47].

Pathophysiology

The pathophysiology of HCM is complex and consists of multiple interrelated abnormalities, including left ventricular outflow tract obstruction, diastolic dysfunction, mitral regurgitation, myocardial ischemia, and arrhythmia (Table 3.4) [48, 49]. HCM may be suspected because of a heart murmur. It is clinically important to distinguish between the obstructive and non-obstructive forms of HCM because the management strategies are largely dependent on the presence or absence of symptoms caused by obstruction. The symptoms of HCM are those of pulmonary congestion which include dyspnea, fatigue, orthopnoea, and proximal nocturnal dyspnea. Impaired consciousness, chest pain, and sudden cardiac death have all been reported [12]. Because of the known familial nature of the illness, up to 25 % of cases are identified incidentally because of an afflicted family member. It is

Table 3.3 Cardiac findings in hypertrophic cardiomyopathy divided by presence or absence of cardiac operation

	Cardiac operation		
Characteristic	0 (n = 153) (%)	+ (n = 77) (%)	Total (n = 230) (%)
Dilated atria	98	100	99
Increased heart weight	95	96	96
Nondilated left ventricle	82	75	80
Thickened anterior mitral leaflet	66	94	75
Mural plaque, LV outflow tract	60	93	71
VS larger than left ventricle	71	63	68
Transmural scarring, VS and/or LV wall	42	43	42
Disorganization, cardiac myocytes	95	95	95
Intramural coronary disease	83	83	83
Interstitial fibrosis, VS and LV wall	90	90	90

Modified and reproduced from Roberts et al. [73]
LV left ventricular, *VS* ventricular septum

Table 3.4 Gross cardiac findings by 3 age groups in 153 patients with hypertrophic cardiomyopathy without cardiac operations

	Age group (years)		
Characteristic	≤10 (n = 15) (%)	11–70 (n = 124) (%)	>70 (n = 14) (%)
Dilated atria	95	100	100
Increased heart weight	80	98	86
Non-dilated left ventricle	73	81	93
Thickened anterior mitral leaflet	27	66	100
Mural plaque, LV outflow tract	27	78	100
VS larger than left ventricle	73	71	79
Transmural scarring, VS and/or LV wall	0	45	50

Modified and reproduced from Roberts et al. [73]
LV left ventricular, *VS* ventricular septum

Table 3.5 Criteria for differential diagnosis of left ventricular (LV) hypertrophy in hypertrophic cardiomyopathy (HCM) and athlete's heart

	HCM	Athlete's heart
Distribution of hypertrophy	Mostly asymmetric	Substantially symmetric
Maximum LV wall thickness	≥16 mm[a]	<16 mm
LV cavity dimension	Normal or reduced (≤45 mm)	Normal or increased (≥55 mm)
LV filling and relaxation (by Doppler and TDI)	Usually abnormal	Normal
Regression of hypertrophy with detraining	Absent (or marginal)	Present
Marked ECG abnormalities[b]	Common	Uncommon
Familial evidence of HCM	Usually present	Absent

Modified and reproduced from Pelliccia et al. [77]
ECG electrocardiogram, *TDI* tissue Doppler imaging
[a]LV wall thickness may also be <16 mm in a subset of HCM patients
[b]most commonly deep Q waves, deeply inverted T waves, markedly increased R and/or S wave amplitudes in precordial leads

important to distinguish between the normal adaptations of the heart to routine physiologic training. It has been shown that measurements of the left ventricle dimensions and wall thickness remain within normal limits however, a small proportion of highly trained athletes develop substantial ventricular hypertrophy [21]. Table 3.5 shows the criteria used for differentiating the diagnosis of HCM from athlete's heart with physiologic left ventricular hypertrophy [21].

The hemodynamic derangements in HCM are caused by a small left ventricular cavity that restricts ventricular filling during diastole. The ejection fraction, in the initial phases of the illness, is normal or increased. There are many causes of diastolic dysfunction which includes abnormal chamber geometry, myocyte hypertrophy, myocyte and myofibrillar disarray and myocardial ischemia. Collagen turnover is increased, with collagen type 1 synthesis prevailing over degradation; there is also evidence for abnormal inhibition of matrix metalloproteinases (MMP-1 and MMP-2). Subaortic pressure gradient is present in a little over half of patients, and is often variable and labile [50, 51].

Echocardiographically, the hallmarks of HCM include left ventricular hypertrophy, a small ventricular cavity,

systolic anterior motion of the anterior leaflet of the mitral valve, and a characteristic ground-glass appearance of the myocardium. Asymmetric hypertrophy is typical, occurring in 80–98 % of cases [15]. The distribution of left ventricular hypertrophy is heterogeneous, encompassing extensive and diffuse wall thickening to mild and segmental thickening. The anterior ventricular septum is thickened in 96 % of patients, and in 83 % is the predominant area of hypertrophy [15]. True mitral valve prolapse is observed in 3 % of patients, and is not considered an increased incidence over the general population. A greater extent of left ventricular hypertrophy is associated with younger age and more marked mitral valve systolic anterior motion and outflow obstruction but shows no relation to symptoms or gender [15].

In addition to echocardiography, magnetic resonance imaging (MRI) should also be considered for routine family screening especially if echocardiography is equivocal. Today high resolution MRI is considered superior to echocardiography especially for the characterization of phenotype – for example, the presence and extent of left-ventricular hypertrophy in the anterolateral free wall [52, 53], apex [53], or posterior septum [53] and the identification of high risk apical aneurysms, along with the determination of subaortic obstruction, e.g., elongated or enlarged mitral valve [54] or accessory and displaced papillary muscles [55].

Sudden death is not an uncommon complication of HCM, and is often precipitated by exercise. The frequency of sudden death in HCM is up to 1 % per year in adults with 2–4 % per year in children and adolescents [21]. In a series of athletes younger than age 30 years dying suddenly, HCM is among the most common findings at autopsy [56] in the USA [14], whereas in the Italian series arrhythmogenic right ventricular cardiomyopathy is the most common cause of sudden death [57].

Those features that most reliably identify high-risk patients include age younger than 35 years and a family history of HCM with sudden death, African American athletes, genetic abnormalities associated with increased prevalence of sudden death, sustained ventricular or supraventricular tachycardia, recurrent syncope in the young, non-sustained ventricular tachycardia, bradycardia, and massive myocardial thickening >3 cm (Table 3.6). A seminal paper has been published that showed that the presence of 2 or more of these risk factors was associated with a higher annual risk of 3–6 %, while the presence of any single risk factor correlated with an annual risk of approximately 1 % [21, 58].

The clinical course of patients with HCM is highly variable. Overall, there is approximately 2–3 % mortality per year in adults and a somewhat higher rate of mortality in children [59, 60]. In 10 % of patients or more, there is a progression to dilated cardiomyopathy. Hearts from patients dying with the dilated form of HCM may show diffuse scarring with myofiber disarray and an absence of asymmetric hypertrophy or even thinning of the ventricular septum. According to Barry Maron extensive ventricular scarring with dilatation of the left ventricular cavity is observed in 2 % of patients. It is believed that the scarring may be related to the presence of intramyocardial coronary artery thickening. HCM also appears to predispose to infective endocarditis. A few patients (2 %) may develop severe mitral or aortic regurgitation, or both, requiring valve replacement secondary to infective endocarditis [61]. Vegetations usually developed on the anterior mitral valve leaflet but can also involve the outflow tract endocardium at the point of mitral-septal contact or may involve the aortic valve. Therefore it has traditionally been recommended that patients with HCM, particularly patients with outflow obstruction receive prophylactic antibiotic therapy before dental or high risk surgical procedures that predispose to infective endocarditis [62, 63]. Formal guidelines, however, do not consider prophylaxis mandatory in HCM, with or without obstructive physiology [64].

Treatment for HCM includes medical therapy, cardiac pacing and, in patients with outflow tract obstruction, surgical myectomy or percutaneous alcohol septal ablation. Atrioventricular synchronous pacing with appropriate placement of the lead in the right ventricular apex has been reported

Table 3.6 Risk factors for sudden death

Secondary prevention
Cardiac arrest or sustained ventricular tachycardia
Conventional primary prevention risk markers
Family history of sudden death due to hypertrophic cardiomyopathy
Unexplained recent syncope
Multiple repetitive non-sustained ventricular tachycardia (on ambulatory ECG)
Hypotensive or attenuated blood pressure response to exercise
Massive left-ventricular hypertrophy (thickness, ≥30 mm[a])
Extensive and diffuse late gadolinium enhancement
Potential high-risk subsets for primary prevention
End-stage phase (ejection fraction <50 %)
Left-ventricular apical aneurysm and scarring
Potential arbitrators for primary prevention[b]
Substantial left-ventricular outflow gradient at rest
Multiple sarcomere mutations
Modifiable
Intense competitive sports
Coronary artery disease

Modified and reproduced from Maron and Maron [18]
ECG electrocardiogram
[a]Or the equivalent in children according to body size
[b]To arbitrate decision-making about implantable defibrillators in patients for whom risk level remains ambiguous after assessment by the conventional risk factor algorithm

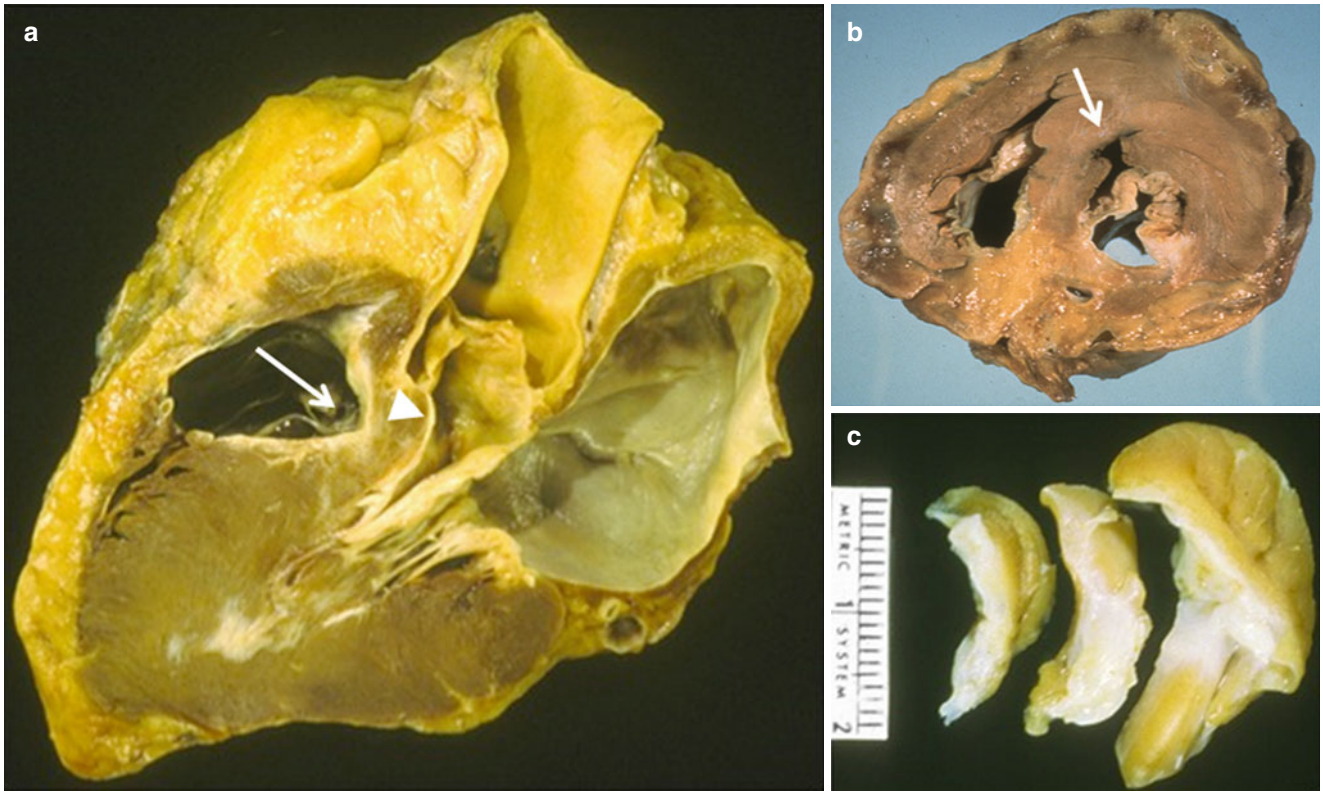

Fig.3.11 Hypertrophic cardiomyopathy, myomectomy. (**a**) Hypertrophic cardiomyopathy treated by myomectomy. The right ventricular approach was used for the performance of myectomy (*arrow*). The discrete plaque in the left ventricular out flow tract (*arrowhead*). (**b**) Hypertrophic cardiomyopathy treated by myomectomy. The left ventricular approach was used for the performance of myectomy (*arrow*). (**c**) The myotomy specimen from the same patient from **b** showing three pieces of the myocardium with marked endocardial thickening (Modified and reproduced from Virmani et al. [75])

to reduce left ventricular outflow obstruction and symptoms in patients with hypertrophic obstructive cardiomyopathy [65]. However, treatment with pacing is controversial and some authorities do not support its use in patients with obstructive HCM and some even consider that it may worsen the prognosis [66]. A low perioperative mortality rate and a high late survival rate (72 % at 15 years' follow-up) have been reported after surgical myectomy [67]. Surgical septal myectomy was first performed in early 1960s which involved removal of 5–10 g of myocardial tissue from the basal ventricular septum (Fig. 3.11). Surgical septal myectomy should be considered in all patients with outflow tract gradients greater than 50 mmHg (at rest or with physiological provocation) and symptoms refractory to medical therapy [48, 68]. This procedure results in a significant reduction in mitral regurgitation, and long-term symptomatic improvement. Notably, operative mortality at surgical centers is now low, reduced to less than 1 % [69]. According to the American College of Cardiology and the American Heart Association guidelines for the diagnosis and treatment of HCM surgical myectomy remains the "first option" and is the "gold-standard" for obstructive HCM. Alternatives to surgical myectomy include a modified Konno procedure, with aortic valve replacement and left ventricular outflow reconstruction [70]. Non-surgical septal reduction using selective coronary alcohol injection (alcohol septal ablation) to induce localized septal infarcts has been popularized and described almost simultaneously by two research groups, one in Germany and the other at the Royal Brompton Hospital, London and multiple studies have shown reduced symptoms and outflow gradient using this technique that mirror that seen with myectomy, in appropriately selected patients [71].

Familial Hypertrophic Cardiomyopathy

The autosomal dominant inheritance of HCM was established 13 years after its initial description in 1958 [2, 8]. An echocardiographic study of 70 families of index cases demonstrated that in 55 % of families at least one member had echocardiographic evidence of HCM, however sporadic cases of de-novo mutations are also seen [72].

Clinical Pearls

- Hypertrophic cardiomyopathy is characterized by asymmetric septal hypertrophy, accompanied by microscopic fibromuscular disarray, and when accompanied by fibrosis there may be dilatation of left ventricular cavity and heart weight is twice the expected heart for weight and height of the individual.
- HCM is not uncommonly associated with sudden death but it may not be the most common cause of sudden cardiac death in young trained athletes.
- HCM is most often familial, with a need for genotyping but sporadic cases are well documented.

References

1. Maron BJ, Epstein SE. Hypertrophic cardiomyopathy. Recent observations regarding the specificity of three hallmarks of the disease: asymmetric septal hypertrophy, septal disorganization and systolic anterior motion of the anterior mitral leaflet. Am J Cardiol. 1980;45(1):141–54.
2. Teare D. Asymmetrical hypertrophy of the heart in young adults. Br Heart J. 1958;20(1):1–8. Epub 1958/01/01.
3. Braunwald E, Lambrew CT, Rockoff SD, Ross Jr J, Morrow AG. Idiopathic hypertrophic subaortic stenosis: a description off the disease based upon an analysis of 64 patients. Circulation. 1964;30 Suppl 4:3–119. Epub 1964/11/01.
4. Frank S, Braunwald E. Idiopathic hypertrophic subaortic stenosis. Clinical analysis of 126 patients with emphasis on the natural history. Circulation. 1968;37(5):759–88.
5. Maron BJ, Roberts WC, Edwards JE, McAllister Jr HA, Foley DD, Epstein SE. Sudden death in patients with hypertrophic cardiomyopathy: characterization of 26 patients with functional limitation. Am J Cardiol. 1978;41(5):803–10. Epub 1978/05/01.
6. Maron BJ, Sato N, Roberts WC, Edwards JE, Chandra RS. Quantitative analysis of cardiac muscle cell disorganization in the ventricular septum. Comparison of fetuses and infants with and without congenital heart disease and patients with hypertrophic cardiomyopathy. Circulation. 1979;60(3):685–96. Epub 1979/09/01.
7. St John Sutton MG, Lie JT, Anderson KR, O'Brien PC, Frye RL. Histopathological specificity of hypertrophic obstructive cardiomyopathy. Myocardial fibre disarray and myocardial fibrosis. Br Heart J. 1980;44(4):433–43.
8. Emanuel R, Withers R, O'Brien K. Dominant and recessive modes of inheritance in idiopathic cardiomyopathy. Lancet. 1971; 2(7733):1065–7. Epub 1971/11/13.
9. Hollman A, Goodwin JF, Teare D, Renwick JW. A family with obstructive cardiomyopathy (asymmetrical hypertrophy). Br Heart J. 1960;22:449–56. Epub 1960/09/01.
10. Geisterfer-Lowrance AA, Kass S, Tanigawa G, Vosberg HP, McKenna W, Seidman CE, et al. A molecular basis for familial hypertrophic cardiomyopathy: a beta cardiac myosin heavy chain gene missense mutation. Cell. 1990;62(5):999–1006. Epub 1990/09/07.
11. Zou Y, Song L, Wang Z, Ma A, Liu T, Gu H, et al. Prevalence of idiopathic hypertrophic cardiomyopathy in China: a population-based echocardiographic analysis of 8080 adults. Am J Med. 2004;116(1):14–8. Epub 2004/01/07.
12. Codd MB, Sugrue DD, Gersh BJ, Melton 3rd LJ. Epidemiology of idiopathic dilated and hypertrophic cardiomyopathy. A population-based study in Olmsted County, Minnesota, 1975–1984. Circulation. 1989;80(3):564–72.
13. Maron BJ, Gardin JM, Flack JM, Gidding SS, Kurosaki TT, Bild DE. Prevalence of hypertrophic cardiomyopathy in a general population of young adults. Echocardiographic analysis of 4111 subjects in the CARDIA Study. Coronary Artery Risk Development in (Young) Adults. Circulation. 1995;92(4):785–9.
14. Maron BJ, Doerer JJ, Haas TS, Tierney DM, Mueller FO. Sudden deaths in young competitive athletes: analysis of 1866 deaths in the United States, 1980–2006. Circulation. 2009;119(8):1085–92. Epub 2009/02/18.
15. Klues HG, Schiffers A, Maron BJ. Phenotypic spectrum and patterns of left ventricular hypertrophy in hypertrophic cardiomyopathy: morphologic observations and significance as assessed by two-dimensional echocardiography in 600 patients. J Am Coll Cardiol. 1995;26(7):1699–708. Epub 1995/12/01.
16. Shah PM, Adelman AG, Wigle ED, Gobel FL, Burchell HB, Hardarson T, et al. The natural (and unnatural) history of hypertrophic obstructive cardiomyopathy. Circ Res. 1974;35((2):suppl II):179–95.
17. Lai ZY, Shih CM, Chang NC, Wang TC. Clinical and morphologic features of hypertrophic cardiomyopathy in elderly patients 85 years or older. Jpn Heart J. 1999;40(2):155–64. Epub 1999/07/27.
18. Maron BJ, Maron MS. Hypertrophic cardiomyopathy. Lancet. 2013;381(9862):242–55. Epub 2012/08/10.
19. Roberts WC, Ferrans VJ. Pathologic anatomy of the cardiomyopathies. Idiopathic dilated and hypertrophic types, infiltrative types, and endomyocardial disease with and without eosinophilia. Hum Pathol. 1975;6(3):287–342.
20. Roberts CS, Roberts WC. Hypertrophic cardiomyopathy as a cause of massive cardiomegaly (greater than 1,000 g). Am J Cardiol. 1989;64(18):1209–10. Epub 1989/11/15.
21. Seggewiss H, Blank C, Pfeiffer B, Rigopoulos A. Hypertrophic cardiomyopathy as a cause of sudden death. Herz. 2009;34(4):305–14. Epub 2009/07/04.
22. Scholz DG, Kitzman DW, Hagen PT, Ilstrup DM, Edwards WD. Age-related changes in normal human hearts during the first 10 decades of life. Part I (growth): a quantitative anatomic study of 200 specimens from subjects from birth to 19 years old. Mayo Clin Proc. 1988;63(2):126–36.
23. Maron BJ, Kragel AH, Roberts WC. Sudden death in hypertrophic cardiomyopathy with normal left ventricular mass. Br Heart J. 1990;63(5):308–10. Epub 1990/05/01.
24. Maron BJ, Spirito P, Wesley Y, Arce J. Development and progression of left ventricular hypertrophy in children with hypertrophic cardiomyopathy. N Engl J Med. 1986;315(10):610–4. Epub 1986/09/04.
25. Spirito P, Maron BJ, Bonow RO, Epstein SE. Occurrence and significance of progressive left ventricular wall thinning and relative cavity dilatation in hypertrophic cardiomyopathy. Am J Cardiol. 1987;60(1):123–9. Epub 1987/07/01.
26. Eriksson MJ, Sonnenberg B, Woo A, Rakowski P, Parker TG, Wigle ED, et al. Long-term outcome in patients with apical hypertrophic cardiomyopathy. J Am Coll Cardiol. 2002;39(4):638–45. Epub 2002/02/19.
27. Sakamoto T, Tei C, Murayama M, Ichiyasu H, Hada Y. Giant T wave inversion as a manifestation of asymmetrical apical hypertrophy (AAH) of the left ventricle. Echocardiographic and ultrasonocardiotomographic study. Jpn Heart J. 1976;17(5):611–29. Epub 1976/09/01.
28. Yamaguchi H, Nishiyama S, Nakanishi S, Nishimura S. Electrocardiographic, echocardiographic and ventriculographic characterization of hypertrophic non-obstructive cardiomyopathy. Eur Heart J. 1983;4 (Suppl F):105–19

29. Davies MJ, McKenna WJ. Hypertrophic cardiomyopathy: an introduction to pathology and pathogenesis. Br Heart J. 1994; 72(6 Suppl):S2–3. Epub 1994/12/01.
30. Maron BJ, Roberts WC. Quantitative analysis of cardiac muscle cell disorganization in the ventricular septum of patients with hypertrophic cardiomyopathy. Circulation. 1979;59(4):689–706. Epub 1979/04/01.
31. Davies MJ. The current status of myocardial disarray in hypertrophic cardiomyopathy. Br Heart J. 1984;51(4):361–3. Epub 1984/04/01.
32. Davies MJ. Hypertrophic cardiomyopathy: one disease or several? Br Heart J. 1990;63(5):263–4. Epub 1990/05/01.
33. Maron BJ, Anan TJ, Roberts WC. Quantitative analysis of the distribution of cardiac muscle cell disorganization in the left ventricular wall of patients with hypertrophic cardiomyopathy. Circulation. 1981;63(4):882–94. Epub 1981/04/01.
34. Varnava AM, Elliott PM, Mahon N, Davies MJ, McKenna WJ. Relation between myocyte disarray and outcome in hypertrophic cardiomyopathy. Am J Cardiol. 2001;88(3):275–9. Epub 2001/07/27.
35. van der Bel-Kahn J. Muscle fiber disarray in common heart diseases. Am J Cardiol. 1977;40(3):355–64. Epub 1977/09/01.
36. Fujiwara H, Hoshino T, Yamana K, Fujiwara T, Furuta M, Hamashima Y, et al. Number and size of myocytes and amount of interstitial space in the ventricular septum and in the left ventricular free wall in hypertrophic cardiomyopathy. Am J Cardiol. 1983;52(7):818–23. Epub 1983/10/01.
37. Unverferth DV, Baker PB, Pearce LI, Lautman J, Roberts WC. Regional myocyte hypertrophy and increased interstitial myocardial fibrosis in hypertrophic cardiomyopathy. Am J Cardiol. 1987;59(9):932–6. Epub 1987/04/15.
38. Frenzel H, Schwartzkopff B, Reinecke P, Kamino K, Losse B. Evidence for muscle fiber hyperplasia in the septum of patients with hypertrophic obstructive cardiomyopathy (HOCM). Quantitative examination of endomyocardial biopsies (EMCB) and myectomy specimens. Z Kardiol. 1987;76 Suppl 3:14–9.
39. Francalanci P, Gallo P, Bernucci P, Silver MD, d'Amati G. The pattern of desmin filaments in myocardial disarray. Hum Pathol. 1995;26(3):262–6. Epub 1995/03/01.
40. Muraishi A, Kai H, Adachi K, Nishi H, Imaizumi T. Malalignment of the sarcomeric filaments in hypertrophic cardiomyopathy with cardiac myosin heavy chain gene mutation. Heart. 1999;82(5):625–9. Epub 1999/10/20.
41. Angelini A, Calzolari V, Thiene G, Boffa GM, Valente M, Daliento L, et al. Morphologic spectrum of primary restrictive cardiomyopathy. Am J Cardiol. 1997;80(8):1046–50. Epub 1997/11/14.
42. Waller TA, Hiser WL, Capehart JE, Roberts WC. Comparison of clinical and morphologic cardiac findings in patients having cardiac transplantation for ischemic cardiomyopathy, idiopathic dilated cardiomyopathy, and dilated hypertrophic cardiomyopathy. Am J Cardiol. 1998;81(7):884–94. Epub 1998/04/29.
43. Maron BJ, Wolfson JK, Epstein SE, Roberts WC. Intramural ("small vessel") coronary artery disease in hypertrophic cardiomyopathy. J Am Coll Cardiol. 1986;8(3):545–57. Epub 1986/09/01.
44. Krams R, Kofflard MJ, Duncker DJ, Von Birgelen C, Carlier S, Kliffen M, et al. Decreased coronary flow reserve in hypertrophic cardiomyopathy is related to remodeling of the coronary microcirculation. Circulation. 1998;97(3):230–3. Epub 1998/02/14.
45. Litovsky SH, Rose AG. Clinicopathologic heterogeneity in hypertrophic cardiomyopathy with regard to age, asymmetric septal hypertrophy, and concentric hypertrophy beyond the pediatric age group. Arch Pathol Lab Med. 1998;122(5):434–41. Epub 1998/05/21.
46. Yetman AT, Hamilton RM, Benson LN, McCrindle BW. Long-term outcome and prognostic determinants in children with hypertrophic cardiomyopathy. J Am Coll Cardiol. 1998;32(7):1943–50. Epub 1998/12/19.
47. Tazelaar HD, Billingham ME. The surgical pathology of hypertrophic cardiomyopathy. Arch Pathol Lab Med. 1987;111(3):257–60. Epub 1987/03/01.
48. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. JAMA. 2002;287(10):1308–20. Epub 2002/03/12.
49. Wigle ED, Rakowski H, Kimball BP, Williams WG. Hypertrophic cardiomyopathy. Clinical spectrum and treatment. Circulation. 1995;92(7):1680–92. Epub 1995/10/01.
50. Lombardi R, Betocchi S, Losi MA, Tocchetti CG, Aversa M, Miranda M, et al. Myocardial collagen turnover in hypertrophic cardiomyopathy. Circulation. 2003;108(12):1455–60. Epub 2003/09/04.
51. Mundhenke M, Schwartzkopff B, Stark P, Schulte HD, Strauer BE. Myocardial collagen type I and impaired left ventricular function under exercise in hypertrophic cardiomyopathy. Thorac Cardiovasc Surg. 2002;50(4):216–22. Epub 2002/08/08.
52. Maron MS, Lesser JR, Maron BJ. Management implications of massive left ventricular hypertrophy in hypertrophic cardiomyopathy significantly underestimated by echocardiography but identified by cardiovascular magnetic resonance. Am J Cardiol. 2010;105(12):1842–3. Epub 2010/06/12.
53. Maron MS, Maron BJ, Harrigan C, Buros J, Gibson CM, Olivotto I, et al. Hypertrophic cardiomyopathy phenotype revisited after 50 years with cardiovascular magnetic resonance. J Am Coll Cardiol. 2009;54(3):220–8. Epub 2009/07/11.
54. Maron MS, Olivotto I, Harrigan C, Appelbaum E, Gibson CM, Lesser JR, et al. Mitral valve abnormalities identified by cardiovascular magnetic resonance represent a primary phenotypic expression of hypertrophic cardiomyopathy. Circulation. 2011;124(1):40–7. Epub 2011/06/15.
55. Klues HG, Roberts WC, Maron BJ. Anomalous insertion of papillary muscle directly into anterior mitral leaflet in hypertrophic cardiomyopathy. Significance in producing left ventricular outflow obstruction. Circulation. 1991;84(3):1188–97. Epub 1991/09/01.
56. Maron BJ, Shirani J, Poliac LC, Mathenge R, Roberts WC, Mueller FO. Sudden death in young competitive athletes. Clinical, demographic, and pathological profiles. JAMA. 1996;276(3):199–204.
57. Corrado D, Basso C, Rizzoli G, Schiavon M, Thiene G. Does sports activity enhance the risk of sudden death in adolescents and young adults? J Am Coll Cardiol. 2003;42(11):1959–63. Epub 2003/12/10.
58. Elliott PM, Poloniecki J, Dickie S, Sharma S, Monserrat L, Varnava A, et al. Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. J Am Coll Cardiol. 2000;36(7):2212–8. Epub 2000/12/29.
59. McKenna WJ. The natural history of hypertrophic cardiomyopathy. Cardiovasc Clin. 1988;19(1):135–48. Epub 1988/01/01.
60. Spirito P, Bellone P. Natural history of hypertrophic cardiomyopathy. Br Heart J. 1994;72(6 Suppl):S10–2. Epub 1994/12/01.
61. Roberts WC, Kishel JC, McIntosh CL, Cannon 3rd RO, Maron BJ. Severe mitral or aortic valve regurgitation, or both, requiring valve replacement for infective endocarditis complicating hypertrophic cardiomyopathy. J Am Coll Cardiol. 1992;19(2):365–71. Epub 1992/02/01.
62. Maron BJ, Lever H. In defense of antimicrobial prophylaxis for prevention of infective endocarditis in patients with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2009;54(24):2339–40. author reply 40. Epub 2009/12/05.
63. Spirito P, Rapezzi C, Bellone P, Betocchi S, Autore C, Conte MR, et al. Infective endocarditis in hypertrophic cardiomyopathy: prevalence, incidence, and indications for antibiotic prophylaxis. Circulation. 1999;99(16):2132–7. Epub 1999/04/27.
64. Wilson W, Taubert KA, Gewitz M, Lockhart PB, Baddour LM, Levison M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular

Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation. 2007;116(15):1736–54. Epub 2007/04/21.
65. Gadler F, Linde C, Juhlin-Dannfeldt A, Ribeiro A, Ryden L. Influence of right ventricular pacing site on left ventricular outflow tract obstruction in patients with hypertrophic obstructive cardiomyopathy. J Am Coll Cardiol. 1996;27(5):1219–24. Epub 1996/04/01.
66. Maron BJ, Josephson ME. Long-term consequences of the right ventricular pacing mania of the 1990s for obstructive hypertrophic cardiomyopathy. Am J Cardiol. 2014;113(1):191–2. Epub 2013/11/19.
67. Schonbeck MH, Brunner-La Rocca HP, Vogt PR, Lachat ML, Jenni R, Hess OM, et al. Long-term follow-up in hypertrophic obstructive cardiomyopathy after septal myectomy. Ann Thorac Surg. 1998;65(5):1207–14. Epub 1998/05/22.
68. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011;124(24):2761–96. Epub 2011/11/10.
69. Ommen SR, Maron BJ, Olivotto I, Maron MS, Cecchi F, Betocchi S, et al. Long-term effects of surgical septal myectomy on survival in patients with obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol. 2005;46(3):470–6. Epub 2005/08/02.
70. Quinones JA, DeLeon SY, Vitullo DA, Hofstra J, Cziperle DJ, Shenoy KP, et al. Regression of hypertrophic cardiomyopathy after modified Konno procedure. Ann Thorac Surg. 1995;60(5):1250–4. Epub 1995/11/01.
71. Knight C, Kurbaan AS, Seggewiss H, Henein M, Gunning M, Harrington D, et al. Nonsurgical septal reduction for hypertrophic obstructive cardiomyopathy: outcome in the first series of patients. Circulation. 1997;95(8):2075–81. Epub 1997/04/15.
72. Maron BJ, Nichols 3rd PF, Pickle LW, Wesley YE, Mulvihill JJ. Patterns of inheritance in hypertrophic cardiomyopathy: assessment by M-mode and two-dimensional echocardiography. Am J Cardiol. 1984;53(8):1087–94. Epub 1984/04/01.
73. Roberts WC, et al. Fifty years of hypertrophic cardiomyopathy. Am J Cardiol. 2009;103:431–4.
74. Maron BJ, et al. Sudden cardiac arrest in hypertrophic cardiomyopathy in the absence of conventional criteria for high risk status. Am J Cardiol. 2008;101:544–47.
75. Virmani R, et al. Cardiomyopathy. In: Virmani R, Burke A, Farb A, Atkinson JB, editors. Cardiovascular pathology. 2nd ed. Philadelphia: W.B. Saunders Company; 2001.
76. Burke A, Virmani R. Histopathological basis of cardiomyopathic disorders. In: Narula J, Virmani R, Ballester M, Carrió I, Westaby S, Frazier O, Willerson JT, editors. Heart failure. Pathogenesis and treatment. London: Martin Dunitz; 2002.
77. Pelliccia A, et al. Recommendations for participation in competitive sport and leisure-time physical activity in individuals with cardiomyopathies, myocarditis and pericarditis. Eur J Cardiovasc Prev Rehabil. 2006;13:876–85.

Approach to Diagnosis: Echocardiography

4

Beevash Ray and Matthew W. Martinez

Abstract

The diagnosis of HCM can be challenging. Echocardiography has become the primary method for the initial evaluation of patients with suspected hypertrophic cardiomyopathy. The integrated utilization of two-dimensional echocardiography, doppler echocardiography, and stress echocardiography allows for the evaluation of the presence and severity of LV wall thickness, diastolic dysfunction, LVOT obstruction and mitral regurgitation. Thus, echocardiography offers the clinician a comprehensive imaging modality in those with suspected HCM, those previously diagnosed, and those undergoing surveillance or therapeutic intervention. In this chapter, we detail the benefits of echocardiography for the diagnosis, monitoring, and management of those with suspected or known HCM.

Keywords

Hypertrophic Cardiomyopathy • Systolic anterior motion of the mitral valve • Two-Dimensional Echocardiography • Doppler Echocardiography • Stress Echocardiography

Key Points

- Echocardiography is the primary initial imaging modality for evaluating and monitoring those with confirmed and suspected HCM.
- Precise thickness of multiple ventricular walls can be assessed with Two Dimensional Echocardiography.
- Obstruction, either at rest or with physiologic provocation, occurs in the majority of patients with HCM. "SAM septal contact" is the cause of the mechanical LVOT obstruction to blood flow between the septum and components of the mitral valve apparatus in the majority of patients. Gradients as result of the obstruction can be measured accurately with continuous wave Doppler.
- The ability to provoke and measure LVOT gradients is essential for the management of symptomatic HCM and exercise stress echocardiography is the ideal modality for this assessment.
- SAM is not only responsible for LVOT obstruction but typically causes concomitant posteriorly directed mitral regurgitation. Patients with anteriorly directed mitral regurgitation require further investigation for intrinsic mitral valve pathology
- In patients with hypertrophic cardiomyopathy, the TDI values are lower than expected for the age of the individual. This can be helpful to distinguish athletes from hypertrophic cardiomyopathy.
- Patients with apical HCM may require contrast administration. Contrast can be used to evaluate for an "apical pouch" which may contain a thrombus. It is also an important tool for assessment of septal perforator anatomy when considering alcohol septal ablation.

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Introduction

Historically, during the 1960's, the diagnosis of HCM was suspected after a clinical examination suggested outflow tract obstruction. A cardiac catheterization was then required for confirmation of the subvalvular outflow tract obstruction and assessment of the pressure gradient [1, 2]. However, with the advent of M-mode and two dimensional echocardiography, a modality for the precise characterization of the pattern and distribution of wall thickening, became available [3]. Furthermore, with Doppler and stress echocardiography additional information regarding diastolic as well as systolic changes in HCM was established [4, 5]. Today echocardiographic assessment requires a comprehensive assessment in several imaging planes. Careful attention to correct beam alignment in order to minimize errors in the measurement of LV wall thickness and appropriate identification of hypertrophy is required. Integration of all the imaging parameters including diastolic function is often required to distinguish cases without massive hypertrophy. Consequently, for the last 20–30 years, echocardiography has become the modality of choice for the diagnosis, monitoring, and therapeutic assessment of patients with HCM [6].

M-Mode Echocardiography

The first diagnostic criteria utilizing echocardiography for HCM was established using M-Mode imaging. The high temporal resolution of M-Mode echocardiography, which is superior to that of two-dimensional echocardiography, makes it ideal for identification of timing [7]. Consequently, M-mode has been used for the measurement of dimensions at precise times during the cardiac cycle, and is essential for the display of subtle abnormalities of specific cardiac structures [8]. Specifically, structures investigated with M-Mode echocardiography for HCM include asymmetrical septal hypertrophy, systolic anterior motion of the mitral valve (SAM) (Fig. 4.1), left atrial size and premature closure of the aortic valve (Fig. 4.2) [9].

The most important linear measurements made using M-mode echocardiography are that of the posterior wall and septal wall thickness. In the parasternal long axis view a wall thickness of greater than 1.1 cm is considered abnormal; however, hypertrophy of greater than 1.5 cm is usually seen in patients suspected to have HCM [10]. Another important linear measurement made in the parasternal long axis is the anterior-posterior dimension of the left atrium (LA) which approximates left atrial size [11]. Left atrial (LA) diameter is usually increased in patients with HCM because of obstruction, mitral regurgitation, diastolic dysfunction, or concomitant atrial fibrillation. An LA size of greater than 48 mm has been shown to have higher risk of atrial fibrillation, congestive heart failure, and cardiac mortality [12]. Major pitfalls of utilizing M-mode echocardiography for linear measurements include finding a true minor axis dimension and measuring a representative portion of the LV.

In HCM, systolic anterior motion (SAM) of the mitral valve can cause left ventricular outflow tract (LVOT) obstruction, discussed later in the chapter [13]. M-mode echocardiography is well suited to demonstrate the presence and degree of SAM (Fig. 4.1). It is easily seen as contact of the anterior mitral valve leaflet/chordae with the septum when viewing M-mode through the mitral valve along with mid-systolic notching of the aortic valve when viewing the aortic valve (Fig. 4.2) [14]. The severity of SAM and subsequent LVOT obstruction can be inferred from the duration of

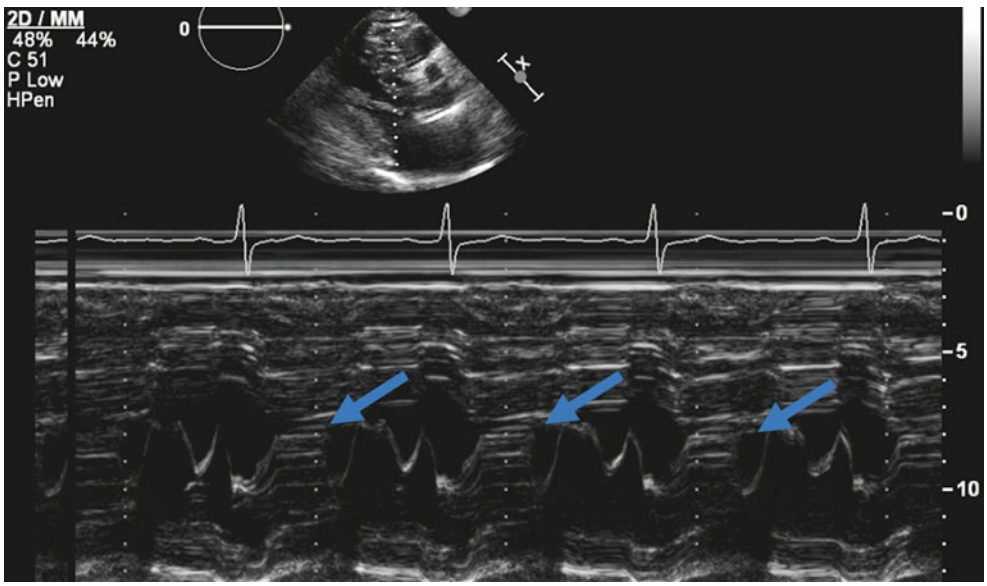


Fig. 4.1 Systolic Anterior Motion. *Blue arrows* show the movement of the anterior leaflet of the mitral valve towards the LVOT during systole

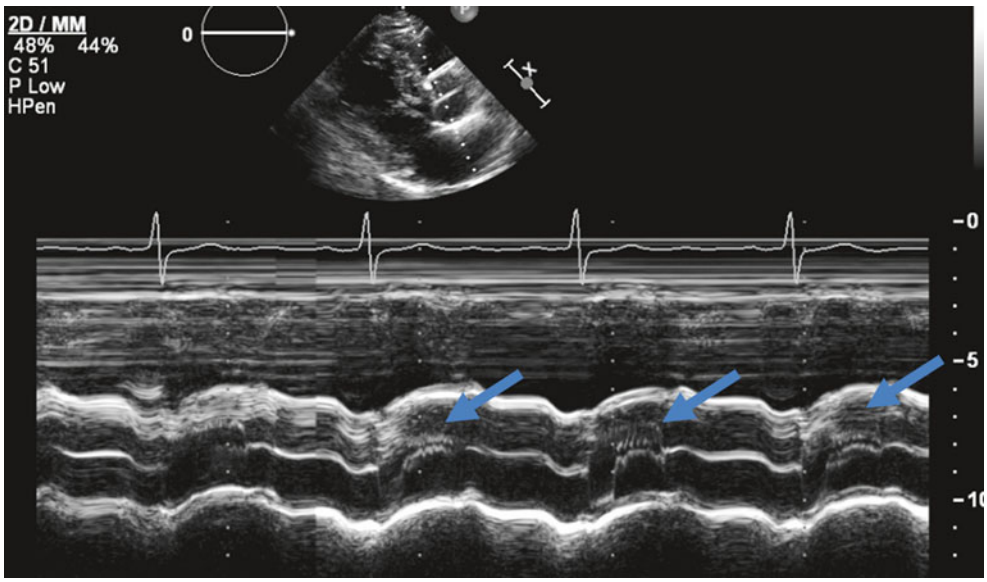


Fig. 4.2 Premature closure of the aortic valve (*blue arrows*) in a patient with HCM and obstructive SAM

leaflet/chordal contact with the septum. Mild obstruction is seen with contact for no more than 10 % of systole and severe if greater than 30 % of systole [15].

Two-Dimensional Echocardiography

Two dimensional (2D) echocardiography is a powerful and important technique for diagnosis, prognosis, and treatment for HCM. It allowed for the first time visualization of the entire heart in one frame, thereby better illustrating the cardiac structural abnormalities associated with HCM. These include evaluation of LV systolic function, LV hypertrophy, LA volume, and SAM. Therefore, 2D echocardiography is the primary initial imaging modality for assessment of those with suspected HCM.

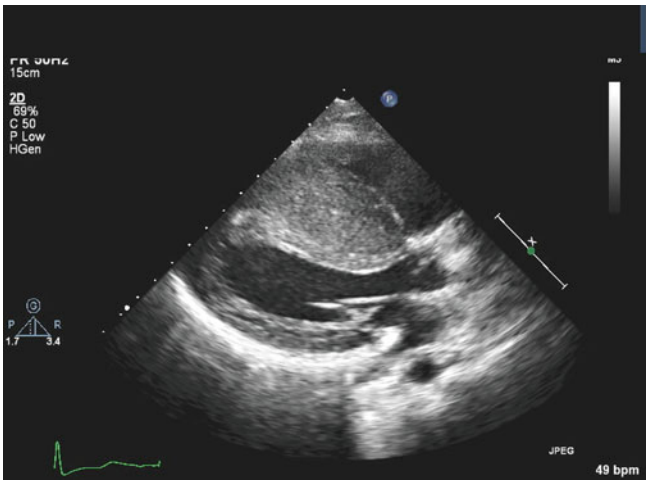


Fig. 4.3 Two dimensional echocardiogram illustrating massive hypertrophy of the anterior septum

LV Hypertrophy

The diagnosis of HCM can be reliably made with the use of two-dimensional transthoracic echocardiography. Imaging features include LV hypertrophy with a non-dilated cavity in the absence of any systemic disease known to cause increased wall thickness [12, 16]. Traditionally, LV wall thickness of greater than 15 mm has been used to define HCM [17]. However, milder forms have been seen with hypertrophy of 13-15 mm, and the use of genetic testing has increased the proportion of HCM patients with milder degrees of hypertrophy seen in clinical practice. This degree of LV hypertrophy is the so called "grey-zone" area as it can be seen in non HCM groups such as highly trained athletes or hypertensive heart disease. Increased wall thickness in athletes has been described and can be difficult to discern from HCM; however even in the highly trained athlete wall thickness rarely exceeds 15 mm [18]. Classically, LV wall thickness measurements are made at end diastole in the parasternal long or short axis views of the septal wall and/or posterior wall. The area of interest is usually the basal septum, but various patterns and distribution of LV hypertrophy (including diffuse and marked) have been reported in HCM [19]. The most clinically important measurement is the maximal wall thickness (MWT) at any LV level [20]. Extreme wall thickness of greater than 30 mm (Fig. 4.3) is associated with sudden cardiac death and is a Class IIa indication for an implantable defibrillator [21]. Although M-mode has better temporal resolution to determine end diastole, the advantage of 2D echocardiography is that a true minor axis measurement can be made.

The presence of LV hypertrophy in the anterior and anterolateral wall may be particularly difficult to detect and quantify. Acoustic windows and close proximity to the lungs account for some of the limited myocardial assessment, and alternative imaging may be required [22]. Sonographers and readers should also be careful to view the apex for discrete hypertrophy or extension of hypertrophy beyond the septum into the apex. [23] Focused views of the apex may be needed to adequately identify hypertrophy as well as the presence of an apical aneurysm. It has been established that apical aneurysms can be a complication of apical HCM or severe long-standing mid-ventricular obstruction. This has been associated with increased risk of adverse cardiovascular complications including sudden cardiac arrest and apical thrombus formation within the cavity, with potential for stroke. Focused views of the apex will also help identify LV non-compaction and is used to differentiate it from the apical form of HCM [24]. Right ventricular hypertrophy has also been described in patients with HCM. In one study right ventricular hypertrophy was seen in 44 % of known HCM patients [25]. Cardiac MRI studies have also shown increased RV mass and hypertrophy [26]. The clinical and prognostic significance of right ventricular hypertrophy, however, is not known.

LV Systolic Function

Most HCM patients have hyperdynamic left ventricular systolic function and a relatively small LV cavity size. Along with 2D echocardiographic visual evaluation of LV function, techniques, such as Simpson's Rule and fractional shortening, have been well validated for estimating ejection fraction [27]. Although ejection fractions above 70 % are typical, LV systolic dysfunction can also be seen and defines end stage HCM or the "burned-out" phase of HCM leading to progressive heart failure [28]. 2D echocardiographic evaluation is characterized by substantial cardiac remodeling and gradual evolution from the typical hypertrophied, non-dilated, and hyper-dynamic state to one of systolic dysfunction [29, 30]. However, left ventricular systolic dysfunction (ejection fraction ≤ 50 %) occurs in only a small subset (~4 %) of HCM patients during midlife and carries a poor prognosis and higher risk of sudden death (SCD) [31, 32]. Serial 2D echocardiograms to assess the ejection fraction, especially if there is a change in symptoms, can be used to evaluate for transition to end stage HCM [33].

Left Atrial Volume

The LA volume as measured in 2D echocardiography is an important clinical and predictive dimension. It is usually measured in the 4 chamber and 2 chamber apical views at end systole. There are several approximations of LA volume involving long and short axes as well as area based on planimetry [34]. Left atrial volumetric remodeling as measured by increasing LA volumes has been shown to predict exercise capacity in non-obstructive HCM and may reflect chronic LV diastolic burden [35]. Furthermore, a left atrial indexed volume of greater than 34 mL/m^2 has been shown to prognosticate more serious cardiovascular events and greater LV hypertrophy, more diastolic dysfunction, and higher filling pressures [36].

Doppler Echocardiography

2D echocardiography and Doppler echocardiography are effectively complementary diagnostic modalities. The former provides anatomic information while the latter provides hemodynamic and physiologic information. The Doppler Effect, described by the Austrian scientist Christian Doppler in 1842, is the basis of Doppler echocardiography [37]. It essentially describes the relationship in mathematical terms between the increases in sound frequency as a sound source moves toward the observer and the decrease in sound frequency as the source moves away from the observer. Based on this principle one can derive a multitude of hemodynamic variables of the heart including gradients between chambers, flow direction, and flow velocities. A comprehensive echocardiogram for HCM patients involves utilizing color Doppler, pulse wave Doppler, continuous wave Doppler, and tissue Doppler for hemodynamic and diastolic assessment of the heart.

Left Ventricular Outflow Tract Obstruction

In HCM, left ventricular outflow obstruction is often attributed to systolic anterior motion of the mitral valve. Most individuals with HCM do not exhibit significant resting obstruction but a dynamic gradient can often be identified in the remaining patients. Therefore, obstruction, either at rest or with physiologic provocation, appears to be a basic characteristic of the majority of patients. LVOT obstruction and resulting pressure gradients are highly variable and strongly influenced by individual physiologic states. Symptomatic patients without a resting gradient must be evaluated further for inducible gradients. LVOT obstruction is most often a combination of mechanisms including narrowing of the LVOT by septal hypertrophy, anterior displacement of the mitral apparatus, and systolic anterior motion (SAM) of the mitral valve. SAM is characterized by an anterior movement of the mitral valve leading to septal wall contact of the mitral valve leaflets. In a subset of patients, other structures of the mitral valve may contribute to obstruction, including abnormally thickened or displaced papillary muscles.

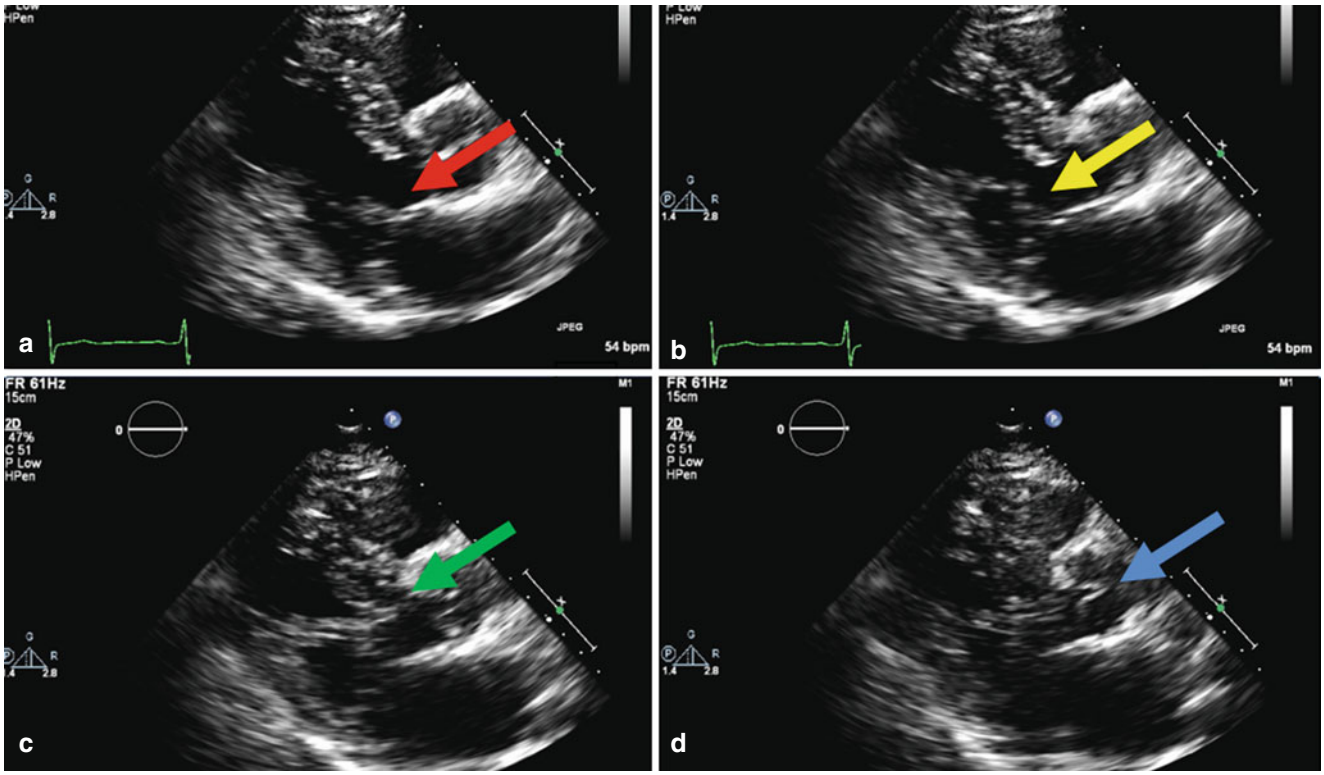


Fig. 4.4 (**a**) The mitral valve is closed in early systole (*red arrow*). (**b**) The anterior leaflet of the mitral valve begins to shifts anteriorly (*yellow arrow*). (**c**) In the middle of systole the mitral valve apparatus moves into the LVOT causing obstruction (*green arrow*). (**d**) The aortic valve closes prematurely (*blue arrow*)

The mechanism for LVOT is controversial but most agree it is attributable to variations of the LVOT and mitral-aortic geometry. First, as already alluded to, papillary muscle displacement leads to diastolic downward vortex forces which pulls the mitral valve into the LVOT [38]. The anterior leaflet of the mitral valve has been found to be longer in patients with HCM and predisposed to act as a sail as it protrudes into the LVOT [40]. Systolic blood flow is directed towards the long anterior leaflet and the acute mitral–aortic angle creates drag forces and moves the mitral valve anteriorly (SAM) making contact with the septal wall causing obstruction [41]. The "SAM septal contact" is the cause of the mechanical LVOT obstruction to blood flow between the septum and components of the mitral valve apparatus in the majority of patients. The obstruction generates a gradient between the LV and aorta [42]. The hemodynamic consequences of SAM include prolongation of ejection time and a reduction in stroke volume. Typically, the anterior leaflet of the mitral valve is involved, but an extremely elongated posterior leaflet of the mitral valve can also be responsible for obstruction [43]. 2D echocardiography is an excellent modality and preferred method for visualizing SAM of the mitral valve and subsequent obstruction (Fig. 4.4). It is usually seen in the parasternal long axis during systole. After visualization of the obstruction, Doppler echocardiography is used to quantify gradients. If SAM is not readily visualized at rest, provocative maneuvers such as the Valsalva maneuver and/or administration of isoproterenol are undertaken.

SAM is not only responsible for LVOT obstruction but typically causes concomitant posteriorly directed mitral regurgitation. Coaptation of the mitral leaflets may be disrupted during SAM resulting in posteriorly directed mitral regurgitation. Complete assessment of the mitral valve should be performed in all patients, especially in those in whom septal reduction therapy is planned. It is well known that the anterior mitral valve leaflet is elongated when compared to those patients without HCM. Other abnormalities of the mitral valve may also include anterior displacement of the mitral apparatus, and insertion of the papillary muscle directly into the anterior mitral valve leaflet. Papillary muscle abnormalities have been demonstrated in over 50 % patients and may require attention and possible papillary muscle ligation at the time of the septal myectomy [44]. Depending on the age of the patient, concomitant degenerative mitral valve disease may be present in addition to SAM as the mechanism for mitral regurgitation. These valves may require surgical repair or replacement. Careful attention to the direction of the mitral regurgitation can lend insight into the presence of intrinsic mitral valve disease [45]. Posteriorly directed mitral regurgitation is expected in those with SAM

whereas anteriorly directed or central mitral regurgitation suggests the presence of intrinsic mitral valve disease and perhaps a flail segment or other etiology may be present [46]. Anteriorly directed regurgitation jets are usually evaluated further by transesophageal echocardiography.

Color Doppler

Color flow Doppler displays inter-cavitary blood flow in different colors representing flow direction and velocity [47]. This makes color Doppler a powerful tool for the evaluation of valvular regurgitation. In obstructive HCM there usually is abnormal mitral leaflet coaptation because of SAM which results in mitral regurgitation (MR) which is best seen in the parasternal long axis. As described above, it is essential to note the direction and severity of the mitral valve regurgitation as this is important when deciding about surgery or alcohol septal ablation; in particular any evidence for significant intrinsic mitral disease would favor surgical myectomy with valve repair or replacement. In the parasternal long axis, five chamber view, and three chamber view turbulent blood flow due to SAM, will be represented as a mixing of colors in the left ventricular outflow tract (Figs. 4.5 and 4.6). SAM tends to produce a mitral regurgitation jet directed posteriorly and laterally, whereas intrinsic mitral valve disease due to annular, papillary or leaflet disease produces an anterior and medially directed jet [48]. Color flow Doppler can be utilized to view the apex for the presence of an apical aneurysm and corresponding flow reversals by continuous wave Doppler (Fig. 4.7). The presence of mid-cavity obstruction may be present with the formation of an apical aneurysm, and this may be associated with ventricular arrhythmias and systemic embolism [49].

Pulse Wave Doppler

In the pulsed wave mode, a single ultrasound crystal sends and receives intermittent or "pulsed" sound beams. The maximal frequency shift that can be determined by pulsed wave Doppler is one-half the pulse repetition frequency which is called the Nyquist frequency. If the frequency shift is higher than the Nyquist frequency, then aliasing occurs [50]. Consequently, there is a maximum velocity that can be resolved using this modality. The advantage of pulse wave is that it determines blood flow velocities of a particular localized region but cannot resolve the high velocities that CW Doppler is able to.

Pulse wave Doppler can be used to interrogate left ventricular outflow tract (LVOT) velocities accurately in HCM [51]. This measurement is made in the apical 5 chamber and/or apical 3 chamber view with careful effort to have the pulse wave beam as parallel to the direction of flow as

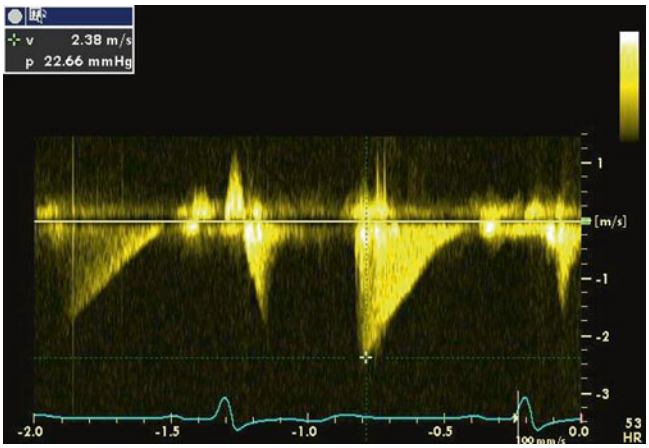
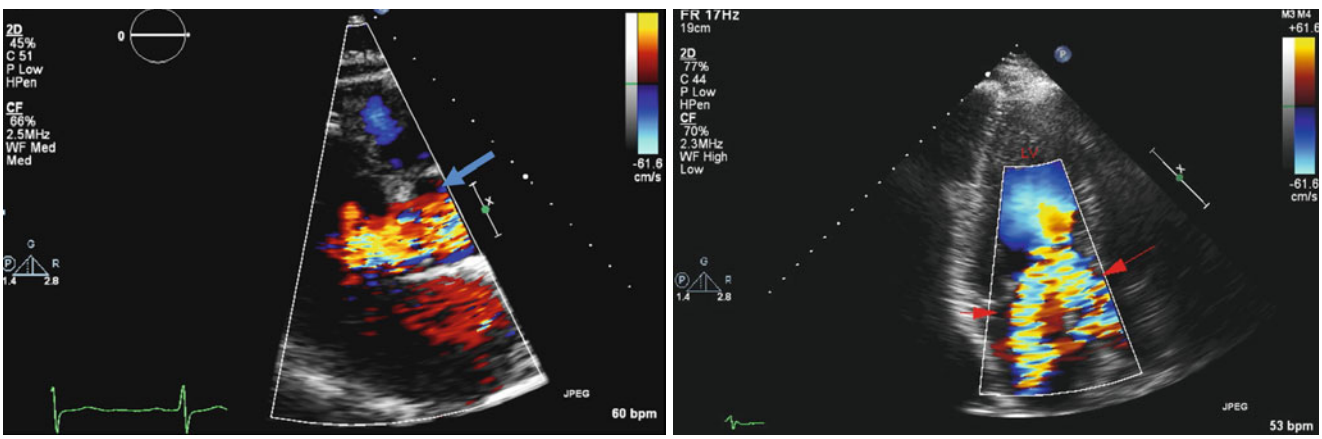


Fig. 4.7 Doppler signal illustrating flow in the apex suggestive of an apical aneurysm with reversal of flow



Figs. 4.5 and 4.6 Color Doppler in the LVOT shows turbulent flow as indicated by the mosaic color pattern (*blue arrow*). Note the posteriorly directed mitral regurgitation present in the long axis view (*red arrow*), and turbulence across the outflow tract and into the aorta

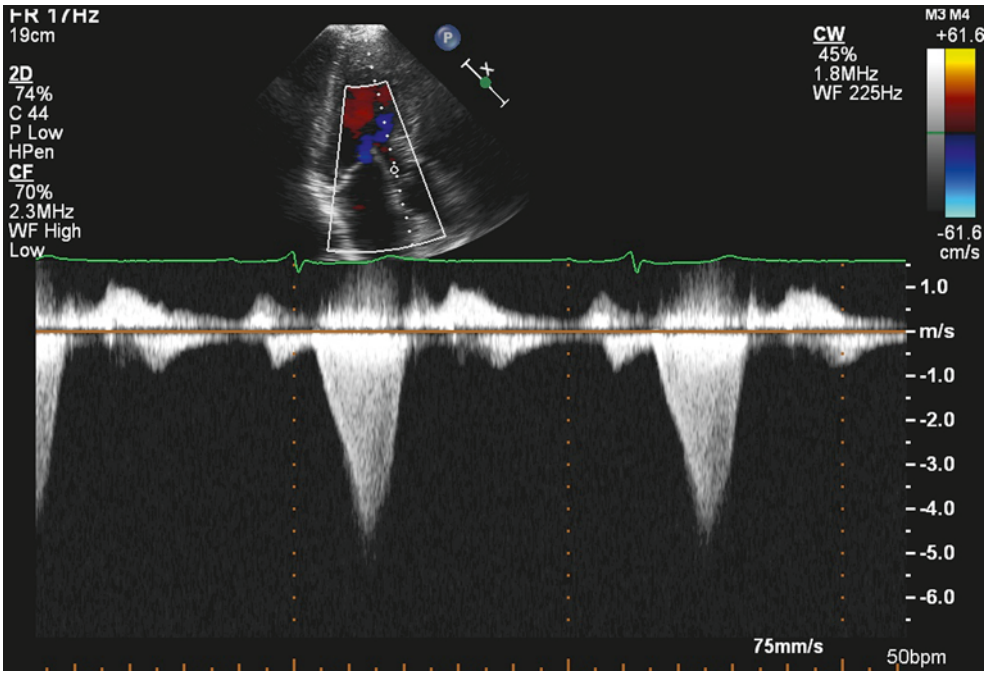


Fig. 4.8 Continuous wave (*CW*) Doppler with characteristic late-peaking dagger shaped (*blue arrow*) LVOT obstruction and severe LVOT gradient (velocity approaching 5 m/s or 100 mmHg)

possible. The velocity can be converted to pressure gradients using the Bernouli equation thereby obtaining a precise measurement of LVOT pressures [52]. Furthermore, obstruction can occur in multiple areas within the LV cavity. Consequently, pulse-wave Doppler is used to sequentially ascertain gradients from the LV apex down to the LVOT and across the aortic valve in order to confirm the anatomical level of obstruction. This is often referred to as "pulsing the septum" and allows the operator to identify the level for obstruction along with visualization of the obstruction with color Doppler. However, often the LVOT velocities exceed the Nyquist limit [53]. Thus, an accurate assessment of LVOT pressures via pulse wave Doppler is not often attainable in HCM patients and typically maximum velocities are only identified by continuous wave Doppler. Pulse wave Doppler is also important in the determination of diastolic dysfunction (discussed later).

Continuous Wave Doppler

Continuous wave (CW) Doppler is dissimilar from pulse wave Doppler as the transducer utilizes two crystals. One of the crystals continuously transmits while the other continuously receives. Since the transmitted signal is not pulsed, the reflected signals all along the ultrasound beam are sampled concurrently. The major disadvantage of this mode is that velocities can come from anywhere along the ultrasound beam and thus, cannot be localized. However, the advantage of this modality in HCM patients is that there is no aliasing and therefore even high velocities can be accurately measured, making the modality particularly beneficial in determining peak velocities and gradients. Careful parallel alignment of the continuous wave beam with the direction of blood flow is necessary to eliminate underestimating the velocity.

As discussed earlier, HCM patients often have LVOT obstruction. This mechanical obstruction manifests as a pressure gradient though the LVOT which can be measured accurately with continuous wave Doppler (Fig. 4.8) [54]. Again, this measurement is made in the apical 5-chamber and/or apical 3 chamber view. About 25 % of patients have a significant LVOT pressure gradient at rest, which is defined as a pressure of greater than 30 mmHg. In symptomatic HCM patients who do not have significant pressure gradients at rest, a dynamic obstruction must be investigated. Maneuvers which can provoke a gradient include having the patient Valsalva, administering amyl nitrite and exercising the patient. Exercise is preferred over the use of pharmacologic agents as these agents can cause gradients in even normal hearts, thus causing false positives [55]. Over 50 % of true HCM patients without significant LVOT obstruction at rest will exhibit outflow gradients greater than 30 mmHg with exercise [56]. Therefore, the majority of patients have either resting or latent (provocable) obstruction. Provocable maneuvers can easily be carried out simultaneously with CW Doppler integration of the LVOT for gradient measurement.

Diastolic Function Evaluation

Nearly all HCM patients have some degree of diastolic dysfunction [57]. It is thought that the decrease in chamber compliance and increase in chamber stiffness because of increased LV mass and myocardial fibrosis in HCM play a prominent role in leading to diastolic dysfunction [58].

Doppler echocardiography with pulse wave assessment allows for an accurate assessment of diastolic function in HCM. Classically diastolic function measurements include pulse wave of the mitral inflow velocities (E for early rapid filling and A for atrial contraction), deceleration time (DT), pulmonary vein predominance and TDI measurements of mitral annulus velocity (known as E' and A'). These measurements are done in the apical 4 chamber view.

Although pulse wave variables by themselves, such as E/A and pulmonary vein predominance, do not correlate well with left ventricular end diastolic pressure (LVEDP) in HCM [59], TDI in combination with pulse wave parameters have been shown to be instrumental in measuring diastolic dysfunction. For example, the E/E' ratio of > 15 (using the TDI-derived E' velocity from the medial mitral annulus) has been shown to correlate with invasively measured left atrial pressures > 15 mmHg 73 % of the time [60]. Prognostically, E/E' ratio changes predict exercise tolerance in adults and children with HCM [61, 62].

Tissue Doppler Imaging

While color Doppler, pulse wave Doppler, and continuous wave Doppler are utilized to examine the velocity properties of red blood cell flow, tissue Doppler imaging (TDI) examines the velocity properties of the myocardium. TDI measures high amplitude, low velocity signals which is ideal for the quantification of radial and longitudinal myocardial motion. This is a highly important technique when evaluating patients for hypertrophic cardiomyopathy. In the apical 4 chamber view a pulsed TDI sample is placed within the myocardium adjacent to the medial or lateral mitral annulus to measure systolic and diastolic myocardial velocities [63]. In patients with hypertrophic cardiomyopathy, the TDI values are lower than expected for the age of the individual (Fig. 4.9). Normal or near normal values in younger patients should be considered abnormal. Furthermore, TDI is helpful to differentiate physiologic hypertrophy such as athlete's heart (normal or supernormal myocardial velocities, Fig. 4.10) and conditions of pathological hypertrophy (abnormal myocardial velocities) [64]. Finally, prognostically a mitral annular systolic velocity less than 4 cm/s measured using TDI has been shown to be an independent predictor of death or hospitalization for worsening heart failure in HCM [65].

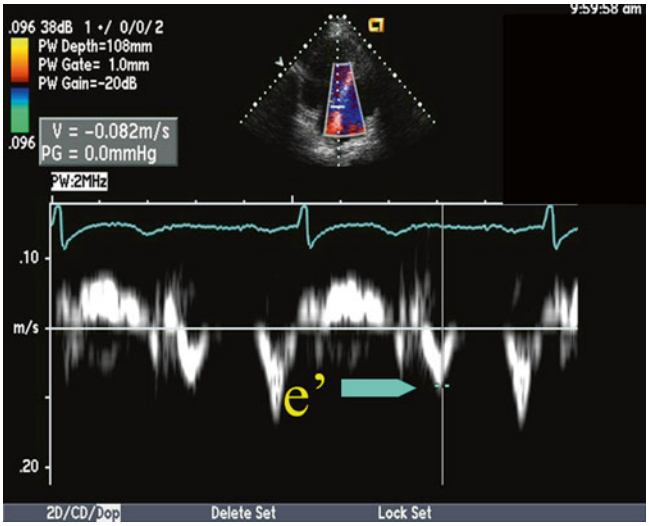


Fig. 4.9 Tissue Doppler images illustrating abnormal values that are reduced in a young person with HCM

Strain and Strain Rate Imaging

Strain measurements assess myocardial motion relative to the adjacent myocardium and are unaffected by translational cardiac motion and tethering in the same way TDI measurements can be. Careful attention to how these measurements are obtained is important as they are angle-dependent measurements. While strain measures myocardial deformation, strain rate measures the local rate of deformation. This technique allows spatial and temporal tracking of longitudinal, circumferential, and radial deformation and the calculation of strain. Patients with HCM have significant reductions in strain in the septal segments and correlate with wall thickness [66] (Fig. 4.11) Studies in patients with HCM have demonstrated a reduction in longitudinal strain, an increase in circumferential strain, and normal systolic twist or torsion, but a reduction in untwisting in diastole [67, 68]. Marked reduction in strain longitudinal measurements have been found to correlate to fibrosis identified by cardiac MRI [69].

Stress Echocardiography and LVOT Provocation

As previously discussed, patients with HCM may not have a significant resting obstruction. HCM is often a dynamic disease process with the presence of LVOT obstruction only present after provocation. Management of this group with a so called labile obstruction requires further search for obstruction [70]. Consequently, the ability to provoke and then measure LVOT gradients is essential for the

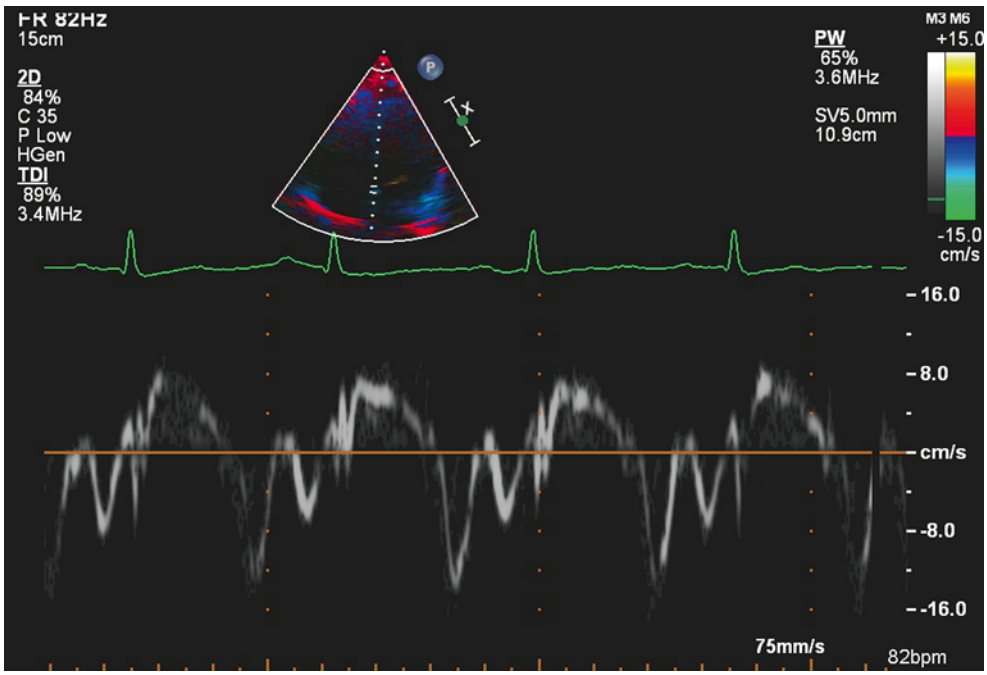


Fig. 4.10 Tissue Doppler images illustrating "supernormal" values in a young athlete

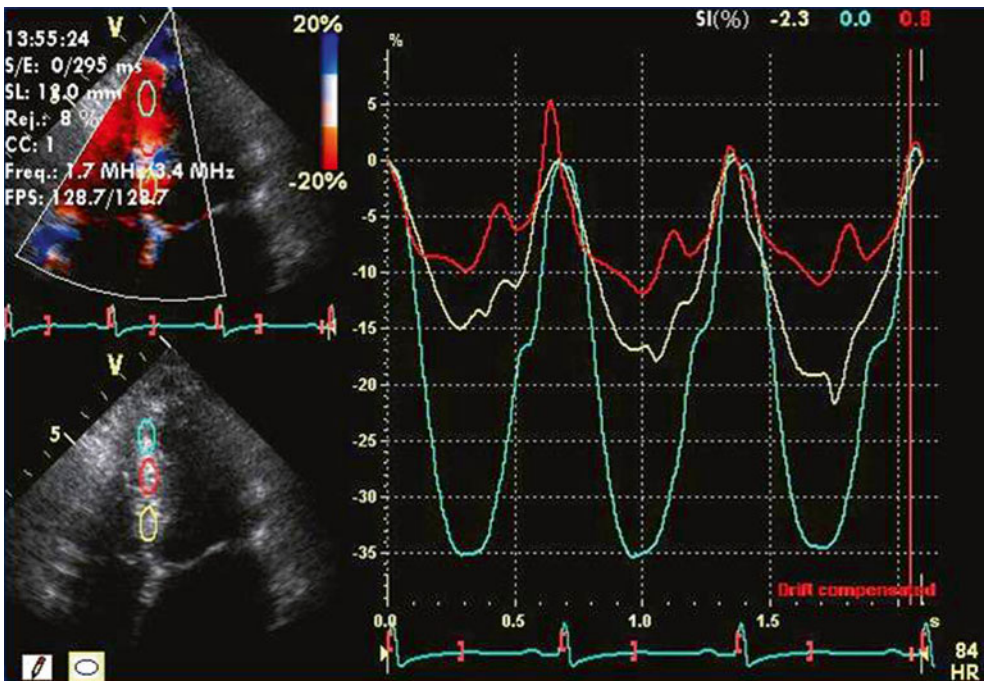


Fig. 4.11 Echocardiographic Doppler derived strain images illustrating abnormal strain values in the area of left ventricular hypertrophy

management of HCM with several options available to elicit the obstruction. Interventions are aimed to diminish LV volume and/or augment contractility. Various exercise and pharmacologic protocols have been proposed for the provocation of dynamic obstructions from a pharmacological stress stand point. Dobutamine, isoproterenol, and amyl nitrite have all been proposed to provoke a gradient. The standard protocol of dobutamine doses of up to 30–40 mcg/kg/min [71] has been described, however LVOT obstruction is a known side effect of dobutamine and may occur in up to 20 % of patients without known HCM or overt hypertrophy [72]. Therefore dobutamine is not recommended in the evaluation of patients with suspected labile obstruction and false positives are likely [73]. Isoproterenol doses of up to 0.005 – 0.02 mcg/kg/min for 5 to 10 min have been used safely in HCM patients and leads to LVOT obstruction by causing tachycardia [74]. Amyl nitrite use entails 2–6 inhalations of the vapor from

one capsule over a period of 1–2 min. Inhaled Amyl nitrite during simultaneous imaging of the LVOT leads to a rise in heart rate and a drop in the blood pressure with subsequent LVOT obstruction in patients with a labile obstruction. This can be repeated if needed but should be stopped if there is severe hypotension or marked symptoms of flushing and/or dizziness [75]. However, these methods are not physiologic assessments and do not mimic the same stresses produced with exercise. Therefore, exercise stress echocardiography is the ideal modality for this as changes in wall motion, outflow gradients, and systolic function can be assessed in simulated stress conditions that are similar to the physiologic stresses of activity that produce patient symptoms [76].

These protocols are similar to routine exercise echocardiography with imaging prior to and during or immediately after the stress. Standard exercise protocols with the treadmill such as the Bruce or Modified Bruce protocol as well as bicycle ergometry can be employed. Bicycle exercise may allow for easier acquisition of imaging data sets along with hemodynamic assessment; however, in this method increased venous return might decrease the likelihood and degree of LVOT obstruction. Of these protocols, stress with exercise is preferred since it most closely resembles physiologic states. Upright exercises are more likely to cause LVOT gradients during exercise than supine and are the preferred method for those with labile LVOT obstruction [77].

2011 ACCF/AHA guidelines for the diagnosis and treatment of HCM assign exercise echocardiography a class IIa recommendation for the detection and quantification of exercise-induced dynamic LV outflow tract (LVOT) obstruction in patients who have a resting peak instantaneous gradient of 50 mmHg or less (level of evidence B). Provocable gradients ≥50 mmHg with exercise in those with symptoms that cannot be controlled with medications represent the conventional threshold for septal reduction intervention [78]. Finally, exercise echocardiography can be used to identify transient regional wall motion abnormalities due to functionally significant CAD. This is important since simultaneous presence of CAD with HCM carries a worse prognosis, may be present in older individuals with cardiovascular risk factors, and is treatable with revascularization techniques, either concomitant to septal reduction therapies or in isolation [79].

Contrast Echocardiography

Myocardial contrast media is typically given intravenously to opacify and view the ventricular cavities in those patients with difficult images. In particular, apical HCM may be difficult to appreciate in some cases, and contrast media can help identify the presence of an aneurysm as well as thrombus formation within the cavity (Fig. 4.12) [80]. Obese patients with poor acoustic windows may also benefit from contrast echocardiography, which can aid in assessing systolic function, cavity size, and wall thickness.

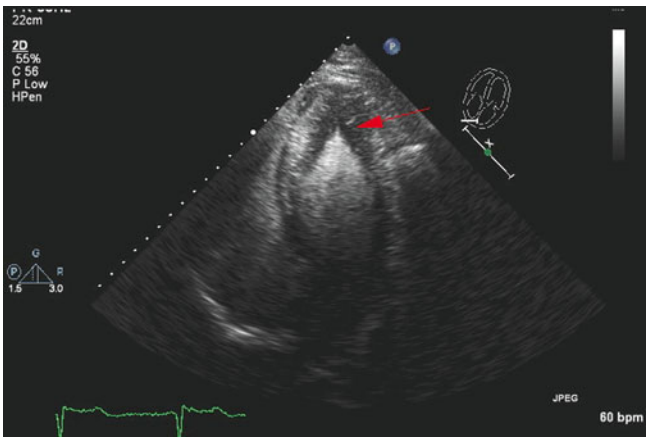


Fig. 4.12 Contrast media enhanced echocardiogram illustrating apical hypertrophy (*red arrow*) with a classic "ace of spades" configuration. No aneurysm or apical thrombus is identified

In patients with HCM, contrast utilization also takes on a different role. Alcohol septal ablation has been introduced for the relief of symptomatic medically refractory obstructive HCM in selected groups of patients [81]. Contrast media is injected into the coronary arteries, to identify and confirm the appropriate septal branch that supplies the myocardium where SAM septal contact occurs (Fig. 4.13a, b). This is important to identify the desired area for ablation and to avoid alcohol injection into a papillary muscle or LV free wall. In addition, myocardial contrast can aid in understanding when additional more proximal or distal septal perforators should be ablated, in order to effect a more efficacious and durable result. Contrast medium is injected into a septal branch of the left anterior descending artery resulting in opacification of the myocardium hopefully in the distribution of the proposed septal branch. Care should be taken to ensure that opacification of any cardiac structure other than the targeted septal area does not occur. Alcohol should not be injected in these cases and alternative septal reduction therapy should be considered. When performed properly and with expertise, myocardial contrast reduced the total amount of ethanol injected and reduced complications including pacemaker implantation rates without impacting clinical efficacy and reduction of peak gradient [82].

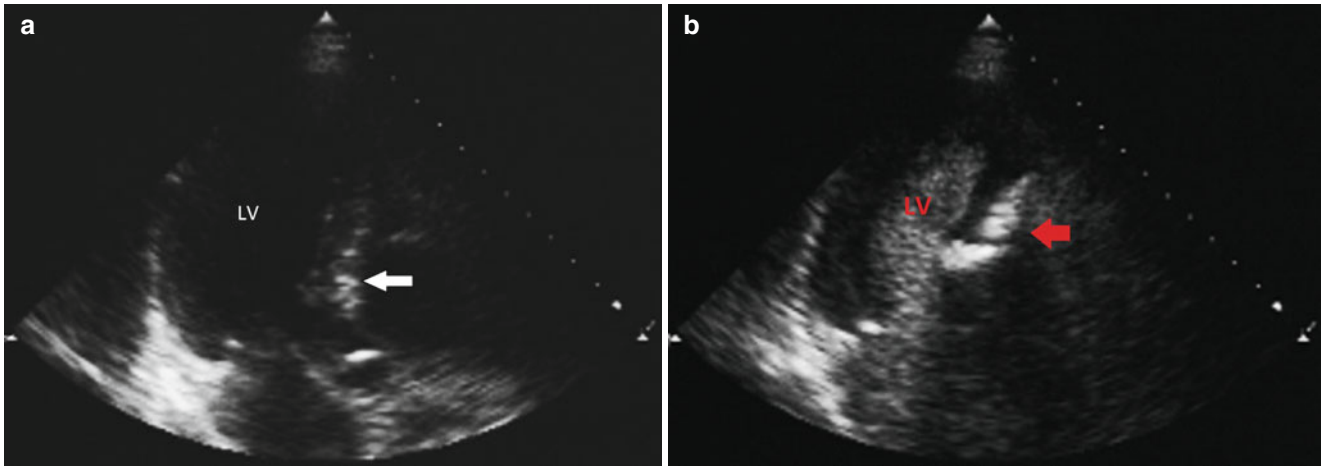


Fig. 4.13 (**a**, **b**) Two dimensional echocardiogram pre (**a**) and post (**b**) contrast media injection. The contrast media enhanced echocardiogram illustrates the area of myocardium supplied by the first septal perforator that will be affected during the alcohol ablation (*white arrow* indicates the anterior septum without contrast, *red arrow* indicates the area in the anterior septum supplied by the first septal perforator after contrast injection). *LV* left ventricle

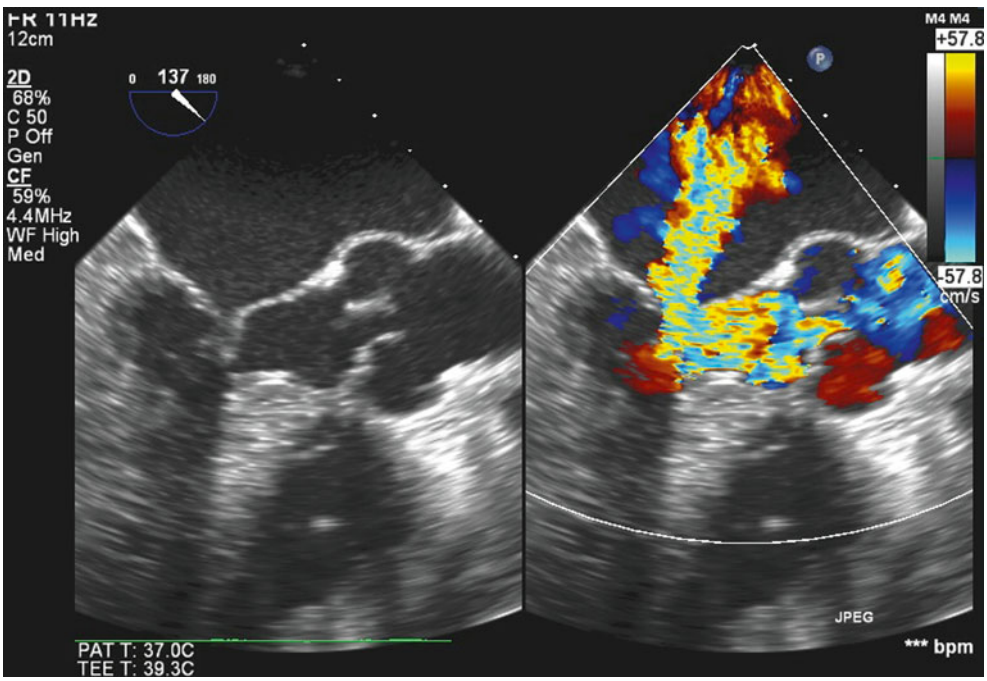


Fig. 4.14 Transesophageal two dimensional echocardiogram illustrating systolic anterior motion (SAM) of the mitral valve with septal contact. Color Doppler illustrating LVOT obstruction with turbulence in the LVOT and corresponding posteriorly directed mitral regurgitation color Doppler signal

Transesophageal Echocardiogram

Transesophageal echocardiography (TEE) is not often required in the evaluation of hypertrophic cardiomyopathy. TEE may be utilized preoperatively to evaluate SAM (Fig. 4.14) in patients with poor 2D echocardiography images or those unable to have a cardiac MRI. TEE evaluation would not be typically employed as a usual measurement tool in HCM but can be helpful in selected patients. For instance, in cases in which suspected intrinsic degenerative mitral valve disease is suspected a TEE will be valuable, especially in cases when anteriorly or medially directed mitral regurgitation is identified and a flail or unsupported segment is suspected. Another area in which TEE is useful is to rule out a subaortic or supra-aortic membrane or partial membrane. Although a subaortic membrane (Fig. 4.15a, b) is a rare condition, it remains an important differential diagnosis in hypertrophic cardiomyopathy with LVOT obstruction

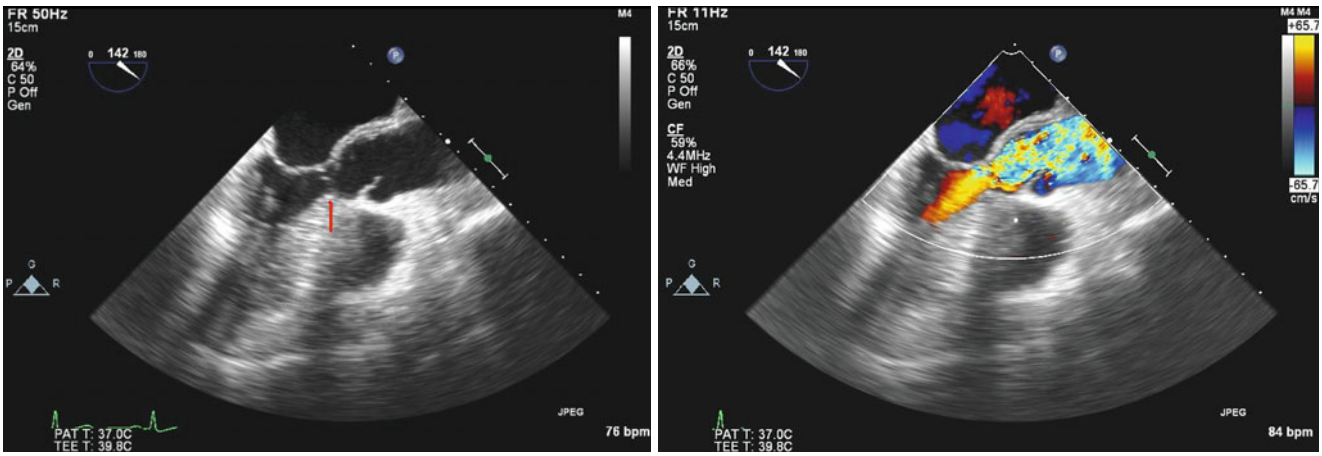


Fig. 4.15 (**a**) Transesophageal echocardiogram of a patient with a subaortic membrane (*red arrow*) (**b**) with severe LVOT obstruction illustrated by color Doppler. Note no systolic anterior motion of the mitral valve, the obstruction occurs at the level of the membrane

and in aortic stenosis, particularly at a young age or in the presence of family history [83]. TEE is also important intraoperatively during septal myectomy, in order to guide the procedure and confirm an optimal result.

Diagnostic Caveats

Potential misdiagnosis may occur in diseases that mimic HCM. Left ventricular hypertrophy can be seen in many other diseases and interpretation of imaging studies should always be done in context of the clinical history. Other forms of hypertrophy may mimic HCM and include but are not limited to physiologic hypertrophy of the highly trained athlete, hypertensive heart disease, aortic valve disease, infiltrative heart disease and glycogen storage diseases. LVH is common in cardiac amyloid; several echocardiographic features may help to distinguish cardiac amyloid from HCM [84, 85]. These include bi-atrial dilatation, thickened interatrial septum, restrictive inflow pattern, thickening of the valve leaflets, and the presence of a pericardial effusion (Fig. 4.16). A longitudinal strain pattern of apical sparing using speckle tracking techniques has been shown to differentiate cardiac involvement from other cardiac pathologies [86]. A cardiac MRI or fat pad biopsy should be done when amyloid is suspected to confirm the diagnosis to ensure the correct treatment strategy. In addition, measurement error can be a common cause of misdiagnosis of HCM. The presence of left ventricular hypertrophy can be erroneously measured if an oblique section of the LV is measured or the right ventricular moderator band is included leading to overestimation of septal thickness.

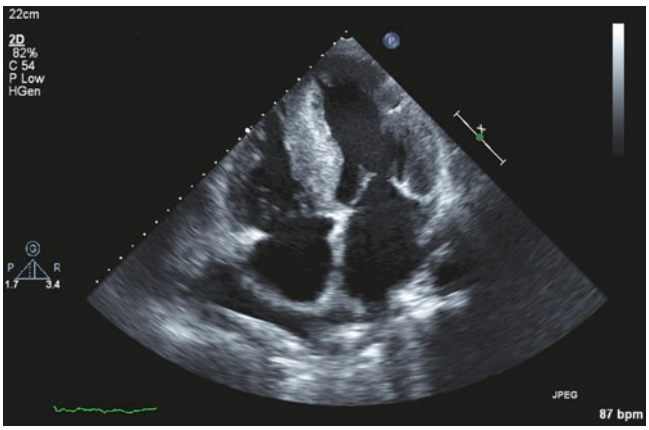


Fig. 4.16 Two dimensional echocardiogram of a patient with Amyloid cardiomyopathy. Note the thickened RV wall, pericardial effusion and thickened valve leaflets

Conclusions

Echocardiography is the primary method for the initial evaluation of patients with suspected hypertrophic cardiomyopathy. The diagnosis of HCM is challenging, and is a clinical diagnosis utilizing historical features, physical examination and echocardiographic assessment, which together promote a comprehensive clinical, anatomic and physiologic understanding of a given patient. Echocardiography allows the clinician to evaluate for the presence and severity of LV wall thickness, diastolic dysfunction, the presence of LVOT obstruction, or mitral regurgitation and assist with therapeutic interventions in both the operating room and catheterization laboratory. Echocardiography is well suited to evaluate all aspects of patients with suspected HCM and those with

HCM who are undergoing evaluation for new or changing symptoms.

Clinical Pearls

- Obstruction is a hallmark of symptomatic HCM. All patients should be evaluated by transthoracic echocardiography with provocation to identify the presence and severity of obstruction.
- The ability to provoke and measure LVOT gradients is essential for the management of symptomatic HCM and exercise stress echocardiography is the ideal modality for evaluation of LVOT gradients but care must be taken to avoid signal contamination with mitral regurgitation.
- Accurate measurement of ventricular wall thickness is important for both the diagnosis of HCM and management of massive hypertrophy for ICD decision making. Careful attention to the anterior and lateral walls which often underestimate the maximal wall thickness compared to cardiac MRI.
- Distinguishing adaptive athletic hypertrophy from pathology hypertrophy in HCM is often accompanied by evaluating diastolic function. Athletes should not have abnormal diastolic function or lower TDI values for their age and degree of athleticism. This can be helpful to distinguish athletes from hypertrophic cardiomyopathy.

References

1. Adelman AG, McLoughlin MJ, Marquis Y, et al. Left ventricular cineangiographic observations in muscular subaortic stenosis. Am J Cardiol. 1969;24:689–97.
2. Braunwald E, Lambrew CT, Rockoff SD, et al. Idiopathic hypertrophic subaortic stenosis. I. A description of the disease based upon an analysis of 64 patients. Circulation. 1964;30 Suppl 4:3–119.
3. Maron BJ, Gottdiener JS, Epstein SE. Patterns and significance of distribution of left ventricular hypertrophy in hypertrophic cardiomyopathy. A wide angle, two dimensional echocardiographic study of 125 patients. Am J Cardiol. 1981;48:418–28.
4. Geske JB, Sorajja P, Nishimura RA, Ommen SR. Evaluation of left ventricular filling pressures by Doppler echocardiography in patients with hypertrophic cardiomyopathy: correlation with direct left atrial pressure measurement at cardiac catheterization. Circulation. 2007;116:2702–8.
5. Yang H, Sun JP, Lever HM, Popovic ZB, Drinko JK, Greenberg NL, et al. Use of strain imaging in detecting segmental dysfunction in patients with hypertrophic cardiomyopathy. J Am Soc Echocardiogr. 2003;16:233–9.
6. Maron BJ, McKenna WJ, Danielson GK, et al. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. J Am Coll Cardiol. 2003;42:1687–713.
7. Feigenbaum H, Armstrong WF, Ryan T, Feigenbaum H. Feigenbaum's echocardiography. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 139. Print.
8. Oh JK, Seward JB, Jamil Tajik A. The echo manual. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 22. Print.
9. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, Moss AJ, Seidman CE, Young JB. Contemporary definitions and classification of the cardiomyopathies. Circulation. 2006;113:1807–16.
10. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naidu SS, Nishimura RA, Ommen SR, Rakowski H, Seidman CE, Towbin JA, Udelson JE, Yancy CW. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011;124:2761–96.
11. Harvey F, Armstrong WF, Ryan T, Feigenbaum H. Feigenbaum's echocardiography. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 181. Print.
12. Nistri S, Olivotto I, Betocchi S, Losi MA, Valsecchi G, Pinamonti B, Conte MR, Casazza F, Galderisi M, Maron BJ, Cecchi F. Prognostic significance of left atrial size in patients with hypertrophic cardiomyopathy (from the Italian Registry for Hypertrophic Cardiomyopathy). Am J Cardiol. 2006;98:960–5.
13. Wigle ED, Sasson Z, Henderson MA, et al. Hypertrophic cardiomyopathy. The importance of the site and the extent of hypertrophy. A review. Prog Cardiovasc Dis. 1985;28:1–83.
14. Maron BJ, Epstein SE. Hypertrophic cardiomyopathy. Recent observations regarding the specificity of three hallmarks of the disease: asymmetric septal hypertrophy, septal disorganization and systolic anterior motion of the anterior mitral leaflet. Am J Cardiol. 1980;45:141–54.
15. Williams LK, Frenneaux MP, Steeds RP. Echocardiography in hypertrophic cardiomyopathy diagnosis, prognosis, and role in management. Eur J Echocardiogr. 2009;10:iii9–14.
16. Wigle ED, Sasson Z, Henderson MA, et al. Hypertrophic cardiomyopathy. The importance of the site and the extent of hypertrophy. A review. Prog Cardiovasc Dis. 1985;28:1–83.
17. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naidu SS, Nishimura RA, Ommen SR, Rakowski H, Seidman CE, Towbin JA, Udelson JE, Yancy CW. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011;124:2761–96.
18. Basavarajaiah S, Wilson M, Whyte G, Shah A, McKenna W, Sharma S. Prevalence of hypertrophic cardiomyopathy in highly trained athletes: relevance to pre-participation screening. J Am Coll Cardiol. 2008;51:1033–9.
19. Klues HG, Schiffers A, Maron BJ. Phenotypic spectrum and patterns of left ventricular hypertrophy in hypertrophic cardiomyopathy: morphologic observations and significance as assessed by two-dimensional echocardiography in 600 patients. J Am Coll Cardiol. 1995;26:1699–708.

20. Spirito P, Maron BJ. Relation between extent of left ventricular hypertrophy and occurrence of sudden cardiac death in hypertrophic cardiomyopathy. J Am Coll Cardiol. 1990;15:1521–6. 20.
21. Spirito P, Bellone P, Harris KM, Bernabo P, Bruzzi P, Maron BJ. Magnitude of left ventricular hypertrophy and risk of sudden death in hypertrophic cardiomyopathy. N Engl J Med. 2000;342: 1778–85.
22. Rickers C, Wilke NM, Jerosch-Herold M, Casey SA, Panse P, Panse N, Weil J, Zenovich AG, Maron BJ. Utility of cardiac magnetic resonance imaging in the diagnosis of hypertrophic cardiomyopathy. Circulation. 2005;112:855–61.
23. Martinez MW. Mid-cavitary obstruction in hypertrophic cardiomyopathy. Heart. 2008;94(10):1287.
24. Monserrat L, Hermida-Prieto M, Fernandez X, Rodríguez I, Dumont C, Cazón L, Cuesta MG, Gonzalez-Juanatey C, Peteiro J, Alvarez N, Penas-Lado M, Castro-Beiras A. Mutation in the alpha-cardiac actin gene associated with apical hypertrophic cardiomyopathy, left ventricular non-compaction, and septal defects. Eur Heart J. 2007;28:1953–61.
25. McKenna WJ, Kleinebenne A, Nihoyannopoulos P, Foale R. Echocardiographic measurement of right ventricular wall thickness in hypertrophic cardiomyopathy: relation to clinical and prognostic features. J Am Coll Cardiol. 1988;1:351–8.
26. Maron MS, Hauser TH, Dubrow E, Horst TA, Kissinger KV, Udelson JE, Manning WJ. Right ventricular involvement in hypertrophic cardiomyopathy. Am J Cardiol. 2007;100:1293–8.
27. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr. 1989;2:358–67.
28. Maron BJ, Spirito P. Implications of left ventricular remodeling in hypertrophic cardiomyopathy. Am J Cardiol. 1998;81:1339–44.
29. Olivotto I, Girolami F, Nistri S, Rossi A, Rega L, Garbini F, Grifoni C, Cecchi F, Yacoub MH. The many faces of hypertrophic cardiomyopathy: from developmental biology to clinical practice. J Cardiovasc Transl Res. 2009;2:349–67.
30. Maron BJ, Spirito P. Implications of left ventricular remodeling in hypertrophic cardiomyopathy. Am J Cardiol. 1998;81:1339–44.
31. Fujiwara H, Onodera T, Tanaka M, Shirane H, Kato H, Yoshikawa J, Osakada G, Sasayama S, Kawai C. Progression from hypertrophic obstructive cardiomyopathy to typical dilated cardiomyopathy-like features in the end stage. Jpn Circ J. 1984;48:1210–4.
32. Harris KM, Spirito P, Maron MS, et al. Prevalence, clinical profile, and signifi cance of left ventricular remodeling in the end-stage phase of hypertrophic cardiomyopathy. Circulation. 2006;114: 216–25.
33. Douglas PS, Garcia MJ, Haines DE, Lai WW, Manning WJ, Patel AR, Picard MH, Polk DM, Ragosta M, Ward RP, Weiner RB. ACCF/ASE/AHA/ASNC/HFSA/HRS/SCAI/SCCM/SCCT/SCMR 2011 appropriate use criteria for echocardiography: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Society of Echocardiography, American Heart Association, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance Endorsed by the American College of Chest Physicians. J Am Coll Cardiol. 2011;57:1126–66.
34. Feigenbaum H, Armstrong WF, Ryan T, Feigenbaum H. Feigenbaum's echocardiography. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 184. Print.
35. Sachdev V, Shizukuda Y, Brenneman CL, Birdsall CW, Waclawiw MA, Arai AE, Mohiddin SA, Tripodi D, Fananapazir L, Plehn JF. Left atrial volumetric remodeling is predictive of functional capacity in nonobstructive hypertrophic cardiomyopathy. Am Heart J. 2005;149(4):730–6.
36. Yang H, et al. Enlarged left atrial volume in hypertrophic cardiomyopathy: a marker for disease severity. J Am Soc Echocardiogr. 2005;18(10):1074–82.
37. Hatle L, Angelsen B. Doppler ultrasound in cardiology. 2nd ed. Philadelphia: Lea & Febiger; 1985.
38. Izgi C, Akgun T, Men EE, Feray H. Systolic anterior motion of the mitral valve in the absence left ventricular hypertrophy: role of mitral leaflet elongation and papillary muscle displacement. Echocardiography. 2010; 27:E36–8.
39. Lefebvre XP, He S, Levine RA, Yoganathan AP. Systolic anterior motion of the mitral valve in hypertrophic cardiomyopathy: an in vitro pulsatile flow study. J Heart Valve Dis. 1995;4:422–38.
40. He S, Hopmeyer J, Lefebvre XP, Schwammenthal E, Yoganathan AP, Levine RA. Importance of leaflet elongation in causing systolic anterior motion of the mitral valve. J Heart Valve Dis. 1997; 6:149–59.
41. Sherrid MV, Gunsburg DZ, Moldenhauer S, Pearle G. Systolic anterior motion begins at low left ventricular outflow tract velocity in obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol. 2000;36:1344–54.
42. Maron MS, Olivotto I, Zenovich AG, et al. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. Circulation. 2006;114:2232–9.
43. Klues HG, Roberts WC, Maron BJ. Morphological determinants of echocardiographic patterns of mitral valve systolic anterior motion in obstructive hypertrophic cardiomyopathy. Circulation. 1993; 87:1570–9.
44. Hoigne P, Attenhofer Jost CH, Duru F, Oechslin EN, Seifert B, Widmer U, et al. Simple criteria for differentiation of Fabry disease from amyloid heart disease and other causes of left ventricular hypertrophy. Int J Cardiol. 2006;111:413–22.
45. Yu EH, Omran AS, Wigle ED, Williams WG, Siu SC, Rakowski H. Mitral regurgitation in hypertrophic obstructive cardiomyopathy: relationship to obstruction and relief with myectomy. J Am Coll Cardiol. 2000;36:2219–25.
46. Kaple RK, Murphy RT, DiPaola LM, Houghtaling PL, Lever HM, Lytle BW, et al. Mitral valve abnormalities in hypertrophic cardiomyopathy: echocardiographic features and surgical outcomes. Ann Thorac Surg. 2008;85:1527–35. 1535.
47. Omoto R, Kasai C. Physics and instrumentation of Doppler color flow mapping. Echocardiography. 1987;4:467–83.
48. Yu EH, Omran AS, Wigle ED, Williams WG, Siu SC, Rakowski H. Mitral regurgitation in hypertrophic obstructive cardiomyopathy: relationship to obstruction and relief with myectomy. J Am Coll Cardiol. 2000;36:2219–25.
49. Maron MS, Finley JJ, Bos JM, Hauser TH, Manning WJ, Haas TS, et al. Prevalence, clinical significance, and natural history of left ventricular apical aneurysms in hypertrophic cardiomyopathy. Circulation. 2008;118:1541–9.
50. Oh JK, Seward JB, Jamil Tajik A. The echo manual. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 60. Print.
51. Maron BJ, Gottdiener JS, Arce J, et al. Dynamic subaortic obstruction in hypertrophic cardiomyopathy: analysis by pulsed Doppler echocardiography. J Am Coll Cardiol. 1985;6:1–18.
52. Hatle L, Angelsen B. Doppler ultrasound in cardiology. 2nd ed. Philadelphia: Lea & Febiger; 1985.
53. Bom K, de Boo J, Rijsterborgh H. On the aliasing problem in pulsed Doppler cardiac studies. J Clin Ultrasound. 1984;12: 559–67.
54. Panza JA, Petrone RK, Fananapazir L, Maron BJ. Utility of continuous wave Doppler echocardiography in the noninvasive assessment of left ventricular outflow tract pressure gradient in patients with hypertrophic cardiomyopathy. J Am Coll Cardiol. 1992; 19(1):91–9.

55. Maron MS, Olivotto I, Zenovich AG, et al. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outfl ow tract obstruction. Circulation. 2006;114:2232–9.
56. Shah JS, Esteban MT, Thaman R, Sharma R, Mist B, Pantazis A, Ward D, Kohli SK, Page SP, Demetrescu C, Sevdalis E, Keren A, Pellerin D, McKenna WJ, Elliott PM. Prevalence of exercise-induced left ventricular outflow tract obstruction in symptomatic patients with non-obstructive hypertrophic cardiomyopathy. Heart. 2008;94:1288–94.
57. Briguori C, Betocchi S, Losi MA, et al. Noninvasive evaluation of left ventricular diastolic function in hypertrophic cardiomyopathy. Am J Cardiol. 1998;81:180–7.
58. Maron BJ, Spirito P, Green KJ, Wesley YE, Bonow RO, Arce J. Noninvasive assessment of left ventricular diastolic function by pulsed Doppler echocardiography in patients with hypertrophic cardiomyopathy. J Am Coll Cardiol. 1987;10:733–42.
59. Nishimura RA, Appleton CP, Redfield MM, Ilstrup DM, Holmes Jr DR, Tajik AJ. Noninvasive Doppler echocardiographic evaluation of left ventricular filling pressures in patients with cardiomyopathies: a simultaneous Doppler echocardiographic and cardiac catheterization study. J Am Coll Cardiol. 1996;28:1226–33.
60. Geske JB, Sorajja P, Nishimura RA, Ommen SR. Evaluation of left ventricular filling pressures by Doppler echocardiography in patients with hypertrophic cardiomyopathy: correlation with direct left atrial pressure measurement at cardiac catheterization. Circulation. 2007;116:2702–8.
61. Matsumura Y, Elliott PM, Virdee MS, Sorajja P, Doi Y, McKenna WJ. Left ventricular diastolic function assessed using Doppler tissue imaging in patients with hypertrophic cardiomyopathy: relation to symptoms and exercise capacity. Heart. 2002;87:247–51.
62. McMahon CJ, Nagueh SF, Pignatelli RH, et al. Characterization of left ventricular diastolic function by tissue Doppler imaging and clinical status in children with hypertrophic cardiomyopathy. Circulation. 2004;109:1756–62.
63. Ho CY, Solomon SD. A clinician's guide to tissue Doppler imaging. Circulation. 2006;113:e396–8.
64. Vinereanu D, Florescu N, Sculthorpe N, Tweddel AC, Stephens MR, Fraser AG. Differentiation between pathologic and physiologic left ventricular hypertrophy by tissue Doppler assessment of long-axis function in patients with hypertrophic cardiomyopathy or systemic hypertension and in athletes. Am J Cardiol. 2001;88:53–8.
65. Bayrak F, Kahveci G, Mutlu B, Sonmez K, Degertekin M. Tissue Doppler imaging to predict clinical course of patients with hypertrophic cardiomyopathy. Eur J Echocardiogr. 2008;9:278–83.
66. Yang H, Sun JP, Lever HM, Popovic ZB, Drinko JK, Greenberg NL, et al. Use of strain imaging in detecting segmental dysfunction in patients with hypertrophic cardiomyopathy. J Am Soc Echocardiogr. 2003;16:233–9.
67. Carasso S, Yang H, Woo A, Vannan MA, Jamorski M, Wigle ED, et al. Systolic myocardial mechanics in hypertrophic cardiomyopathy: novel concepts and implications for clinical status. J Am Soc Echocardiogr. 2008;21:675–83.
68. Van Dalen BM, Kauer F, Soliman OI, Vletter WB, Michels M, ten Cate FJ, et al. Influence of the pattern of hypertrophy on left ventricular twist in hypertrophic cardiomyopathy. Heart. 2009;95:657–61.
69. Popovic ZB, Kwon DH, Mishra M, et al. Association between regional ventricular function and myocardial fibrosis in hypertrophic cardiomyopathy assessed by speckle tracking echocardiography and delayed hyperenhancement magnetic resonance imaging. J Am Soc Echocardiogr. 2008;21:1299–305.
70. Nishimura RA, Ommen SR. Hypertrophic cardiomyopathy: the search for obstruction. Circulation. 2006;114:2200–2.
71. Okeie K, Shimizu M, Yoshio H, Ino H, Yamaguchi M, Matsuyama T, Mabuchi H. Left ventricular systolic dysfunction during exercise and dobutamine stress in patients with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2000;36(3):856–63.
72. Pellikka PA, Oh JK, Bailey KR, Nichols BA, Monahan KH, Tajik AJ. Dynamic intraventricular obstruction during dobutamine stress echocardiography. A new observation. Circulation. 1992;86(5):1429–32.
73. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naidu SS, Nishimura RA, Ommen SR, Rakowski H, Seidman CE, Towbin JA, Udelson JE, Yancy CW. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Thorac Cardiovasc Surg. 2011;142:1303–8.
74. Kawano S, Iida K, Fujieda K, Yukisada K, Magdi ES, Iwasaki Y, Sugishita Y. Response to isoproterenol as a prognostic indicator of evolution from hypertrophic cardiomyopathy to a phase resembling dilated cardiomyopathy. J Am Coll Cardiol. 1995;25(3):687–92.
75. Marwick TH, Nakatani S, Haluska B, Thomas JD, Lever HM. Provocation of latent left ventricular outflow tract gradients with amyl nitrite and exercise in hypertrophic cardiomyopathy. Am J Cardiol. 1995;75(12):805–9.
76. Maron MS, Olivotto I, Zenovich AG, Link MS, Pandian NG, Kuvin JT, Nistri S, Cecchi F, Udelson JE, Maron BJ. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. Circulation. 2006;114:2232–9.
77. Schwammenthal E, Schwartzkopff B, Block M, Johns J, Lösse B, Engberding R, Breithardt G. Doppler echocardiographic assessment of the pressure gradient during bicycle ergometry in hypertrophic cardiomyopathy. Am J Cardiol. 1992;69(19):1623–8.
78. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naidu SS, Nishimura RA, Ommen SR, Rakowski H, Seidman CE, Towbin JA, Udelson JE, Yancy CW. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Thorac Cardiovasc Surg. 2011;142:1303–8.
79. Argulian E, Chaudhry FA. Stress testing in patients with hypertrophic cardiomyopathy. Prog Cardiovasc Dis. 2012;54:477–82.
80. Nagueh SF, Lakkis NM, He ZX, Middleton KJ, Killip D, Zoghbi WA, Quiñones MA, Roberts R, Verani MS, Kleiman NS, Spencer III WH. Role of myocardial contrast echocardiography during non-surgical septal reduction therapy for hypertrophic obstructive cardiomyopathy. J Am Coll Cardiol. 1998;32:225–9.
81. Sigwart U. Non-surgical myocardial reduction for hypertrophic obstructive cardiomyopathy. Lancet. 1995;346:211–4.
82. Alam M, Dokainish H, Lakkis N. Alcohol septal ablation for hypertrophic obstructive cardiomyopathy: a systematic review of published studies. J Interv Cardiol. 2006;19:319–27.
83. Teis A, Sheppard MN, Alpendurada F. Subaortic membrane: correlation of imaging with pathology. Eur Heart J. 2010;31:2822.
84. Rahman JE, Helou EF, Gelzer-Bell R, Thompson RE, Kuo C, Rodriguez ER, et al. Noninvasive diagnosis of biopsy-proven cardiac amyloidosis. J Am Coll Cardiol. 2004;43(3):410–5.
85. Badano L, Fox K, Sicari R, Zamorano JL. Disease with a main influence on myocardial tissue damage. In: EAE textbook of echocardiography. 1st ed. Oxford (UK): Oxford Medical Press; 2011. p. 335–6.
86. Phelan D, Collier P, Thavendiranathan P, Popovic ZB, Hanna M, Plana JC, et al. Relative 'apical sparing' of longitudinal strain using two-dimensional speckle-tracking echocardiography is both sensitive and specific for the diagnosis of cardiac amyloidosis. Heart. 2012;98(19):1442–8.

Cardiac MRI in Diagnosis and Management

5

Jonathan Kahan, Juan Gaztanaga, and Mario Jorge Garcia

Abstract

Cardiac magnetic resonance imaging (CMR) is an essential tool in the diagnosis, risk stratification and treatment of patients with hypertrophic cardiomyopathy (HCM). CMR works by manipulating protons found in myocytes and contrast agents such as Gadolinium, using magnetic pull to create and then detect energy differences and thus obtain images. CMR is ideal for detecting the location and extent of hypertrophy, presence or absence of membranes, the distribution of fibrosis and the anatomy and physiology of the mitral valve, all of which are crucial for diagnosis of HCM, which can be missed on standard echocardiography. This is especially true for hard to see areas of the heart such as the apical area as well as atypical presentations such as focal segmental hypertrophy or mass-like HCM. Additionally, extremely accurate assessments of the left ventricular volumes, mass and function are prognostic as well as diagnostic. Magnetic resonance tagging and delayed-enhancement with Gadolinium allow for strain and perfusion analysis, further increasing the utility of CMR to detect regional function and cardiac microvascular ischemia, of which HCM patients are particularly susceptible. Delayed enhancement distribution and extent may also impact risk stratification for sudden cardiac death. Limitations of CMR include assessment of the left ventricular outflow tract gradient and highly mobile structures on the mitral valve, although newer protocols and improved technology may be able to compensate for these deficits in the future.

Keywords

Cardiac magnetic resonance imaging • MRI safety • Late gadolinium enhancement • Fibrosis • Microvascular ischemia • Sudden cardiac death risk factor

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Key Points

- When a strong magnetic field is applied to hydrogen atoms in myocytes, the protons align in higher energy states. When a perpendicular magnet is applied the energy given off and absorbed by the surrounding tissue is detected as the protons relax. This is called spin echo and is also known as T1. If energy is absorbed and detected from one proton to another this is known as T2 MRI.
- Cardiac MRI (CMR) has many applications in the field of cardiology. CMR is the gold standard for quantification of ventricular volumes, masses, fibrosis and ejection fractions, with excellent spatial resolution, accuracy and reproducibility. Additionally it is not limited by body habitus or poor acoustic windows. Cardiac stents, grafts and closure devices are generally safe and implantable cardiac defibrillators and pacemakers are being developed which will be MRI safe.
- Chelated Gadolinium is the main contrast agent used in cardiac MRI. It has an excellent safety profile with its most serious complication being nephrogenic systemic fibrosis, although this is rare. Gadolinium is used in delayed enhancement to detect areas of ischemia, scar and infarction.
- Hypertrophic cardiomyopathy (HCM) has many phenotypes, the most common being asymmetric septal hypertrophy. CMR can diagnose and detect the extent of various HCM presentations, especially in hard to see areas on echocardiography, such as the apex and lateral wall.
- A multitude of cardiac diseases can mimic HCM, especially hypertensive heart disease, athlete's heart, infiltrative cardiac disease and valvular diseases. CMR has the ability to distinguish between this vast array of illnesses and should be used to aid in definitive diagnosis.
- Mitral valve regurgitation is the most common valve disorder in HCM, where papillary muscle dysfunction, fibrosis and systolic anterior motion can readily be detected and quantified by CMR. Abnormal papillary muscles, including abnormal hypertrophy or placement, as well as membranes, are easily distinguished by CMR.
- HCM patients are at increased risk for myocardial microvascular ischemia, which can lead to heart failure and sudden death. Delayed enhancement CMR can readily detect myocardial perfusion defects and fibrosis, allowing for accurate diagnosis and prognosis, facilitating the cardiologist in creating a tailored treatment plan for his/her HCM patients.

Introduction

A variety of non invasive modalities are used in the diagnosis of Hypertrophic Cardiomyopathy (HCM). Appropriate imaging should be used when HCM is the suspected diagnosis based on relevant signs and symptoms. Imaging can help not only to establish diagnosis, but also for risk stratification of sudden cardiac death (SCD) and evaluation of treatment options, making its use critical for proper management. Advances in imaging technology through cardiac magnetic resonance imaging (CMR) have given new insight and understanding into the morphologic diversity of HCM patients. Assessing global and regional left ventricular (LV) function, location and extent of hypertrophy, distribution and burden of fibrosis, as well as the anatomy and physiology of the mitral valve (MV), are all key to establishing a firm diagnosis, prognosis and treatment plan. This chapter will outline the basic principles of how CMR functions, and its role in the diagnosis and treatment of HCM, with a special emphasis on current and future clinical applications.

General Principles of CMR

Magnetic resonance imaging (MRI) is one of the most widely used diagnostic techniques in Medicine. Cardiac MRI or CMR has emerged as a valuable modality for detection of both static and dynamic cardiovascular processes.

MR Physical Principles

All materials in nature have magnetic properties, where movement of electrical charge creates magnetic field lines perpendicular to the charge. Furthermore, any nuclei that have an odd number of protons and neutrons will have magnetic moments, where a magnetic field with direction will surround said nuclei, simply based on movement of charges within the atom. In order to create a uniform magnetic field where field lines are parallel to each other, it is necessary to have a solenoid configuration, where an electric charge creates a magnetic field surrounding the object that the field passes over. Since the body is largely made up of water, hydrogen atoms with a single positively charged proton can be used to create electrical charge and therefore can create a magnetic dipole (bi-directional magnetic impulses originating from a single plane). Normally, these electrical charges and magnetic fields are pointed in random directions, cancelling each other out. However, when a strong magnetic field is applied, the vectors of all of the magnetic momentums line up either parallel (low energy state) or anti-parallel (high energy state) to the direction of the magnetic field source. In other words, when a strong, external magnetic field is applied

to the hydrogen atoms in the form of water in the human body, those protons align either facing towards or away from the field. A strong external magnet does not just line up the molecules, but causes them to resonate (rotate). Another name for this rotation is precession. Each nucleus has a unique frequency proportional to the strength of the magnetic field to which it resonates and this is called resonant frequency. It can be calculated by using the Larmor equation where:

$$\text{Resonant Frequency (F)} = B_0 \times \text{Larmor Constant (42.57 MHz/T for a } H^1 \text{ nucleus)}$$

B_0 is the strength of the external magnetic field, and T is a Tesla unit, which equals 10,000 times the strength of the earth's magnetic field.

Therefore, another way to look at procession is that all protons will wobble or rotate around the plane of B_0 in either a parallel or anti-parallel fashion.

All images are detections of energy from a given source. In order to obtain CMR images, it is necessary to detect the energy given off by the protons. This is accomplished by briefly applying a second magnetic field (B_1) perpendicular to the initial strong magnetic field, and measuring the energy (in the form of absorption of energy into surrounding tissue) as protons return from a high to low energy state (anti-parallel to parallel) and as they slow down their rotation (resonance). The energy given off by these relaxations is called spin, and can be detected by radiofrequency signals or echo.

It is important to note that an atom can relax or "spin" in two different ways. When a strong magnetic field is applied, and all protons are aligned around B_0, the magnetic moments of each individual proton can be measured in either the longitudinal (z axis) or transverse axis (XY axis). It makes sense that if protons are essentially in line with each other, then there is not a statistical transverse movement and therefore all transverse vectors cancel out, leaving a total of either parallel or anti-parallel oriented protons; the sum of the vectors of this is called net magnetization M. Note that for net magnetization in the longitudinal plane, it is called M_Z and for the transverse plane it is called M_{XY}.

When a brief radiofrequency (electromagnetic) pulse is applied, suddenly protons will align towards the transverse (higher energy state), instead of longitudinal plane. After the electromagnetic pulse is turned off, the protons relax (spin) from a high to lower energy state, and excess energy given off is absorbed by the surroundings, also known as the lattice. This spin-lattice relaxation is also known as T1 relaxation, and different relaxation times reflect different sizes and consistencies of molecules in tissue. In technical terms, T1 is the amount of time it takes for 63.2 % of the original M_Z to recover. T2 (spin-spin) relaxation works on similar principals, except it is detecting the effect of one proton's magnetic field on another, and therefore is not influenced by the strong external magnetic field like T1 relaxation time. Of note, T2 is the time it takes for 63.2 % of the initial M_{XY} to disappear. After one RF-pulse and a magnetic field, a gradient echo (GRE) is created from the spin of the energy decayed protons. After two successive RF pulses a spin echo is created.

Instrumentation

The main components of an MRI system include the magnet, the magnetic field gradients (RF pulses), radiofrequency system and cardiac receiver coil, in addition to software to control all the components and monitor the patient.

The superconducting magnet is stationary and creates the strong homogenous magnetic field. Superconducting magnets are made of niobium-titanium alloy wire to create 1.5–3 T magnetic fields (although currently for experimental purposes up to 10 T magnets have been created). The radiofrequency system generates RF pulses leading to the excitation of protons and then uses a receiver to obtain signals from the protons. Note that these two actions occur through coils, which are usually numerous and small to eliminate background noise in CMR. It is also possible to activate more than one gradient coil at the same time, leading to oblique RF pulses and different angles of measurement from 90 and 180°.

Images obtained are stored in a k-space, or temporary image space. This is usually a matrix which is where the raw image data from the RF signals are stored. At the end of the scan, the data collected in k-space from different pulse sequences is used to produce an image. This concept becomes important when discussing different imaging modes (see below). From the k space matrix, near limitless sequences can be applied to the raw data to transform it into images that contain different structural and functional information. A few types of these images, as applied to HCM, are discussed in a later section.

Contrast Agents

Most MRI contrast agents use various chelations of gadolinium, and their use is equivalent to the use of iodinated contrast agents in computed tomography. Most commonly gadolinium is injected at 0.2 mmol/kg, however, single and triple doses can be used. Initially, gadolinium is injected intravenously, where it then partitions to the extra cellular matrix. In tissues with increased vascularity, more gadolinium will bind to these structures. Once gadolinium is bound to extravascular spaces, it shortens both T1 and T2 (increasing relaxation) leading to an increase in signal intensity. Some compounds have the ability to lead to signal loss and it

is important to understand that the same contrast agent can both increase and decrease the signal intensity depending on which imaging sequence is being used.

There are currently five gadolinium-based agents approved by the Food and Drug Administration (FDA), although none are labeled specifically for CMR use. Most have similar T1 relaxivity, while Gadobenate dimeglumine (Multihance®) has a higher T1 relaxivity, and therefore smaller dosing protocols.

Chelated gadolinium has an excellent safety profile, with a <1 % adverse reaction rate, most commonly flushing, headache, and nausea. Allergic reactions are reported at <0.05 % while severe anaphylaxis has only been shown in isolated case reports. At larger doses however, acute renal failure may develop, especially in patients with underlying renal dysfunction. Gadolinium does carry a FDA warning of nephrogenic systemic fibrosis, a potentially lethal reaction involving fibrosis of the skin and organs. However, the EuroCMR study, which analyzed over 11,000 patients undergoing CMR with gadolinium, found no cases of nephrogenic systemic fibrosis [1]. Nevertheless, it is important to measure a patient's creatinine to avoid the risk of developing fibrosis, as patients with end stage renal disease have a higher chance of contracting this rare but deadly complication.

MR Protocols and Cardiovascular Applications

Cardiac MRI (CMR) can be used to evaluate the structure, perfusion, function and metabolism of the heart. This is achieved through a multitude of imaging protocols, each designed to detect a certain component of the heart. In most cases, images are collected and analyzed in segments, most commonly following the American Heart Association 17 segment model [2]. Most sequences can further be divided into bright blood (gradient echo) sequences and black blood (spin echo) sequences. Both bright and black blood sequences are names applied to the appearance of blood in the imaging, and refer to the method of obtaining these images (Generically called T1 and T2, see section "MR physical principles".).

Initially, the patient completes a MRI safety screen to avoid most of the possible complications/contraindications (see section "Absolute and relative contraindications".). Once inside the scanner, an EKG signal is attached for gating purposes. If EKG can not be obtained, then peripheral pulse signal can be used. If stress testing is being employed, a blood pressure cuff must also be used. Hearing protection should be given, as the magnetic gradients deliver extremely loud tapping noises.

Once the patient is inside the CMR scanner, a low resolution localizer image is obtained with a single-shot steady state free precession (SSFP), acquiring a single image in the axial, coronal and sagittal planes. Not only does this help localize the heart, but these fast images can show gross abnormalities such as aortic aneurysms, masses, congenital defects etc.

Another concept applied to numerous sequences is phase contrast (PC) imaging, which is used to obtain velocities through an area (i.e. valves) from which gradients can be calculated (see section on valvular stenosis). In this technique, the blood is given a magnetic energy pulse before the valve and its spin is measured immediately after the excitation plane, allowing for a flow velocity to be obtained.

Cine imaging involves the use of segmented SSFP images, determining the T2/T1 ratio of tissues and therefore is less dependent on inflowing blood. This leads to an excellent endocardial definition, as well as increased temporal resolution, quality and reproducibility [3]. Each heartbeat or segment leads to acquisition of a k-space, and temporal resolution is determined by the time between two consecutive k spaces, or in other words, the product of the repetition time by the number of k spaces acquired per heartbeat. In general, temporal resolution for CMR should be <45 ms. Spatial resolution in cine is determined by the imaging matrix size and the field of view and should be <2 mm in the x and y axis [4]. During a cine image, the patient must hold their breath for 5–10 s or 8–12 heartbeats. If patients have limited breath hold capacity, images can be obtained with averages of 3–4 short breath holds or with respiratory navigators during free-breathing. Gating can be accomplished both retrospectively and prospectively, wherein prospective gating the QRS initiates imaging acquisition and stops obtaining images before the next QRS while in retrospective gating images are obtained throughout the cardiac cycle, and is therefore the preferred method for CMR image acquisition [5]. In patients with severe arrhythmias or limited breath holding, real time cardiac function can be ascertained using variations of SSFP and echo planar imaging (EPI) [6].

Ventricular function is obtained in cine through multiple short-axis slices approximately 6–10 mm thick and are usually contiguous but can be separated by <5 mm gaps. Figure 5.1 Images are also obtained in multiple dimensions, with standard 4-, 3- and 2-chamber views as well as the long axis of the right ventricle. Figure 5.2 From these images the size, shape and wall thickness of both ventricles are obtained with remarkable detail, leading to views of dyskinesia, remodeling or other structural abnormalities. Newer sequences have been able to recreate the full three dimensional anatomy in a single breath hold [7].

First pass perfusion imaging is a useful technique used to detect microvascular obstruction (MVO) and perfusion in the myocardium. In this technique, chelated gadolinium is injected into the bloodstream and saturation recovery gradient-echo images are obtained as the contrast passes through the myocardium and tissue [8]. In cases where detection of ischemia is desired, such as acute myocardial

infarctions and coronary artery disease, adenosine or dipyridimole is given to dilate resistant arterioles before addition of contrast [8]. Areas of reversible ischemia will appear as hypoperfusion on stress images but not at rest.

Exact quantification of perfusion can be obtained for each myocardial segment by creating signal versus time curves during contrast first pass, however exact analysis of perfusion is time consuming due to extensive post processing and complex mathematics [9]. Myocardial signal intensity is then corrected for background noise, baseline signal and blood pool signal, giving a percentage of hypodensity in each segment. Small doses of contrast are used because there is a non linear relationship between signal intensity and contrast dose, however dual-bolus injection protocols and other

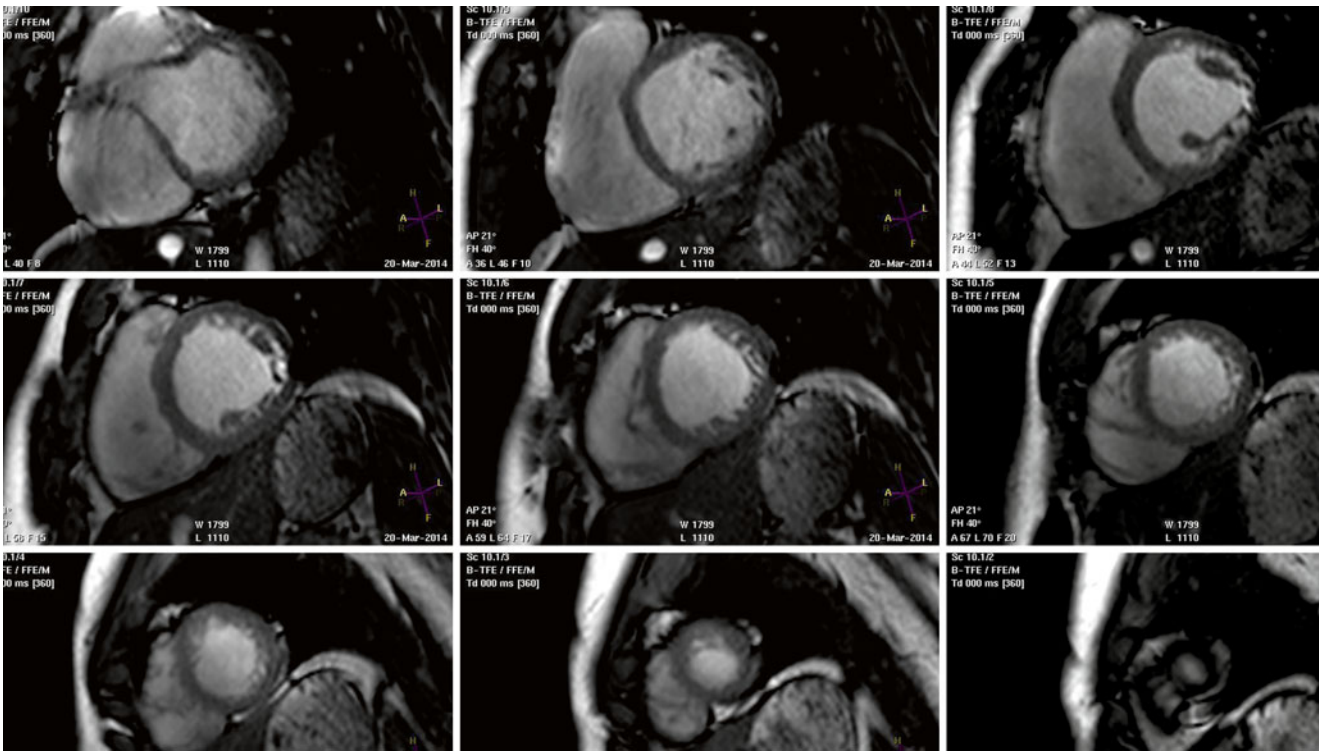

Fig. 5.1 Image of short axis stack cine from base to the apex of a normal heart using steady state free precession (SSFP) sequence

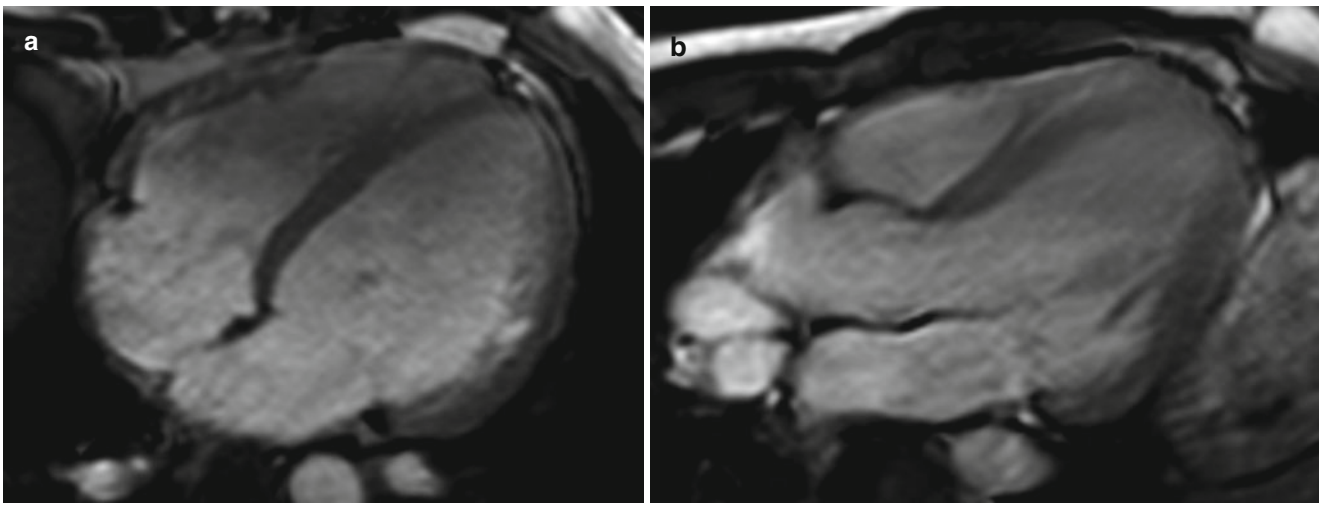

Fig. 5.2 SSFP long axis cine images of (**a**) the four-chamber view, (**b**) three-chamber view, (**c**) two-chamber view and (**d**) right sided two-chamber view demonstrating the right atrium (*RA*), right ventricle (*RV*) and pulmonary artery (*PA*)

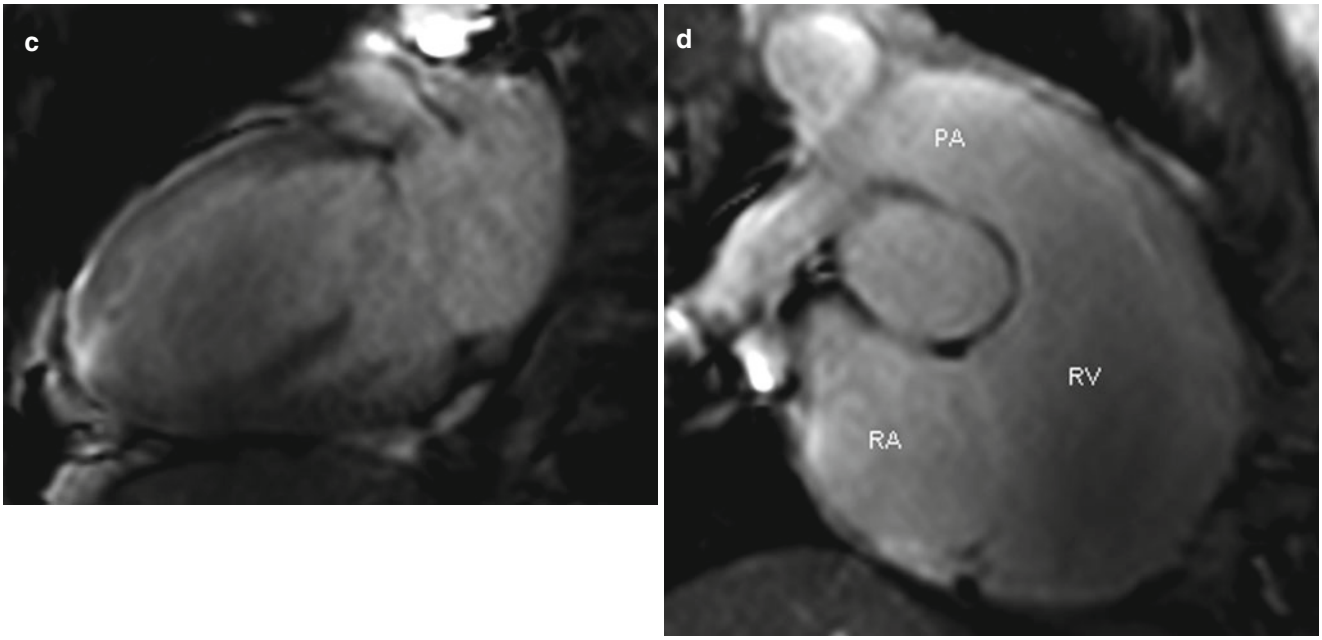

Fig. 5.2 (continued)

sequences may be used to overcome this limitation [8]. Image acquisition is rapid during both rest and stress, as most contrast diffuses to extracellular tissues after a short time. From this, semi quantitative analysis can be performed, most commonly by measuring the upslope of perfusion during stress versus rest and comparing it to an established perfusion reserve index

Delayed enhancement CMR is another sequence that is used to detect scar or fibrosis, this time in the tissue itself and not through perfusion like first pass imaging. Figure 5.3 In this modality, contrast (again variations of chelated gadolinium) is given intravascularly. This time, it is allowed to diffuse into tissues over a short amount of time (typically 10–20 min). In normal myocardium with an intact cell membrane, gadolinium is unable to diffuse into the cell. In cells that are damaged, such as in an acute myocardial infarction, the cell's membranes are disrupted, allowing gadolinium to enter the cells [10]. This leads to hyperenhancement which can be easily detected. In scar formation, such as old myocardial infarctions, gadolinium will bind to the collagen matrix, and therefore will also hyperenhance.

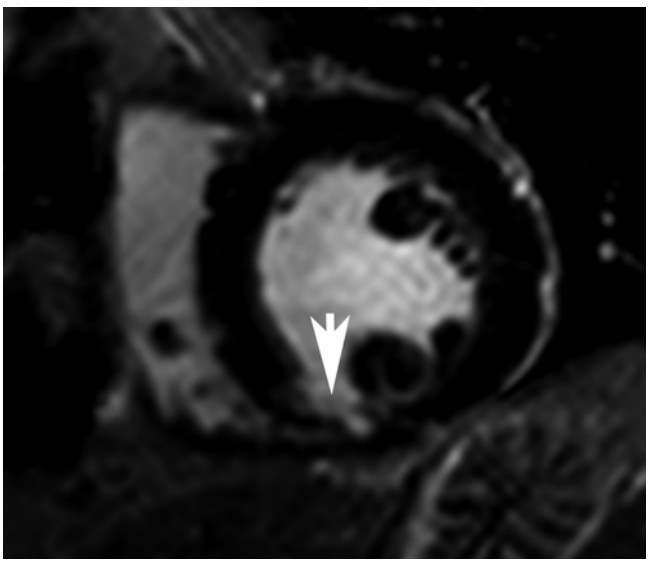

Fig. 5.3 Delayed enhancement short axis image demonstrating subendocardial enhancement of the inferior wall (*arrow*) segments representing scar/infarction

Absolute and Relative Contraindications

Before any MRI procedure, a patient should undergo a checklist screening and remove any metals from the body such as piercings, glasses, watches, hearing aids etc. The checklist should include any internal metals, such as pacemakers, stents, shrapnel etc. In addition, the patient should be asked about claustrophobia, because most MRI scanners consist of large, enclosed tubes with loud noises; claustrophobia is considered a relative contraindication to MRI.

Due to the relative longer duration of the CMR scan, and that cardiopulmonary resuscitation and other life saving techniques can not be performed while a patient is in the

scanning bed, unstable patients are generally considered to be an absolute contraindication to undergoing a CMR. Note that MR safe ventilators are available and intubation is not a contraindication for CMR.

The Food and Drug Administration has stated that the effects of MRI on the fetus is unknown, based on lack of long term studies on fetuses exposed to MRI [11]. The 2007 American College of Radiology Guidelines however state that pregnant patients can receive MRI if the benefit outweighs the risk to the mother and fetus [12]. Therefore, it is prudent to discuss the potential benefits of CMR and the potential risks to the fetus, including potential teratogenicity during the first trimester (although this has yet to be demonstrated in the human model) and theoretical acoustic damage [13].

Gadolinium has demonstrated clear teratogenic properties in pregnant patients, and has been labeled pregnancy class C by the Food and Drug Administration [12]. Gadolinium is recommended only if use is "absolutely necessary" and the benefit outweighs the potential harm. It is important to wait 24 h after gadolinium contrast administration before breastfeeding and any milk expressed during this time period should be discarded.

Several external and internal foreign bodies can be affected by CMR. Patient preparation can easily avoid complications, and all rings/jewelry, hearing aids, glasses and medications such as patches should be removed before imaging. Most relevant to the cardiologist are coronary stents and implanted pacemakers. It is important to note that devices are tested at a specific Tesla level, and devices labeled safe at 1.5 T may not be safe at a higher magnetic field level. Most coronary stents (even immediately following implantation), graft closure devices, PFO/ASD closure devices, inferior vena cava filters, coils and prosthetic/metal valves are labeled as MR safe according to the American Heart Association 2007 statement and can undergo ≤3 T MRIs following a brief manufacturing check [14]. It is also possible to look online for safety information at www.mrisafety.com. If devices are weakly ferratogenic, MRI safety should be individualized and it is prudent if possible to wait for up to 6 weeks following implantation.

Swan Ganz catheters and retained pacing leads are usually considered unsafe, secondary to possible movement and heating up of the catheter/leads within the pulmonary artery/cardiac tissue. Pacemakers and defibrillators have been generally considered an absolute contraindication to CMR, although newer studies have demonstrated safety, especially at the 1.5 T magnetic level [15]. Furthermore, when given the fact that 50–75 % of patients will have an indication for MRI during the lifetime of their device, it is an important area of research to find MRI safe devices and protocols for implantation [16]. This may be especially true for HCM patients, where the confluence of need for both ICD and MRI is high.

Further relative contraindications include patient's ability to perform breath hold maneuvers and follow simple instructions, be able to lie in the decubitus position for long periods of time and morbid obesity (>200 kg in most scanners). Claustrophobia (discussed above) occurs at a rate of 2–4 % [17].

CMR Applications in HCM

The role of non invasive imaging is paramount to the diagnosis of HCM. CMR can assess the size and function of the ventricles with accuracy, as well as help the clinician in differentiating similar disease presentations and echocardiographic findings. Valves, especially the aortic and mitral valve can be assessed in three dimensions; quantified gradients and flows across these valves can also be obtained, thus guiding the clinician in terms of valvular management and disease specific phenotypes.

Assessment of LV Volumes, Mass and Function

Cardiac MRI is considered the gold standard for the quantification of ventricular volumes, masses, and ejection fractions, with excellent spatial resolution, accuracy and reproducibility [18]. In CMR, short axis images are stacked using Simpson's method to obtain the minimum and maximum ventricular dimensions to define the endocardial and epicardial borders. Figure 5.4 The volume of each ventricular cavity can then be assessed by multiplying the difference between the maximum and minimum area and the slice thickness. Once this has been obtained, end-diastolic and end systolic volumes (EDV, ESV respectively) can be derived by adding the cavity volumes of different slices. Ejection Fraction and Stroke Volume can be calculated from the EDV and ESV.

Ventricular mass is calculated by multiplying the density of the myocardium (1.05 g/mL) by the volume of the total myocardium (mL^3). Note that papillary muscles are excluded from such calculations and are considered to contribute insignificant mass overall, although this may not always be the case in patients with HCM, some of whom have extensive papillary hypertrophy [19] (Fig. 5.5).

As in echocardiography, a 17-segment model of the LV is used, and each region is given a score based on the radial thickening [20].

Regional Morphology and Functional Assessment

The morphology and function are usually evaluated simultaneously using cine images with SSFP. Steady state free precession (SSFP) with contrast can determine T2/T1 ratios,

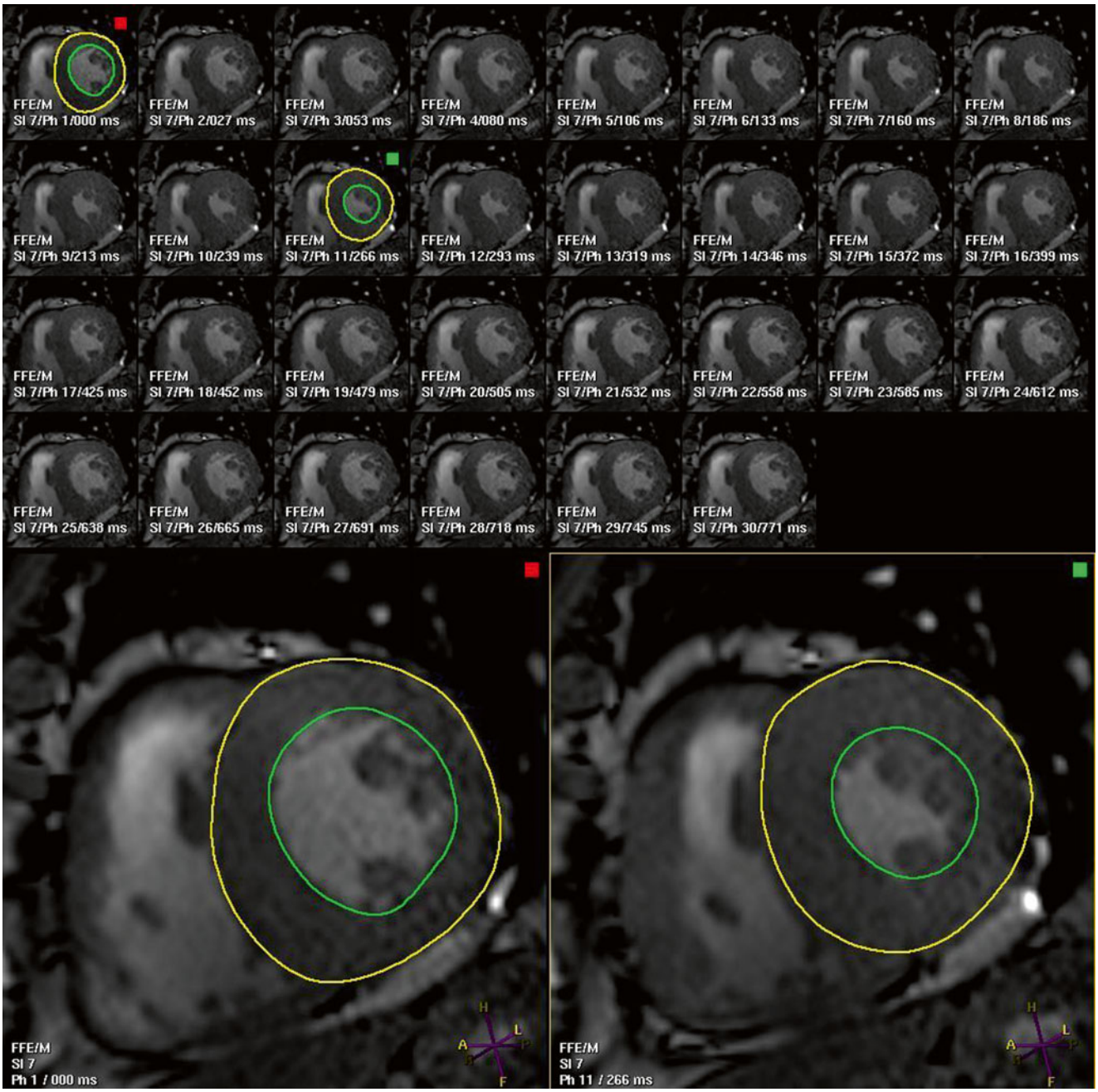

Fig. 5.4 Short axis cine stack demonstrating endocardial and epicardial contours in end-diastole and end systole for functional and volumetric analysis. The *yellow* and *green circle* represent the epicardial and endocardial borders of the left ventricle (*LV*), respectively

allowing for better definition of the endocardial border and less dependence on blood inflow. HCM can present as many different morphologic types characterized below. Hypertrophy in HCM can be focal or diffuse, with asymmetric septal hypertrophy the most common phenotype. In fact, more than 80 % of HCM patients have septal hypertrophy, 9 % have anteriorlateral free wall hypertrophy and apical, mass-like and mid-LV make up the rest of the HCM morphologic expressions [21]. The apical form has been shown to be more common in Asia, however. Figure 5.6 Prognosis is usually unaffected by the morphologic type, but rather dependent on extent of maximal thickness, in graded fashion [22].

Asymmetric Septal Hypertrophy

Asymmetric septal hypertrophy is the most common HCM morphologic presentation. Patients may present asymptomatic, with dyspnea, syncope, chest pain or sudden death [23]. There is up to a 30 % chance of resting obstruction of the LVOT with asymmetric hypertrophy during systole [24]. This obstruction can be present at rest, dynamic with increased cardiac contraction, or labile (occurring at random times), and therefore in total it is now felt that resting or labile obstruction is present in the majority of patients with HCM [25]. Its presence can be affected by preload, afterload and contractility [26]. Diagnosis based on CMR is made

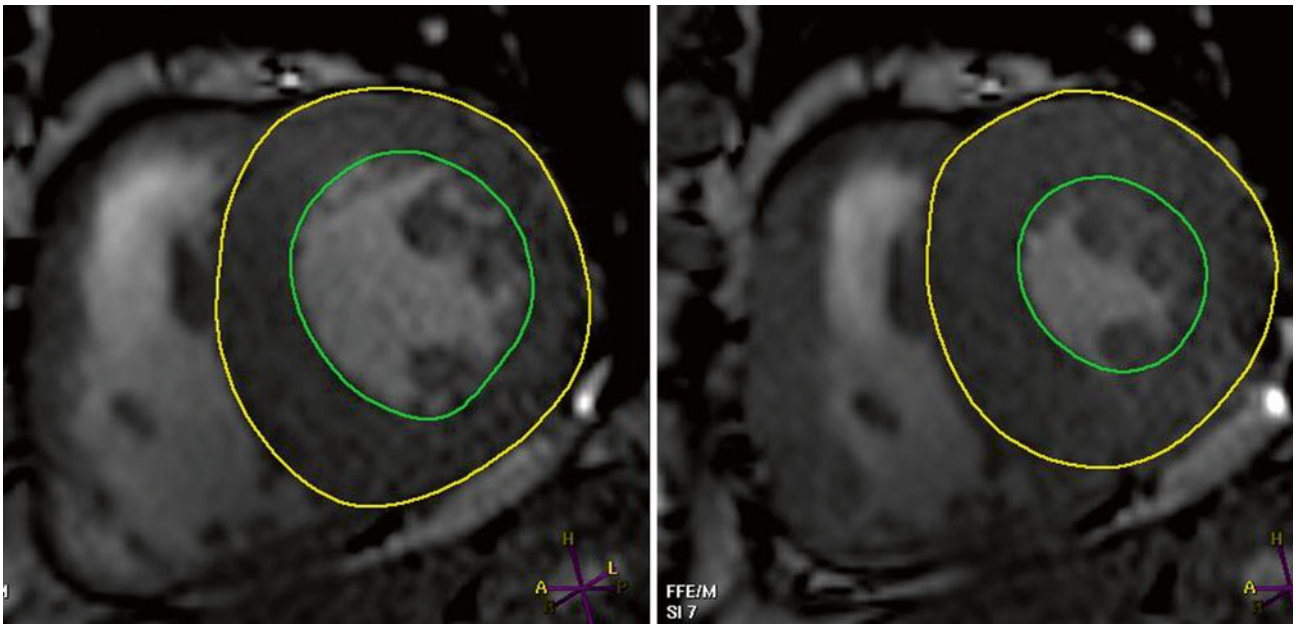

Fig. 5.5 Short axis cine image showing end-diastole and end-systole excluding papillary muscles for functional and volumetric analysis. The *yellow* and *green circle* represent the epicardial and endocardial borders of the left ventricle (*LV*), respectively

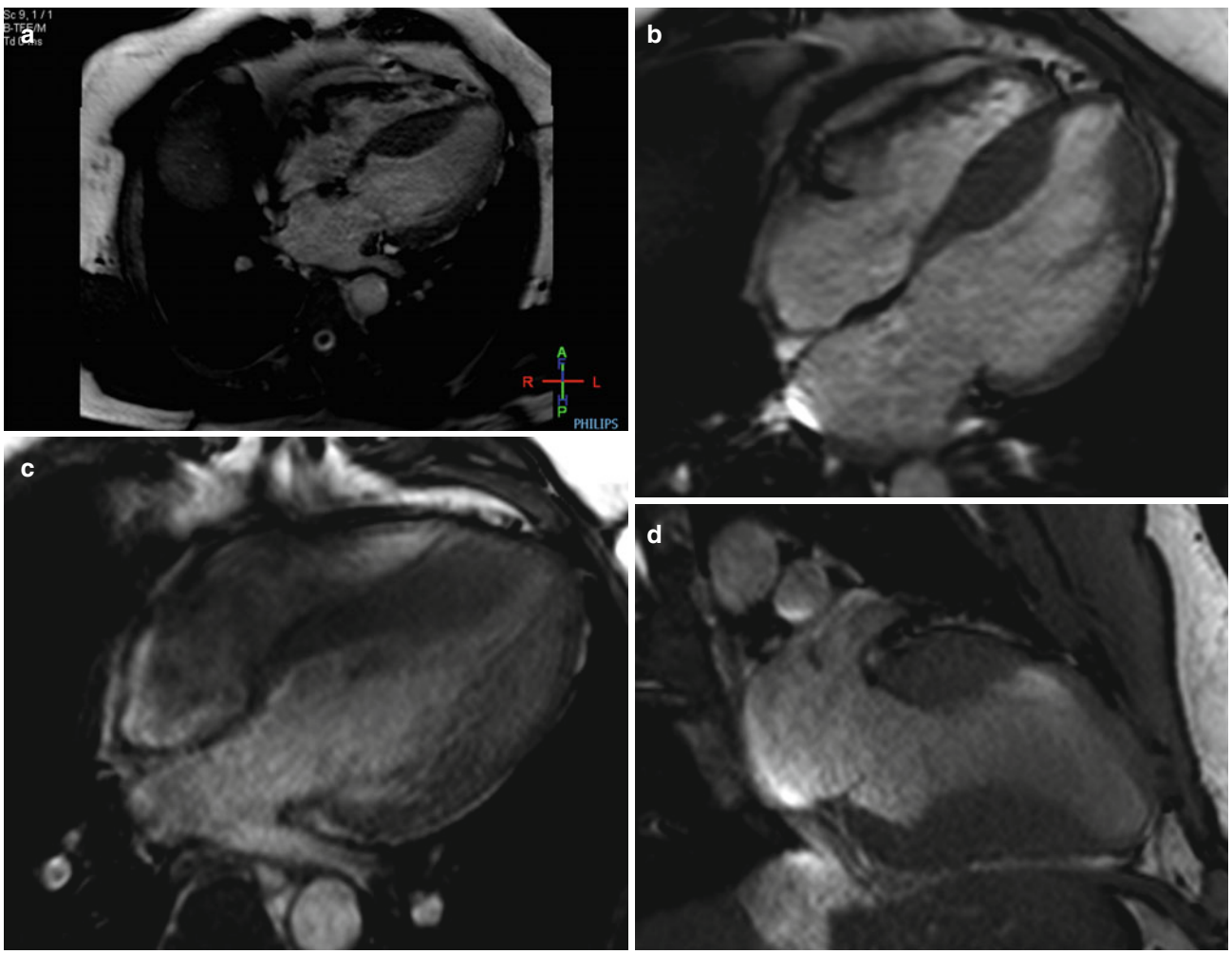

Fig. 5.6 SSFP cine image demonstrating (**a**) four chamber view with mid septal hypertrophic cardiomyopathy, (**b**) four chamber view with mid septal and distal lateral wall hypertrophic cardiomyopathy, (**c**) four chamber view with apical hypertrophic cardiomyopathy, and (**d**) two chamber view with basal anterior and mid inferior hypertrophic cardiomyopathy

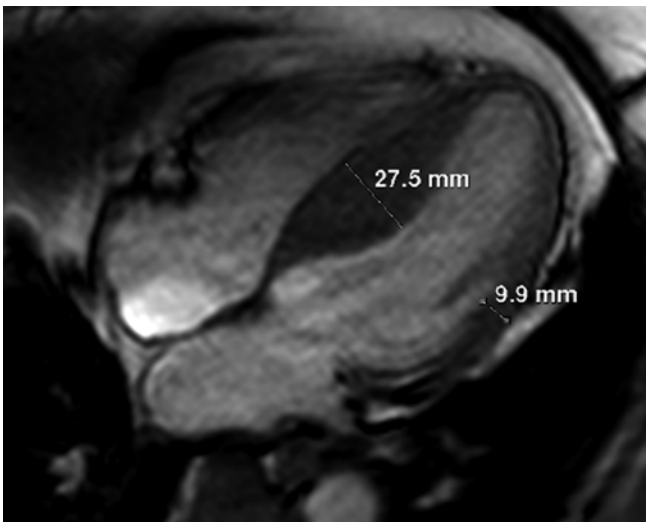

Fig. 5.7 SSFP cine image showing >1.5 cm thickness in the septum with a >1.3 ratio of septum to lateral LV wall

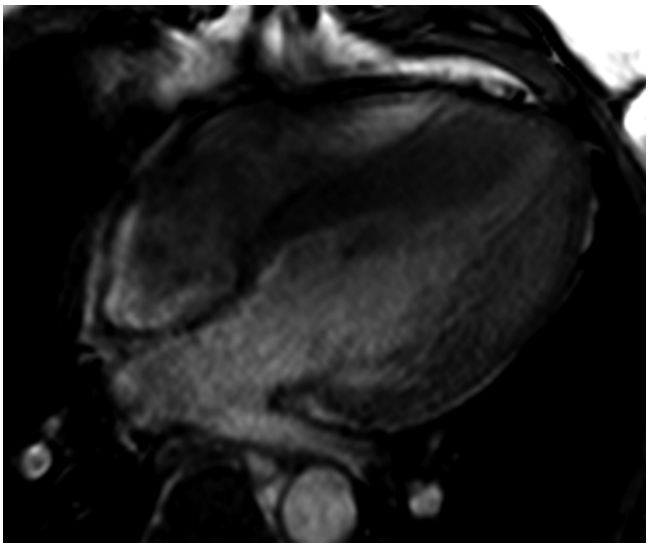

Fig. 5.8 SSFP cine image of apical hypertrophic cardiomyopathy

when the inter-ventricular septum is ≥15 mm in end diastole and the ratio of septum to lateral LV wall is ≥1.3 in normotensive patients or ≥1.5 in hypertensive patients without left ventricular hypertrophy [27]. Asymmetry in and of itself, in the absence of qualifying maximal thickness, is not considered diagnostic of HCM. Figure 5.7 These findings correlate with echocardiography, where similar criteria apply. Valente et al. [28] and Devlin et al. [29] examined the utility of echocardiography and CMR directly to diagnose HCM in patients with and without left ventricular hypertrophy. While both CMR and echocardiography reached the same conclusion 90 % of the time, both authors concurred that CMR is superior to echocardiography in diagnosing HCM, likely secondary to increased detail in anatomical reading as well as less geometric assumptions and miss with CMR. Indeed, CMR excels at areas of the heart typically difficult to visualize with echocardiography, such as the apex and areas of the lateral wall. In addition, RV structure and function, including RV outflow tract obstruction, can also be visualized.

Apical HCM

Apical HCM is more common in Asian populations then Western countries, and rates of occurrence vary as high as 25 % in Japan to less than 2 % in Western regions [30]. In up to half the cases, EKG readings will show deeply negative T waves in the precordial leads (>10 mV), although there is no correlation between the extent of the T wave depressions and wall thickness [30, 31]. Apical HCM is commonly missed on standard echocardiography due to foreshortening of the apex, although some studies have shown a >90 % sensitivity, and use of contrast agents can substantially aid in echocardiographic diagnosis [20]. The diagnostic criteria for apical HCM is an absolute apical wall thickness of >15 mm or the ratio of apical LV and basal LV wall thickness totaling ≥1.3–1.5 [20, 31]. Figure 5.8 Other possible signs include a failure to identify a decreased wall thickness towards the apex of the heart and obliteration of the LV apical cavity during systole. Apical HCM carries a better prognosis, with lower symptom burden and a higher long term survival, likely because hypertrophy does not extend beyond the mid-ventricle level and therefore does not block the LVOT, although a few studies have shown that this is not an entirely benign phenotype [32, 33]. Indeed, some patients are plagued by severe diastolic dysfunction and reduction in cardiac output due to substantial cavity obliteration (small volumes) and impaired tissue diastology.

Atypical Presentations

Previously, it was assumed that asymmetric septal hypertrophy was the only phenotype of HCM. However, it has been shown that HCM can occur as diffuse global hypertrophy or focal segmental hypertrophy, as well as many other atypical patterns.

Focal segmental hypertrophy may only involve one or two segments, with hypertrophied segments separated by normal regional wall thickness [34]. Figure 5.9 This is distinguished from hypertensive heart disease, which would cause global hypertrophy, and HCM, where LV mass is usually increased. This phenotype can occur in up to 12 % of HCM patients and is challenging to be detected by transthoracic echocardiography due to acoustic window limitations, leading to 6 % of HCM patients being missed [23, 34].

Mid-LV concentric hypertrophy is another uncommon form of HCM, leading to mid-LV obstruction and apical akinesis or aneurysms. Occurring in 2.2 % of HCM patients, concentric hypertrophy leads to an intercavitary pressure

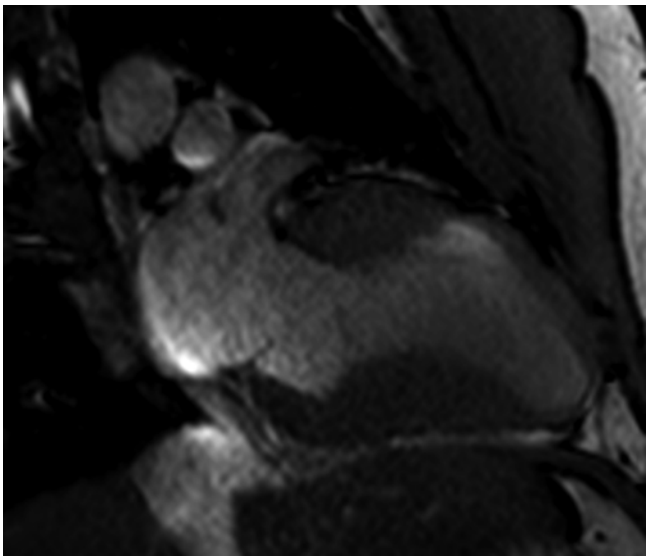

Fig. 5.9 SSFP cine image demonstrating hypertrophic cardiomyopathy involving two different (anterior and inferior) myocardial territories

gradient in the apical LV, result in aneurysm formation and increased risk of progressive heart failure, thromboembolic phenomena and sudden death [35].

Rarely, HCM can present as a mass-like thickening of the LV, which unlike a true mass (vegetation, tumor etc.) will demonstrate contractile properties. MR tagging is a useful tool in this scenario (see below) which highlights the contractile mass in HCM but will not tag a tumor [36].

Whereas echocardiography remains the reference standard for evaluation of the mitral valve leaflets, quantification of LVOT gradients and dynamic assessment during exercise and load altering maneuvers, CMR provides more complete assessment of the subvalvular apparatus, including the papillary muscles.

Abnormal Papillary Muscle Morphology

HCM patients have a higher incidence of abnormal papillary muscle morphology, such as bifid or multiple accessory papillary muscles [37]. Abnormal placements, such as anteroapical papillary muscles, can displace into the LVOT during systole and be a cause of obstruction [37, 38]. Additionally, these patients are at increased risk for systolic anterior motion (SAM, see below) and higher left ventricular outflow tract (LVOT) gradients independent of septal wall thickness, which in some cases can be normal [39]. In fact, this may be the only abnormality seen on CMR, and patients can have LVOT obstruction without cardiac muscle hypertrophy.

Mitral Valve Anomalies

The mitral valve is the most common valvular abnormality associated with HCM. It is independently related to abnormal genetics of HCM and Echocardiography and CMR are required for detecting and defining its abnormalities [40]. Furthermore, unrelated primary pathologies such as rheumatic heart disease or myxomatous degeneration may confound diagnosis. Common disorders of the mitral valve related to HCM include increased leaflet area (with elongation of one cusp or leaflet), abnormal origination and/or insertion of the papillary muscles and abnormal systolic anterior motion (which is the most common abnormality seen) [41, 42] (Fig. 5.10)

Systolic anterior motion (SAM) results from a longer anterior leaflet, leading to exaggerated anterior motion and obstruction of the LVOT. The papillary muscle inserts directly into the anterior leaflet in 10 % of patients with obstructive HCM without the chordae tendinae connecting to it [22]. The severity of the resulting mitral regurgitation (MR) secondary to SAM is directly proportional to the severity of the LVOT gradient [43]. Alternative diagnosis, such as vegetations on the valve, mitral valve prolapse and severe mitral annular calcification (MAC) should be excluded and are readily differentiated on CMR. Of note, patients with long standing SAM can develop fibrosis of the anterior mitral leaflet due to contact with the septum and can independently lead to mitral regurgitation [44]. Elongated, redundant cords, which may contribute to outflow tract obstruction or mitral regurgitation, can also be evaluated by MRI.

MR Tagging for Strain Analysis

MR tagging is a technique that can be used to assess the function of the myocardium. In this technique, RF pulses are delivered immediately after the QRS complex. This nulls the signal in planes perpendicular to the image leading to a grid of dark lines (tags) that can be visualized and tracked during the cardiac cycle. Figure 5.11 Quantification of tag changes reveals the deformation and displacement of the myocardium, giving accurate regional and overall systolic and diastolic functions. In other words, the radial, longitudinal and circumferential strains, ventricular torsion and strain rates are obtained. Harmonic phase analysis greatly reduces the post-processing times, making this a valuable tool for assessment of myocardial function and strain. Phase displacement encoding can further lead to increased spatial and temporal resolution strain quantification [33].

Evaluation of LV Outflow Tract Obstruction

Left ventricular outflow tract obstruction (LVOTO) (at baseline or provocable) is present in 70 % of the cases of HCM and directly relates to the disease's pathophysiology as well as treatment considerations [45]. In most patients, septal hypertrophy leads directly to LVOT obstruction, although patients can have hypertrophy without obstruction

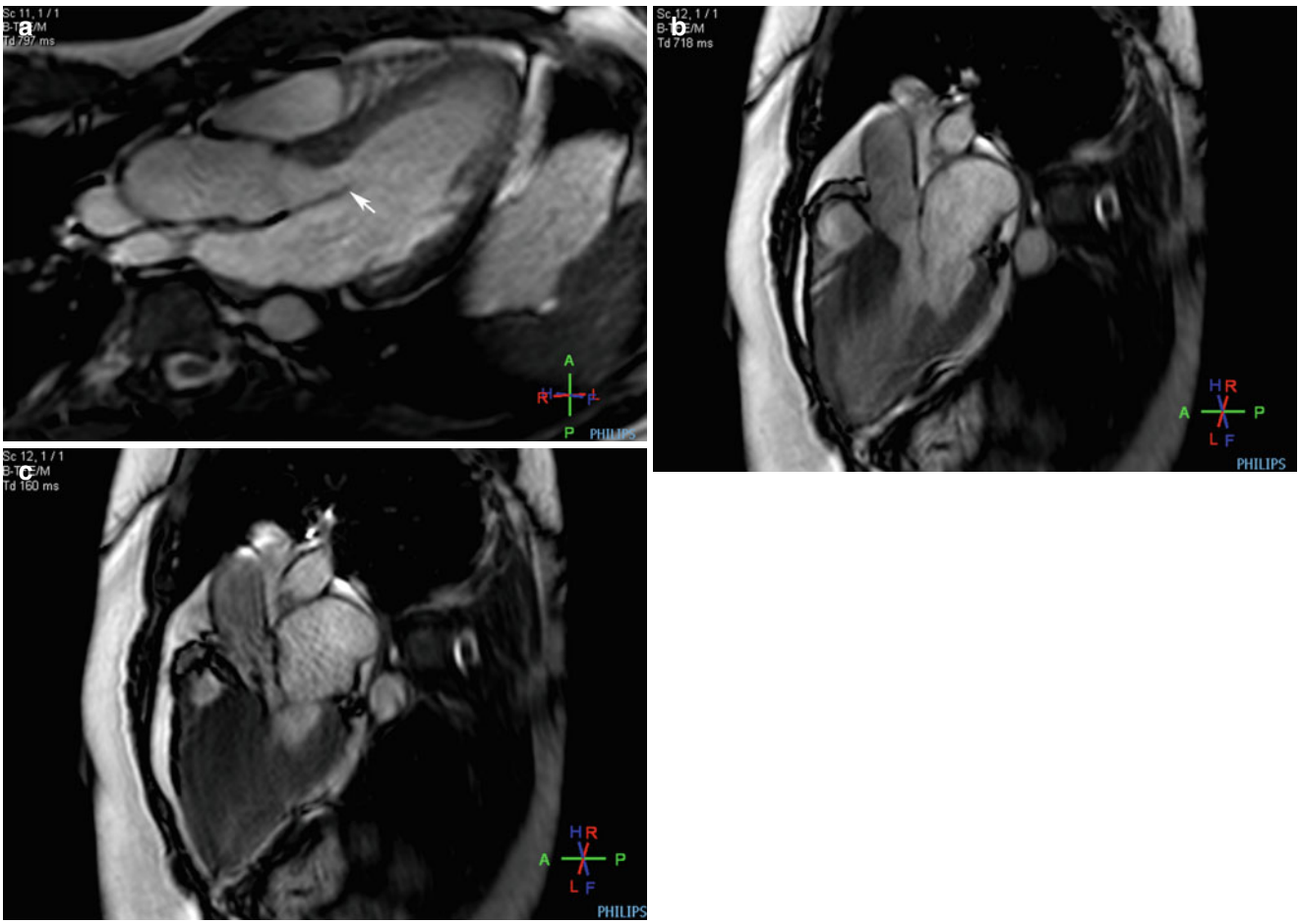

Fig. 5.10 SSFP three chamber cine image showing (**a**) redundant anterior mitral valve leaflet (*arrow*), (**b**) narrowed left ventricular outflow tract during diastole, (**c**) significant left ventricular outflow obstruction during systole

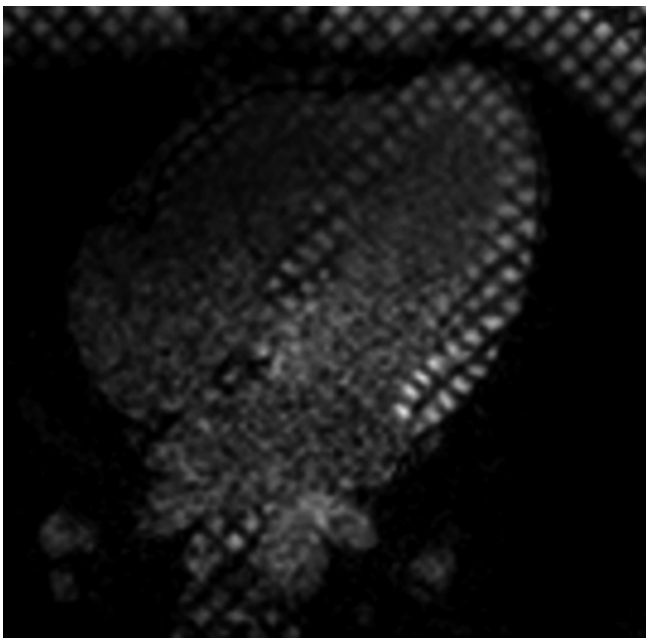

Fig. 5.11 Four chamber view with MRI Tagging sequence.

and vise-versa. HCM patients without hypertrophy but with LVOT obstruction are due to papillary muscle and subvalvular abnormalities, such as membranes [38]. Mid-ventricular obstruction should also be considered, due to concentric hypertrophy. While echocardiography, whether transthoracic or transesophageal, is initially used to quantify the LVOT gradients, CMR has the ability to define the anatomy of the papillary muscles, the systolic anterior motion contact, concomitant mid-venticular hypertrophy and membranes, and give incredible detail to the subvalvular apparatus. Short axis cine images are used to evaluate the LVOT while long axis cine images can demonstrate the subvalvular anatomy, especially in patients without asymmetric septal hypertrophy but with LVOT obstruction. Next a three dimensional LV is created with gating of the whole heart, allowing for reconstruction of the papillary muscles and the subvalvular apparatus. Accurate evaluation of the level of obstruction is vital when contemplating septal reduction therapy in particular, as alcohol septal ablation is typically reserved for patients with outflow tract obstruction due to asymmetric basal septal hypertrophy and SAM.

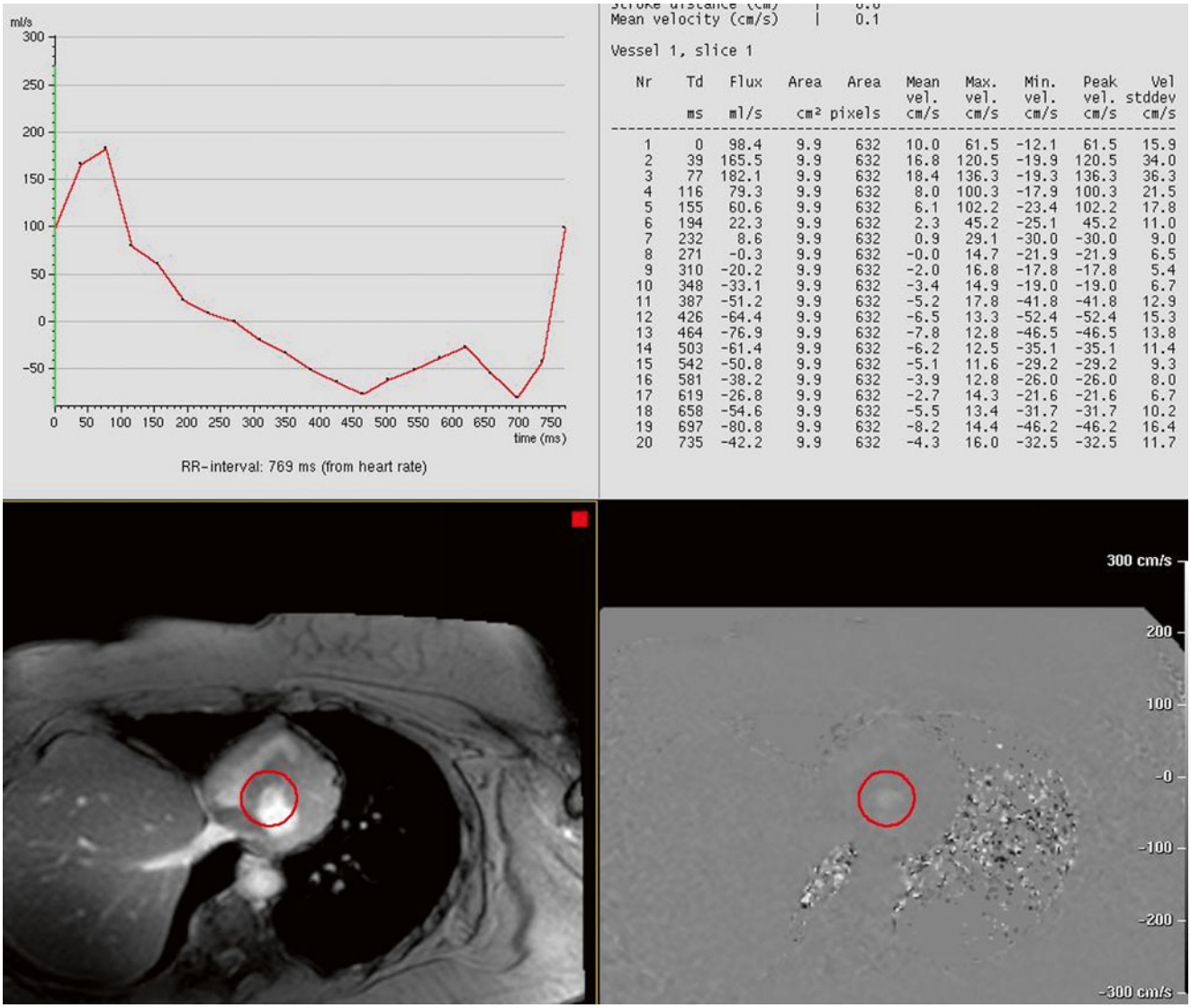

Fig. 5.12 Phase contrast imaging of a short axis view with the region of interest at the left ventricular outflow tract demonstrating no significant gradient with a maximum velocity of 136.3 cm/s

While LVOT gradients, acceleration and flow turbulence can be measured using CMR, echocardiography remains the gold standard. Flow sensitive gradient echo in CMR is used to define flow turbulence and acceleration while phase contrast flow-sensitive sequences are used to estimate the LVOT gradient. Figure 5.12 Precise alignment, signal loss and provocation during exercise can all confound the techniques described above. Newer CMR sequences, such as three dimensional flow pattern/velocities not limited to imaging planes, real time velocity encoding and accurate sequence enhanced turbulent jet velocities, may all contribute to an accurate assessment of LVOT functionality [46–48]. Despite the dynamic nature of the LVOT, if gradients are found to be >30 mmHg, it denotes an increased risk of stroke, heart failure, arrhythmia and sudden cardiac death [45].

Qualitative and Quantitative Assessment of Mitral Regurgitation

CMR has the ability to image valve morphology in any plane without the limitation of poor acoustic windows or supra-sub valvular disease (i.e. membranes). However, echocardiography has a high temporal and spatial resolution (especially trans-esophageal) for highly mobile structures, such as leaflet abnormalities, vegetations and ruptured chordae tendonae and can be obtained in real time, making it the test of choice for these diagnoses. Images are obtained in CMR through SSFP, although fast GRE sequences can result in less artifact in areas of pulsatile flow. Turbulent flow, such as in mitral regurgitation, are seen as areas of signal void (spin dephasing) in SSFP and fast GRE bright blood images [49]. Figure 5.13 By mea-

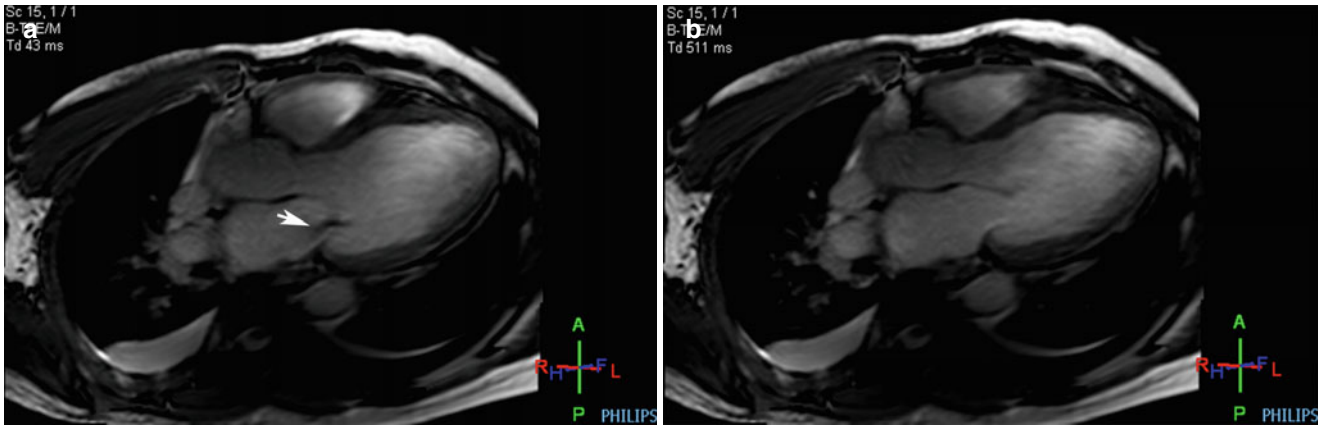

Fig. 5.13 SSFP three chamber cine image demonstrating significant mitral regurgitation with turbulent flow (*arrow*) during systole (**a**) in comparison to in diastole (**b**)

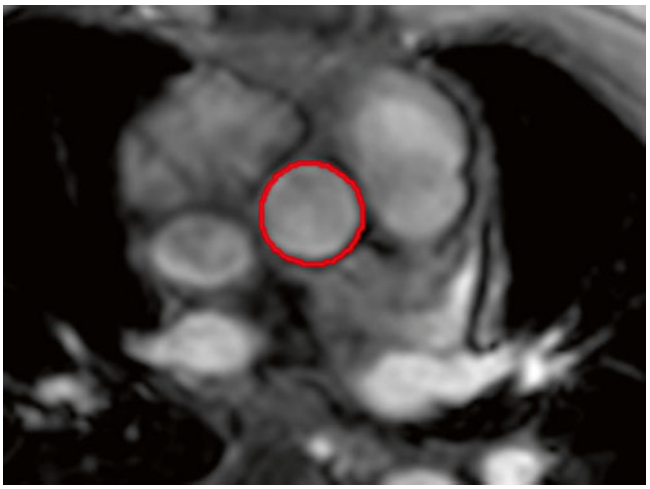

Fig. 5.14 Phase contrast imaging of the ascending aorta. The *red circles* represent the Contour of the ascending aorta

suring the size of the signal void, a semi quantitative disease severity can be obtained. However, like echocardiography, several imaging parameters such as angle, velocity of the jet and dispersion of flow can skew the true size of the regurgitant jet. CMR however, is able to truly quantify regurgitant jets using volumes determined from the difference in left and right ventricular SV calculations in cine imaging (see section i.). For the atrioventricular valves, specifically the mitral valve, the difference between the LV SV (from cine images) and forward SV (from phase contrast images of the ascending aorta [Fig. 5.14]) is obtained, and using the equation below, the exact quantification of the regurgitant jet is elicited:

Regurgitation Fraction = Regurgitation Volume/Total SV

Important clues regarding the MR jet can lead to phenotypic information for HCM patients. For example, if the MR jet is posterior, then most likely the patient has SAM as the etiology, while a anterior/medial jet is a sign of posterior motion [39]. As discussed above, if MR is related to SAM, then relieving obstruction and correcting hemodynamics will treat both MR and LVOT obstruction. However, if MR is independent of SAM in a HCM patient, then surgical treatment for a primary or concomitant valve pathology may be required.

Myocardial Perfusion and Delayed Enhancement

Myocardial perfusion and delayed enhancement is increasingly being used in the risk stratification of HCM patients, and it is well known that myocardial ischemia contributes to angina, dyspnea, heart failure, arrhythmias and sudden death [50]. This is most easily accomplished with visual interpretation, with the main limitation being dark rim artifacts (blood at the endocardium border resulting in hypointensity). Some common causes of this artifact are insufficient k space sampling, motion artifact or contrast-related magnetic susceptibility, especially using SSFP sequences, higher dye loads and faster injection rates [8]. To eliminate dark rim artifact, stress and rest images are compared, to see if the dark rim artifact is present in both types of imaging.

Perfusion abnormalities can be demonstrated with single photon computed tomography (SPECT), positron emission tomography (PET) and CMR via first pass perfusion. In the absence of significant coronary artery disease, midwall perfusion defects during adenosine stress can be seen in the hypertrophied segments, which demonstrates MVO. Figure 5.15 As one would expect, the presence of perfusion abnormalities correlates with a poor prognosis. In one prospective study, 51 patients with HCM found that those with an abnormal vasodilator response had a strongly predictive negative outcome [50].

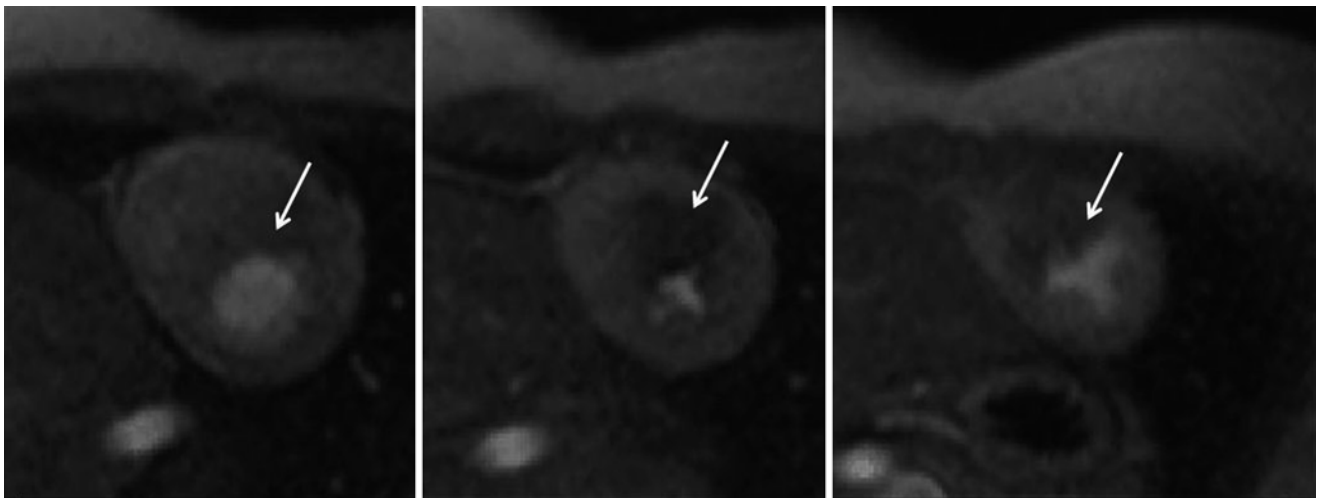

Fig. 5.15 Stress adenosine MRI showing basal to apical short axis views with perfusion defects (*arrows*) in the mid hypertrophied septum demonstrating microvascular ischemia

Delayed enhancement with Late Gadolinium Enhancement (LGE) is used to assess normal myocyte uptake and architecture, and has the ability to distinguish normal, infarcted tissue, stunned myocardium and fibrosis [10]. LGE is either qualitatively or quantitatively performed, with quantification and phase sensitive inversion recovery (STIR) sequences done to improve accuracy. However, in HCM analysis, it can be used to assess increased myocardial fibrosis secondary to collagen deposition. Fibrosis in the setting of HCM has been associated to microvascular ischemia, coronary arteriole dysplasia, and/or sarcomere gene mutations [31, 51]. Owing to the heterogeneity of HCM several patterns of LGE exist, such as subendocardial to transmural LGE which may be difficult to distinguish from coronary artery disease, to high enhancement at the insertion point of the right ventricle into the ventricular septum, and most commonly patchy intramyocardial LGE which may appear similar to infiltrative diseases [52]. Figure 5.16 Interestingly, areas of increased fibrosis also correlate with areas of wall motion abnormalities, and tend to occur in the thickest segments of the heart affected by HCM [53]. Similarly, hyperenhancement has been found in a majority of HCM patients corresponding only to areas of hypertrophy and scarring, mainly in middle third of the ventricle in a multi-focal distribution, although the right ventricle can also be involved [54, 55]. This is thought to correlate to areas of myocardium susceptible to ventricular arrhythmias, ectopy and ICD discharges [56]. Initial trials, despite a low predictive value, showed that LGE correlates with the risk of sudden cardiac death [57]. Furthermore, a meta-analysis done by Green et al. [58] showed that LGE has prognostic value to predict cardiovascular mortality, heart failure death and all cause mortality, although the relationship with sudden cardiac death was not significant. According to the most recent ACC/AHA guidelines published in 2011 however, there is no consensus regarding when or if LGE should be performed in the clinical assessment of HCM assessment, although it is increasingly utilized by experts in the field [56]. Indeed, many experts utilize the extent of LGE as a risk modifier that aids in determination of the need for ICD implantation in borderline cases.

Differential Diagnosis

A multitude of diseases can mimic HCM, both in terms of symptoms and EKG, as well as CMR. The most common diseases that are confused with HCM are hypertensive heart disease and aortic stenosis. Both present with concentric hypertrophy, instead of asymmetric LV hypertrophy as HCM. Figure 5.17 In general, hypertension leads to an increase in LV wall thickness that is <15 mm. Note that myocardial fibrosis on LGE sequences can occur in hypertensive, HCM, and aortic stenosis heart disease [59, 60]. In the rare case of HCM patients with aortic stenosis, CMR can identify the jet turbulence to distinguish if it is coming predominantly from the ventricle or the aortic valve.

Since most patients with HCM are diagnosed at a young age, athlete's heart is also in the differential. Athlete's heart is characterized by symmetric LV thickening that is less than 15 mm, and normal function on Doppler echocardiography (to distinguish from hypertensive heart disease). CMR is able to accurately measure LV volumes, mass and function, with the wall thickness indexed to the end-diastolic ventricular volume allowing for distinction between athlete's heart and HCM [61].

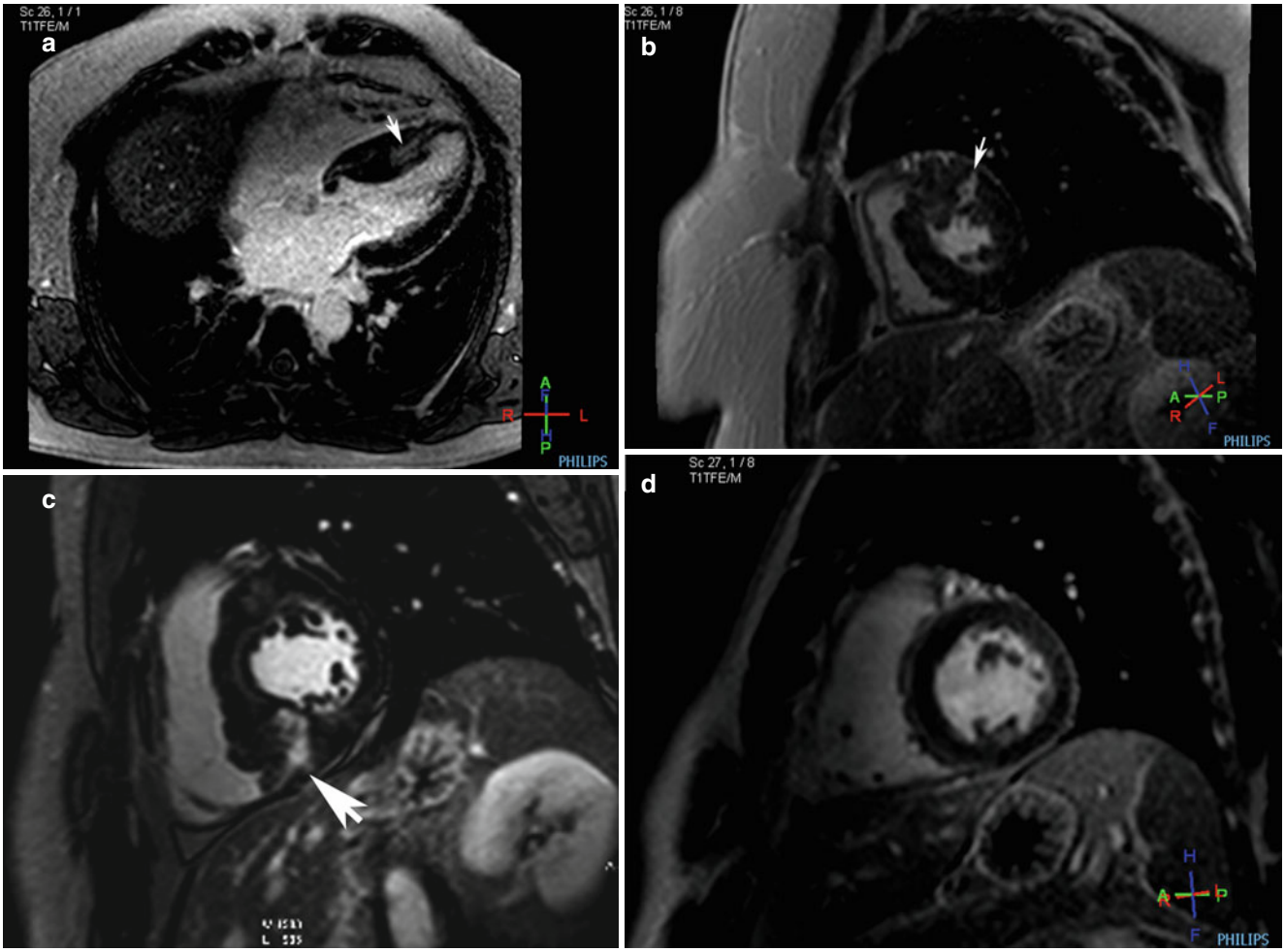

Fig. 5.16 Delayed enhancement imaging demonstrating (**a**) four chamber view with intramyocardial patchy fibrosis (*arrow*) of the septal wall, (**b**) short axis view with patchy intramyocardial fibrosis of the anterior wall (*arrow*), (**c**) short axis view with patchy fibrosis of the right ventricular insertion points (*arrow*), and (**d**) short axis view showing linear midwall fibrosis of the septal wall

Ventricular noncompaction is another disease that can mimic HCM. In noncompaction, there are prominent LV trabeculations. Figure 5.18 CMR can distinguish between compacted and noncompacted layers, with an end-diastolic ratio of compacted to noncompacted layers of >1:2.3 being diagnostic. Additionally, CMR can reveal the transition zone between the two layers.

Valvular Aortic Stenosis

The approach to valvular aortic stenosis is similar with MRI and echocardiography. Phase contrast images and velocities can be used along with the modified Bernoulli equation ($\Delta P = 4\ V^2$) to obtain accurate mean and peak pressure gradients. The point of maximum velocity can be obtained through in plane and through plane phase contrast imaging, or by measuring the flow at the LVOT and the tip of the aortic leaflets to obtain the velocity-time integrals (VTI). With LVOT measurements (mentioned above), the aortic valve area (AVA) can be calculated by using the same continuity equation used in echocardiography [62].

By using SSFP images, direct planimetry cine images can be obtained, most commonly by using several thin (5 mm) contiguous images parallel to the annulus and extending across the valve in order to capture the tips of the leaflets. Figure 5.19 The valvular orifice is traced during maximal opening in the most distal slice and calcifications resulting in signal void are generally included.

Subaortic Membrane

Once thought to be a disease only in children, subaortic membranes leading to discrete subaortic stenosis and regurgitation has been shown in adult populations [63]. In this disorder, a congenital or acquired subaortic membrane

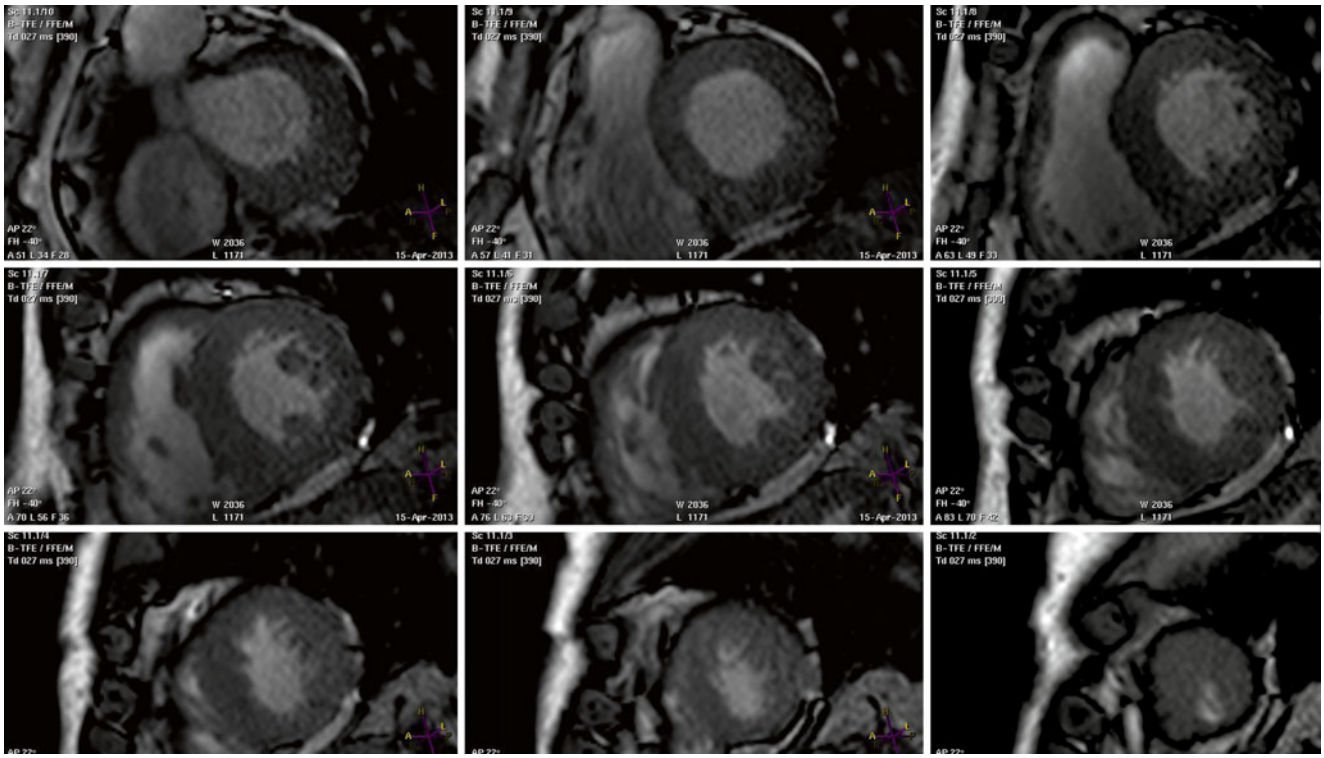

Fig. 5.17 SSFP short-axis cine stack demonstrating concentric left ventricular hypertrophy

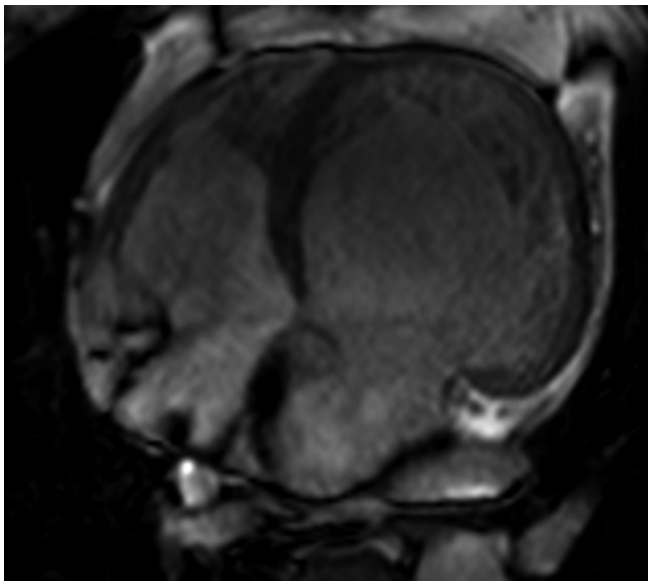

Fig. 5.18 SSFP four chamber cine image demonstrating left ventricular non-compaction

forms, leading to a fixed defect resulting in combined aortic stenosis and regurgitation secondary to blockage of the LVOT. This is associated with rheumatic mitral valve disease most commonly, however patients can have ventricular septal defects, coarctation of the aorta and bicuspid aortic valvular stenosis [63]. Subaortic membranes usually lead to progressive LVOTO and are usually corrected surgically. Although the membrane itself may be difficult to visualize by CMR due to spatial resolution limitations, the diagnosis can be easily established by the detection of abnormal turbulent flow in the absence of valvular, muscular (i.e. asymmetric hypertrophy with SAM), or abnormal papillary/chordal substrate.

Infiltrative Cardiomyopathies

Infiltrative heart diseases can also mimic HCM, with various CMR techniques allowing for distinction between the two entities. Amyloidosis causes diffuse LV wall thickening and diffuse LGE, with shortening of the null time on inversion recovery sequences [64, 65]. Figure 5.20 Sarcoidosis presents as restrictive cardiomyopathy with generalized LV thickening. The LGE pattern usually involves the basal and lateral segments and asymmetric basal septal involvement is possible [66]. Hypereosinophilic syndrome can lead to apical fibrosis and cavitary obliteration and apical mural thrombus, mimicking apical HCM on TTE [67]. Fabry's disease, an X-linked glycolipid storage disease, results in concentric hypertrophy with a fifty percent chance of LGE, usually in the basal inferiolateral region on CMR [31]. Genetic testing may be useful in Fabry's disease as well.

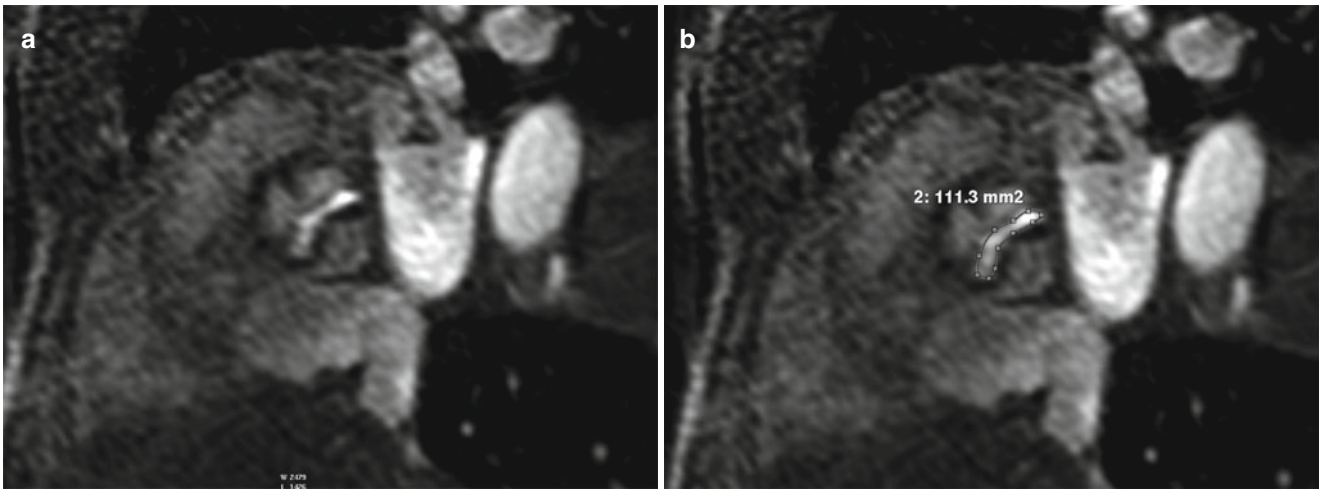

Fig. 5.19 Short axis SSFP view during systole (**a**) showing a bicuspid aortic valve and (**b**) planimetry of the valve demonstrating moderate aortic stenosis

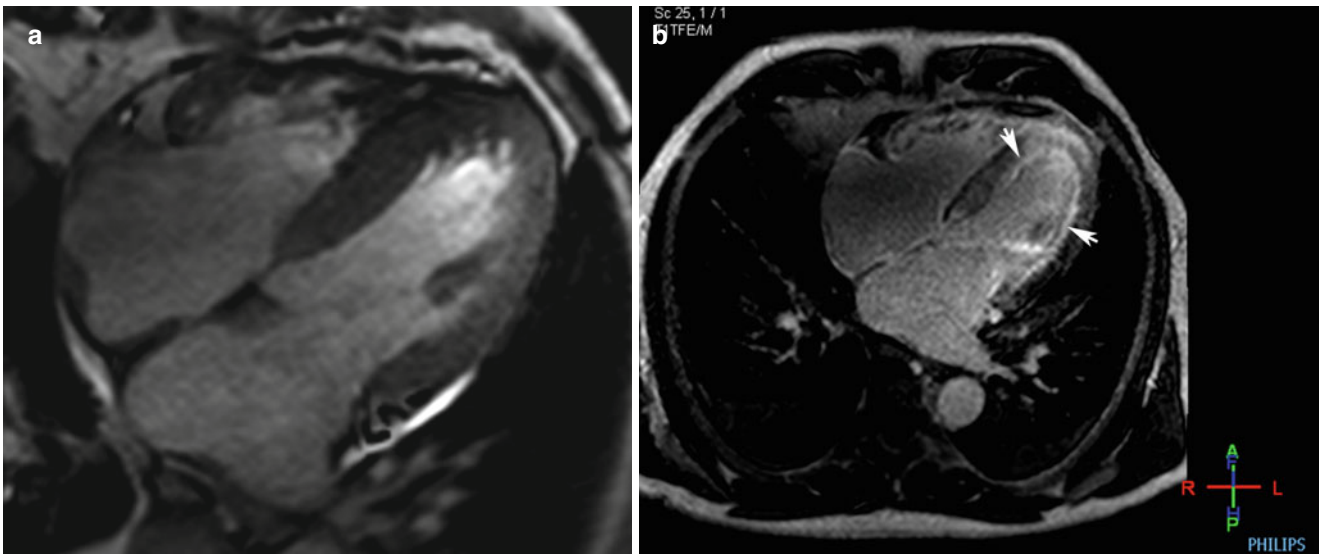

Fig. 5.20 (**a**) Four chamber SSFP image of a patient with cardiac amyloidosis. (**b**) Delayed enhancement four chamber image of diffuse subendocardial enhancement (*arrows*) in the same patient with amyloidosis

Practical Implications

In clinical practice, there is variation in the use of cardiac MRI, with some HCM programs electing to perform cardiac MRI on all patients with HCM and other programs invoking a more selective strategy. Routine MRI at the time of initial diagnosis can aid in a more robust understanding of structure and function, elimination of alternate diagnoses, as well as define more accurately the maximal thickness of the ventricle at all locations. In addition, data regarding LGE is available and can aid prognosis determination and supplement decision-making, especially with regards to ICD implantation. On the other hand, cardiac MRI is costly and some programs favor a more selective approach. These programs utilize MRI when patients have some risk factors for SCD, but the added information of LGE extent would be helpful in making a final decision. In addition, patients with mild or borderline LVH by echocardiography may be found to have larger degrees of LVH by MRI, thereby confirming a diagnosis. Patients with gene positive phenotype negative by echocardiography may actually be phenotype positive by MRI, prompting a confirmation of diagnosis and further treatment, including lifestyle modification. This is important given that the number of patients identified as carriers has increased with the advent of commercial gene testing. And, on the other end of the spectrum, patients with >2.5 cm thickness may have higher

degrees of hypertrophy elucidated by MRI that would place them at high enough risk of SCD to warrant ICD implantation. Finally, patients in whom an alternate diagnosis is suspected, such as amyloidosis, sarcoid or non-compaction, or in whom areas of the heart are poorly visualized by echo due to body habitus or acoustic windows, such as the apex or lateral walls, are good examples of when selective cardiac MRI may be considered. According to the guidelines, a routine application is currently not recommended; rather MRI is advised in a more selective approach, as described above.

Future Directions

Non invasive cardiac imaging has provided important insights into the phenotypic expression, natural history, prognosis and treatment of hypertrophic cardiomyopathy patients. Evolution of CMR technology, such as real time imaging, inversion recovery and enhancement will lead to a better understanding of the clinical significance of various phenotypic expressions in HCM. Genetic testing, such as sarcomere mutations, coupled with advanced imaging, will allow for early detection of disease, before overt symptoms are present. This will help facilitate treatment monitoring and strategies, as well as allow for specific prognostication, not just for patients but for families. Future CMR techniques will give quantification to gradients, rotation, torsion and twist which will drive diagnosis and treatment tailored to the individual.

Clinical Pearls

- In patients with signs/symptoms of HCM, including abnormal electrocadiography, but without typical echocardiographic findings, think about performing CMR to detect atypical presentations like apical HCM or focal segmental HCM. This is especially true in patients of Asian descent, where apical HCM in particular has increased prevalence. Patients who are genotype positive but phenotype negative by echocardiography may be particularly well served by CMR for this purpose.
- In HCM patients with angina or heart failure symptoms, prompt CMR evaluation with delayed enhancement with gadolinium can be obtained to assess perfusion and scar. HCM patients are at increased risk for microvascular obstruction which can lead to the above symptoms and sudden death. Furthermore, delayed enhancement can aid in ICD implantation decisions, as significant delayed enhancement is a risk modifier.
- CMR is invaluable in distinguishing HCM from other cardiac diseases which can mimic HCM, such as hypertensive heart disease, athlete's heart, ventricular non compaction, infiltrative heart diseases and aortic stenosis. In cases where an HCM patient has aortic stenosis, CMR can identify the location of the turbulent jet to assess whether it is coming from the ventricle or valve.
- Guidelines have not yet defined absolute indications for when to perform CMR in patients with HCM. When known gene phenotypes are positive but echocardiographic findings are lacking, LV hypertrophy is borderline on echocardiography, or wall thickness is borderline for ICD implantation, CMR can help categorize these patients as truly having HCM or needing ICD therapy.
- Studies are ongoing in linking scar burden with prognosis, especially with regards to the incidence of end-stage systolic dysfunction or sudden cardiac death. To this end, patients should have cardiac MRI performed prior to implantation of a non-MRI safe ICD, so that such information is available for them in the future as the field evolves.

References

1. Bruder O, Schneider S, Nothnage D, Dill T, Hombach V, Schulz-Menger J, Nagel E, Lombardi M, van Rossum AC, Wagner A, Schwitter J, Senges J, Sabin GV, Sechtem U, Mahroldt H. EuroCMR [European Cardiovascular Magnetic Resonance] registry. J Am Coll Cardiol. 2009;54(15):1457–66.
2. Cerqueira MD, Weissman NJ, Dilsizian V, Joacobs AK, Kaul S, Laskey WK, Pennell J, Rumberger JA, Ryan T, Verani MS. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. Circulation. 2002;105:539–42.
3. Plein S, Bloomer TN, Ridgway JP, Jones TR, Bainbridge GJ, Sivananthan MU. Steady-state free precession magnetic resonance imaging of the heart: comparison with segmented k-space gradient-echo imaging. J Magn Reson Imaging. 2001;14:230–6.
4. Miller S, Simonetti OP, Carr J, Kramer U, Finn JP. MR Imaging of the heart with cine true fast imaging with steady-state precession: influence of spatial and temporal resolutions on the left ventricular functional parameters. Radiology. 2002;223:263–9.
5. Roussakis A, Baras P, Seimenis I, Andreou J, Danias PG. Relationship of number of phases per cardiac cycle and accuracy of measurement of left ventricular volumes, ejection fraction and mass. J Cardiovasc Magn Reson. 2004;6:837–44.
6. Nagel E, Schneider U, Schalla S. Magnetic resonance real-time imaging for the evaluation of left ventricular function. J Cardiovasc Magn Reson. 2000;2:7–14.
7. Jahnke C, Nagel E, Gebker R. Four-dimensional single breathhold magnetic resonance imaging using kt-BLAST enables reliable assessment of left- and right-ventricular volumes and mass. J Magn Reson Imaging. 2007;25:737–42.

8. Gerber BL, Raman SV, Nayak K. Myocardial first-pass perfusion cardiovascular magnetic resonance: history, theory and current state of the art. J Cardiovasc Magn Reson. 2008;10:18–36.
9. Jerosch-Herold M, Seethamraju RT, Swingen CM, Wilke NM, Stillman AE. Analysis of myocardial perfusion MRI. J Magn Reson Imaging. 2004;19:758–70.
10. Romero J, Kahan J, Kelesidis I, Makani H, Wever-Pinzon O, Medina H, Garcia MJ. CMR imaging for the evaluation of myocardial stunning after acute myocardial infarction: a meta-analysis of prospective trials. Eur Heart J Cardiovasc Imaging. 2013; 14(11):1080–91.
11. Chen MM, Coakley FV, Kaimal A, Laros Jr RK. Guidelines for computed tomography and magnetic resonance imaging use in pregnancy and lactation. Obstet Gynecol. 2008;112(2):333–40.
12. Kanal E, Barkovich AJ, Bell C, Borgstede JP, Bradley Jr WG, Froelich JW. ACR guidance document for safe MR practices: 2007. AJR Am J Roentegnol. 2007;188:1447–74.
13. Heinrichs WL, Fong P, Flannery M, Heinrichs SC, Crooks LE, Spindle A. Midgestational exposure of pregnant BALB/c mice to magnetic resonance imaging conditions. Magn Reson Imaging. 1988;6:305–13.
14. Levine GN, Gomes AS, Arai AE. Safety of magnetic resonance imaging in patients with cardiovascular devices: an american Heart Association scientific statement from the Committee on Diagnostic and Interventional Cardiac Catheterization, Council on Clinical Cardiology, and the Council on Cardiovascular Radiology and Intervention: endorsed by the American College of Cardiology Foundation, the North American Society for Cardiac Imaging, and the Society for Cardiovascular Magnetic REsonance. Circulation. 2007;116:2878–91.
15. Kanal E, Barkovich AJ, Bell C. ACR guidance document for safe MR practices. AJR Am J Roentgenol. 2007;188:1447–74.
16. Kalin R, Stanton MS. Current clinical issues for MRI scanning of pacemaker and defibrillator patients. Pacing Clin Electrophysiol. 2005;28(4):326–8.
17. Francis JM, Pennel DJ. Treatment of claustrophobia for cardiovascular magnetic resonance: use and effectiveness of mild sedation. J Cardiovasc Magn Reson. 2000;2:139–41.
18. McKenna WJ, Spirito P, Desnos M, Dubourg O, Komajda M. Experience from clinical genetics in hypertrophic cardiomyopathy: proposal for new diagnostic criteria in adult members of affected families. Heart. 1997;77:2.
19. Colan SD, Lipshultz SE, Lowe AM, Sleeper LA, Messere J, Cox GF, Lurie PR, Orav EJ, Towbin JA. Epidemiology and cause-specific outcome of hypertrophic cardiomyopathy in children: findings from the Pediatric Cardiomyopathy Registry. Circulation. 2007;115:6.
20. Eriksson MJ, Sonnenberg B, Woo A. Long-term outcome in patients with apical hypertrophic cardiomyopathy. J Am Coll Cardiol. 2002;39:638–45.
21. Olivotto L, Maron MS, Autore C, Lesser JR, Rega L, Casolo G, De Santis M, Quarta G, Nistri S, Cecchi F, Salton CJ, Udelson JE, Manning WJ, Maron BJ. Assessment and significance of left ventricular mass by cardiovascular magnetic resonance in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2008;52(7):559–66.
22. Sakuma H. Late gadolinium enhancement and prognosis of hypertrophic cardiomyopathy. Circ J. 2014;78(4):823–34.
23. Rickers C, Wilke NM, Jerosch-Herold M. Utility of cardiac magnetic resonance imaging in the diagnosis of hypertrophic cardiomyopathy. Circulation. 2005;112:855–61.
24. Elliot P, McKenna WJ. Hypertrophic cardiomyopathy. Lancet. 2004;363:1881–91.
25. Geske JB, Sorajja P, Ommen SR, Nishimura RA. Variability of left ventricular outflow tract gradient during cardiac catheterization in patients with hypertrophic cardiomyopathy. JACC Cardiovasc Interv. 2011;4(6):704–9.
26. Wigle ED. Cardiomyopathy: the diagnosis of hypertrophic cardiomyopathy. Heart. 2001;86:709–14.
27. Noureidin RA, Liu S, Nacif MS, Judge DP, Halushka MK, Abraham TP, Ho C, Bluemke DA. The diagnosis of hypertrophic cardiomyopathy by cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2012;14(17):1–13.
28. Valente AM, Lakdawala NK, Powell AJ, Evans SP, Cirino AL, Orav EJ, MacRae CA, Colan SD, Ho CY. Comparison of echocardiographic and cardiac magnetic resonance imaging in hypertrophic cardiomyopathy sarcomere mutation carriers without left ventricular hypertrophy. Circ Cardiovasc Genet. 2013;6(3):230–7.
29. Devlin AM, Moore NR, Ostman-Smith I. A comparison of MRI and echocardiography in hypertrophic cardiomyopathy. Br J Radiol. 1999;72:258–64.
30. Sperling RT, Parker JA, Manning WJ, Danias PG. Apical hypertrophic cardiomyopathy: clinical, electrocardiographic, scintiagraphic, echocardiographic and magnetic resonance imaging findings of a case. J Cardiovasc Magn Reson. 2002;4:291–5.
31. Moon JC, Fisher NG, McKenna WJ, Pennell DJ. Detection of apical hypertrophic cardiomyopathy by cardiovascular magnetic resonance in patients with non-diagnostic echocardiography. Heart. 2004;90:645–9.
32. Refaat M. Prognosis of apical hypertrophic cardiomyopathy. JAMA. 2007;298(17):2006.
33. Abinader EG. Long-term outcome in patients with apical hypertrophic cardiomyopathy. J Am Coll Cardiol. 2002;40(4):837–8.
34. Maron MS, Maron BJ, Harrigan C. Hypertrophic cardiomyopathy phenotype revisited after 50 years with cardiovascular magnetic resonance. J Am Coll Cardiol. 2009;54:220–8.
35. Maron BJ, Seidman JG, Seidman CE. Proposal for contemporary screening strategies in families with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2004;44(11):2125–32.
36. Bergey PD, Axel L. Focal hypertrophic cardiomyopathy simulating a mass: MR tagging for correct diagnosis. AJR Am J Roentgenol. 2000;184:242–4.
37. Harrigan CJ, Appelbaum E, Maron BJ. Significance of papillary muscle abnormalities identified by cardiovascular magnetic resonance in hypertrophic cardiomyopathy. Am J Cardiol. 2008;101:668–73.
38. Kwon DH, Setser RM, Thamilarasan M. Abnormal papillary muscle morphology is independently associated with increased left ventricular outflow tract obstruction in hypertrophic cardiomyopathy. Heart. 2008;94:1295–301.
39. Desai MY, Ommen SR, McKenna WJ, Lever MH, Elliott PM. Imaging phenotype versus genotype in hypertrophic cardiomyopathy. Circulation. 2011;4:156–68.
40. Maron MS, Olivotto I, Harrigan C, Appelbaum E, Gibson CM, Lesser JR, Haas TS, Udelson JE, Manning WJ, Maron BJ. Mitral valve abnormalities identified by cardiovascular magnetic resonance represent a primary phenotypic expression of hypertrophic cardiomyopathy. Circulation. 2011;123:40–7.
41. Klues HG, Maron BJ, Dollar AL, Roberts WC. Diversity of structural mitral valve alterations in hypertrophic cardiomyopathy. Circulation. 1992;85(5):1651–60.
42. Maron BJ, Nishimura RA, Danielson GK. Pitfalls in clinical recognition and a novel operative approach for hypertrophic cardiomyopathy with severe outflow obstruction due to anomalous papillary muscle. Circulation. 1998;98(23):2505–8.
43. Sherrid MV, Gunsburg EZ, Moldenhauer S, Pearle G. Systolic anterior motion begins at low left ventricular outflow tract velocity in obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol. 2000;22(3):816–25.
44. Kellman P, Arai AE. Imaging sequences for first pass perfusion – a review. J Cardiovasc Magn Reson. 2007;9:525–37.
45. Maron MS, Olivotto I, Betocchi S. Effect of the left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. N Engl J Med. 2003;348:295–303.

46. Hope MD, Meadows AK, Hope TA. Clinical evaluation of aortic coarctation with 4D flow MR imaging. J Magn Reson Imaging. 2010;31:711–8.
47. Macgown CK, Kellenberger CJ, Detsky JS, Roman K, Yoo SJ. Real-time fourier velocity encoding: an in vivo evaluation. J Magn Reson Imaging. 2005;21:297–304.
48. O'Brien KR, Myerson SG, Cowan BR, Young AA, Robson MD. Phase contrast ultrashort TE: a more reliable technique for measurement of high-velocity turbulent stenotic jets. Magn Reson Med. 2009;62:626–36.
49. Krombach GA, Kuhl H, Bucker A. Cine MR imaging of heart valve dysfunction with segmented true fast imaging with steady state free precession. J Magn Reson Imaging. 2004;19:59–67.
50. Cecchi F, Olivotto I, Gistri R, Lorenzoni R, Chiriatti G, Camici PG. Coronary microvascular dysfunction and prognosis in hypertrophic cardiomyopathy. N Engl J Med. 2003;349(11):1027–35.
51. Kitamura M, Shimizu M, Ino H. Collagen remodeling and cardiac dysfunction in patients with hypertrophic cardiomyopathy: the significance of type III and VI collages. Clin Cardiol. 2001;24: 325–9.
52. Harrigan CJ, Peters DC, Gibson CM, Maron BJ, Manning WJ, Maron MS, Appelbaum E. Hypertrophic cardiomyopathy: quantification of late gadolinium enhancement with contrast-enhanced cardiovascular MR imaging. Radiology. 2011;258(1):128–33.
53. Amano Y, Takayama M, Takaham K, Kumazaki T. Delayed hyperenhancement of myocardium in hypertrophic cardiomyopathy with asymmetrical septal hypertrophy: comparison with global and regional cardiac MR imaging appearances. J Magn Reson Imaging. 2004;20:595–600.
54. Moon JC, McKenna WJ, McCrohon JA. Toward clinical risk assessment in hypertrophic cardiomyopathy with gadolinium cardiovascular magnetic resonance. J Am Coll Cardiol. 2003;41: 1561–7.
55. Choudhury L, Mahrholdt H, Wagner A. Myocardial scarring in minimally symptomatic patients with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2002;40:2156–64.
56. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naidu SS, Nishimura RA, Ommen SR, Rakowski H, Seidman CE, Towbin JA, Udelson JE, Yancy CW. 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy, A Report of the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2011;58(25):e212–60.
57. Rubinshtein R, Glockner JF, Ommen SR. Characteristics and clinical significance of late gadolinium enhancement by contrast enhanced magnetic resonance imaging in patients with hypertrophic cardiomyopathy. Circ Heart Fail. 2010;3:51–8.
58. Green JJ, Berger JS, Kramer CM, Salerno M. Prognostic value of late gadolinium enhancement in clinical outcomes for hypertrophic cardiomyopathy. JACC Cardiovasc Imaging. 2012;5(4):370–7.
59. Rudolph A, Abdel-Aty H, Bohl S. Noninvasive detection of fibrosis applying contrast-enhanced cardiac magnetic resonance in different forms of left ventricular hypertrophy relation to remodeling. J Am Coll Cardiol. 2009;53:284–91.
60. Azevedo CF, Nigri M, Higuchi ML. Prognostic significance of myocardial fibrosis quantification by histopathology and magnetic resonance imaging in patients with severe aortic stenosis. J Am Coll Cardiol. 2010;56:278–87.
61. Petersen SE, Selvanayagam JB, Francis JM. Differentiation of athlete's heart from pathological forms of cardiac hypertrophy by means of geometric indices derived from cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2005;7:551–8.
62. Caruthers SD, Lin SJ, Brown P. Practical value of cardiac magnetic resonance imaging for clinical quantification of aortic valve stenosis: comparison with echocardiography. Circulation. 2003;108: 2236–43.
63. Oliver JM, Gonzalez A, Gallego P, Sanchez-recalde A, Benito F, Mesa JM. Discrete subaortic stenosis in adults: increased prevalence and slow rate of progression of the obstruction and aortic regurgitation. J Am Coll Cardiol. 2001;38(3):35–42.
64. Austin BA, Tang WH, Rodriguez ER. Delayed hyper-enhancement magnetic resonance imaging provides incremental diagnostic and prognostic utility in suspected cardiac amyloidosis. J Am Coll Cardiol Img. 2009;2:1369–77.
65. Maceira AM, Joshi J, Prasad SK. Cardiovascular magnetic resonance in cardiac amyloidosis. Circulation. 2005;111:186–93.
66. Smedema JP, Snoep G, van Kroonenburgh MP. Evaluation of the accuracy of gadolinium-enhanced cardiovascular magnetic resonance in the diagnosis of cardiac sarcoidosis. J Am Coll Cardiol. 2005;45:1683–90.
67. Puvaneswary M, Joshua F, Ratnarajah S. Idiopathic hypereosinophilic syndrome: magnetic resonance imaging findings in endomyocardial fibrosis. Australas Radiol. 2001;45:524–7.

Genetics of HCM and Role of Genetic Testing

6

Christopher Semsarian and Jodie Ingles

Abstract

Since 1989, major advances have been made in our understanding of the genetic basis of HCM. Our genetic advances have led to a complete re-definition of HCM as a complex medical genetic disorder of the sarcomere. To date, over 1,300 mutations in at least 13 disease genes have been identified in patients with HCM. This genetic information has had its greatest impact in the setting of predictive testing in at-risk family members. The genetic testing process in HCM requires a multidisciplinary approach, which includes the cardiologist, genetic counselor, geneticists, and patient support groups. Careful phenotyping of HCM patients, comprehensive pre- and post- test genetic counseling, careful interpretation of the genetic reports, and systematic application of the genetic result in the setting of the HCM family are all key components of care. The latest genetic technologies, including whole genome sequencing, will likely translate to a greater understanding of the genetic and molecular underpinnings of HCM.

Keywords

Hypertophic cardiomyopathy • Genetics • Genetic testing • Sarcomere • Predictive testing • Genetic counselling

Key Points

- Genetic testing is commercially available for HCM patients
- Patients need to be accurately phenotyped to ensure a correct clinical diagnosis of HCM
- Genetic counseling pre- and post- genetic testing is essential in all cases
- Genetic testing results need to be carefully interpreted to ensure DNA variants are correctly classified as pathogenic
- The greatest value of genetic testing in HCM is for predictive testing of asymptomatic relatives
- Multiple gene mutations may be found in up to 5 % of HCM patients and may be associated with more severe clinical outcomes
- The multidisciplinary specialized clinic is the preferred model of care in HCM families

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Introduction

Major advances have been made over the last 25 years that have defined the genetic basis of many medical diseases. There are now over 40 different cardiovascular diseases directly caused by mutations in genes that encode cardiac proteins. These cardiovascular diseases include the inherited cardiomyopathies, primary arrhythmogenic diseases, metabolic disorders, and the congenital heart diseases. Identification of the genetic causes of cardiovascular disease has led to improved and earlier diagnosis of at-risk individuals, and in some cases, is helping to guide therapies as well as inform prognosis. This chapter will provide an overview of the current knowledge related to the genetics, and the role of genetic testing specifically, in the most common genetic heart disorder, hypertrophic cardiomyopathy (HCM).

Genetic Basis of HCM

Since 1989, major advances have been made in our understanding of the genetic basis of HCM. In a disease that was defined as a "tumor of the heart" by Donald Teare in 1958 [1], our genetic advances have led to a complete re-definition of HCM as a complex medical genetic disorder of the sarcomere. To date, over 1,300 mutations in at least 13 disease genes have been identified in patients with HCM [2]. The key genes are summarized in Table 6.1. These disease genes encode primarily sarcomere, and sarcomere-related proteins, and are almost exclusively inherited in an autosomal dominant pattern, with offspring of an affected individual having a 50 % chance of inheriting the disease gene. Collectively, these findings have led to the description of HCM as a "disease of the sarcomere" (Fig. 6.1).

Amongst the causative genes, the β-myosin heavy chain (*MYH7*) and myosin-binding protein C (*MYBPC3*) genes are the most commonly described in HCM populations worldwide, accounting for approximately 70 % of all mutations identified. Major advances in defining the genetic basis of HCM have led to commercially available genetic testing for HCM since 2002 [4]. While there is variability amongst testing providers, the standard genetic test currently available commercially for HCM involves sequencing of a 10–12 gene panel (including most of the main genes listed in Table 6.1). The mutation detection rate is currently up to 50 % in HCM. Presence of a positive family history of HCM as well as a family history of sudden death due to HCM, may increase this pick-up rate to beyond 80 % [5].

Most of the causative gene mutations in HCM are of the *missense* type, in which a single base pair change results in the change (or replacement) of one amino acid (so called non-synonymous mutations). These are usually rare (less than 1 %) or completely absent from control populations. Less commonly in HCM, other mutations exist that may cause more significant disruptions to the encoded protein, so-called "*frameshift*" or "*truncation*" mutations, which can lead to a major change in the protein sequence or a loss of amino acids resulting in a shortened protein. The latter mutations are often caused by deletions or insertions of nucleic acids in the coding region.

Table 6.1 Causative genes in HCM

Causative gene	Gene symbol
Thick filament	
β-myosin heavy chain	*MYH7*
Regulatory myosin light chain	*MYL2*
Essential myosin light chain	*MYL3*
Thin filament	
Cardiac troponin T	*TNNT2*
Cardiac troponin I	*TNNI3*
Cardiac troponin C	*TNNC1*
α-tropomyosin	*TPM1*
α-cardiac actin	*ACTC*
Intermediate filament	
Cardiac myosin-binding protein c	*MYBPC3*
Z-disc	
α-actinin2	*ACTN2*
Myozenin2	*MYOZ2*
Other genes implicated in HCM (less evidence)	
α-myosin heavy chain	*MYH6*
Titin	*TTN*
Muscle LIM protein	*CSRP3*
Telethonin	*TCAP*
Calsequestrin	*CASQ2*
Junctophilin2	*JPH2*

Genetics and Prognosis in HCM

While the identification of a HCM disease-causing mutation has significant diagnostic benefits in patients and family members, the prognostic value of knowing the genetic cause of disease remains elusive. Initial studies suggested there may exist overall trends in clinical outcomes with specific disease genes. For example, mutations in *MYH7* were generally more severe with earlier age of presentation [6] while mutations in *MYBPC3* lead to a more benign clinical outcome at later age of onset of disease [7]. These early findings also referred to some mutations being classed as "malignant" (e.g. Arg403Gln in *MYH7* gene) and others "benign" (Arg502Trp in *MYBPC3* gene). However many subsequent studies have shown a lack of correlation of specific mutations with disease outcome [8] and this reflects the clinical heterogeneity *within* HCM families. Similarly, other studies have postulated specific genes and mutations are associated

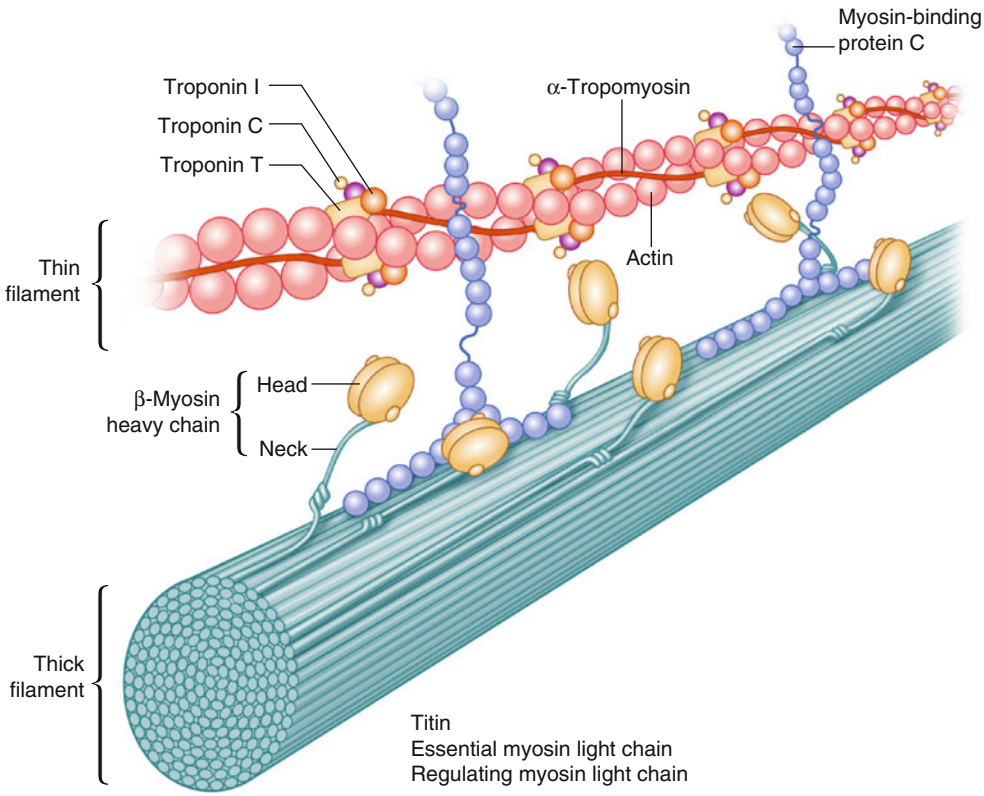

Fig. 6.1 Schematic diagram of the sarcomere with main HCM-causing genes labeled (Adapted from Nabel et al. [3])

with early onset of HCM in children and late onset in the elderly, as well links to variant forms of HCM such as apical, or end-stage "burnt-out" HCM. Unfortunately to date, these studies have been inconclusive and have therefore not led to a specific change in practice in terms of specific gene mutations and prognosis amongst individual patients with HCM.

Role of Genetic Testing in HCM

When considering genetic testing in HCM, a number of basic genetic testing principles, applicable to all genetic heart diseases, need to be considered. These considerations are important to ensure optimal and most effective care of families with HCM.

General Principles

Genetic testing is not a simple blood test. There are many considerations that arise with every family. A complete clinical-genetic evaluation is required, which includes being certain of the clinical diagnosis in the proband, understanding the probabilistic nature of genetic testing, the need for genetic counseling and taking a detailed family history to get a sense of disease penetrance and patterns of disease [9].

Importance of Detailed and Accurate Phenotyping

The cornerstone of genetic testing is accurately defining the clinical phenotype both in the individual patient, and the family. The highest yields from genetic testing are often based on patient cohorts with confirmed disease. In HCM, careful attention to the family history, clinical symptoms, and defining the extent, distribution and severity of hypertrophy are all considered essential in clinically distinguishing HCM from other HCM phenocopies (or mimickers), such as Fabry disease or glycogen storage diseases, which have different genetic etiologies.

Genetic Counseling and Informed Consent

In all patients and families with HCM, genetic counseling is essential. Genetic testing options span all stages of life, from the pre-implanted embryo or fetus, to children and adults. Appropriate pre- and post-test genetic counseling is a vital component of genetic testing. Apart from the diagnostic utility of genetic testing within families, a specific gene result may also provide some information about prognosis. The cardiac genetic counselor therefore plays a key role in the HCM genetic testing process, ensuring that the individual understands the clinical and psychosocial implications of every possible result, limitations of the tests including difficulties in interpretation of the results, as well as discussion of other

issues such as genetic testing of children, prenatal and pre-implantation genetic diagnosis and access to insurance [10].

Commercially Available Genetic Testing in HCM

Over the last decade, commercially available genetic testing for inherited cardiac diseases, including HCM, has expanded significantly. Genetic testing has moved from single gene testing, to concurrent testing of multiple genes in "panels" of ten or more genes, and reflects the genetic heterogeneity seen in HCM. Most recent developments have led to the development of "cardiomyopathy panels" which test for over 50 cardiac genes involved in the pathogenesis of a variety of cardiomyopathies including HCM. Such approaches are likely to expand significantly in the future due to a combination of both our increasing knowledge about causative genes in HCM, and the rapid advances in genetic screening technologies, such as next generation and whole genome sequencing. Importantly, increases in genetic testing panels in HCM are likely to lead to both more causative gene mutations being identified, but also an increased likelihood of identifying incidental genetic findings both in cardiac and non-cardiac genes, further highlighting the essential need of patient education and informed consent prior to testing.

Proband Genetic Testing in HCM

The genetic testing process most frequently begins with testing the proband (or index case). This is often the first person in the family who presents and the clinical diagnosis of HCM is established. Following genetic counseling and informed consent, genetic testing is performed. The outcomes can be divided into (1) those where a mutation(s) is identified that is deemed to be *pathogenic* (disease-causing), (2) those where no causative mutation is identified (an "*indeterminate result*") and (3) those where it is unclear whether the variant is pathogenic or a benign variation in our genetic sequence (*variant of uncertain significance*; VUS). The mutation detection rate for true pathogenic mutations in HCM remains at up to 50 % of all who are tested.

Determining whether a DNA variant is disease-causing ("pathogenic") in HCM is a major challenge and remains the *Achilles heel* of genetic testing. In most genetic testing reports, an effort will be made to determine the likelihood that a variant that has been identified is pathogenic. The important and often misunderstood point is that genetic tests are probabilistic tests rather than deterministic, and this can be difficult to convey to the patient. For the attending cardiologist or geneticist interpreting the genetic result, the decision about pathogenicity flows across a probabilistic spectrum from benign to pathogenic (Fig. 6.2). Specifically, a variant is considered a pathogenic mutation on the basis of a number of factors. These criteria include co-segregation with the disease phenotype in family members, absence of the variant in normal ethnicity-matched controls, altered protein structure and function, the amino acid change located in a highly conserved region of the protein, and in some cases, where the identified mutation has been previously reported to be disease-causing [4, 11].

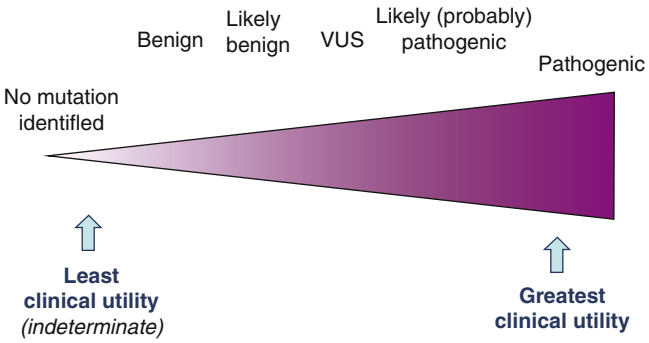

Fig. 6.2 Spectrum of pathogenicity: Determining the probability that a DNA variant is pathogenic relies on a consideration of clinical, genetic, and *in silico* information. Determining pathogenicity is probabilistic (Adapted from Maron et al. [4])

Even after applying the criteria listed above, situations arise where the clinical significance and pathogenicity of a variant remains unknown. In these cases, the variant is termed a variant of uncertain significance (VUS). Recent advances in genetic screening technologies have identified the frequency of VUS to be significant amongst normal populations, and within specific cardiac disease genes. Given this current ambiguity, a VUS is considered an indeterminate result and is not considered reliable in the setting of predictive testing in other family members (Fig. 6.3). Importantly, with the recent emergence of large whole exome and genome datasets, reclassification of variants, e.g. downgrading of a DNA change from pathogenic to benign due to new genetic information, is an important consideration for previously tested HCM families. Periodic re-evaluation of DNA variants is therefore recommended in HCM families [11].

Predictive Testing of HCM Family Members

The greatest utility of genetic testing is for early diagnosis of family members. Once a pathogenic mutation has been identified in the proband, this information can be used in asymptomatic first-degree relatives and beyond, to identify those people who carry the gene mutation and, as importantly, those who do not. This process, called *predictive or cascade genetic testing*, is the primary utility of HCM genetic testing. Importantly, a negative predictive test result means the individual no longer requires ongoing clinical screening, eliminating the need for decades of expensive cardiac investigations based on current clinical guidelines. This is the major driver for the established cost effectiveness of genetic testing in HCM [12]. A positive predictive genetic test result allows a more targeted screening approach, with the goal to prevent serious cardiac events. Just

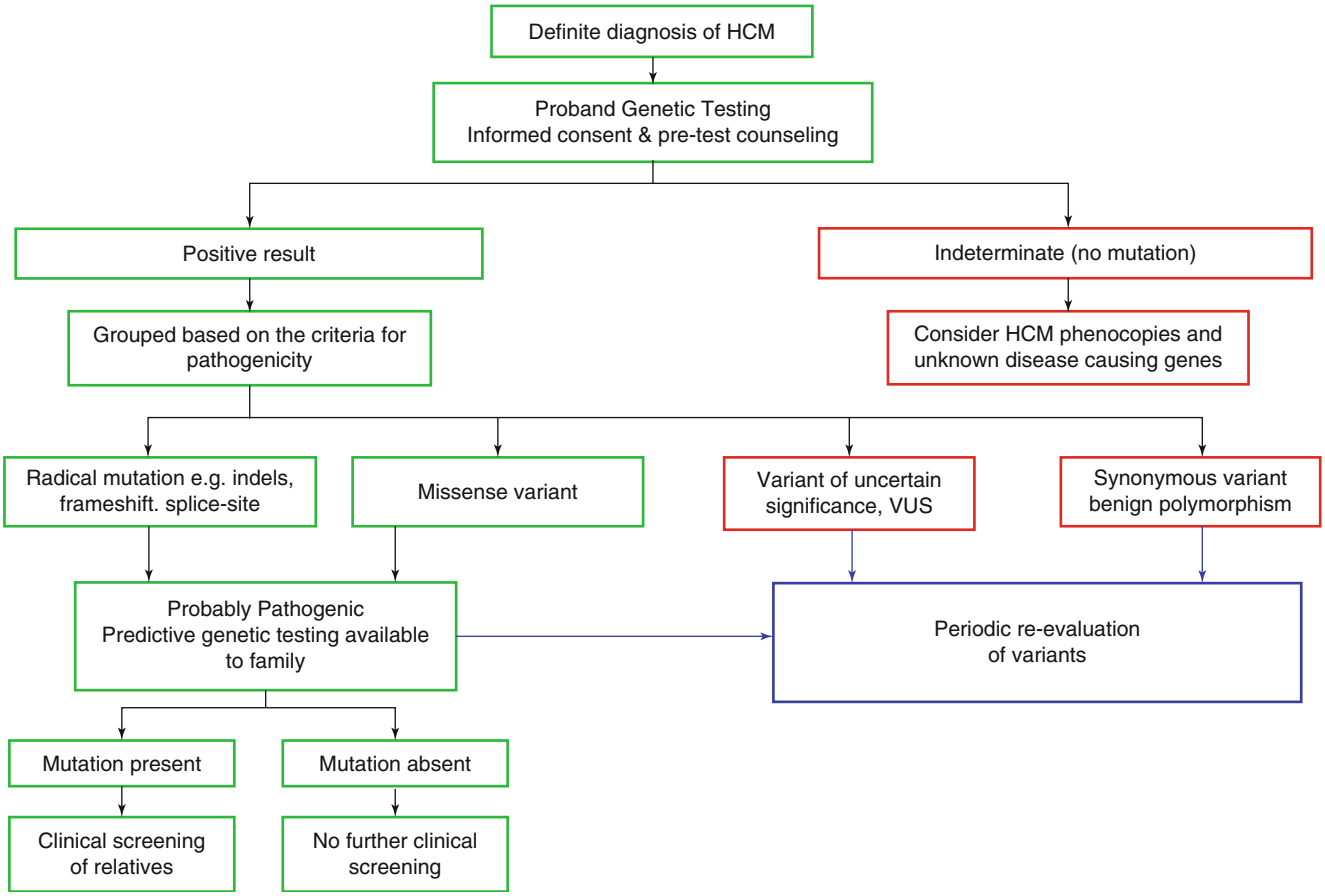

Fig. 6.3 Flow diagram for genetic testing in HCM and DNA variant classification (Adapted from Das et al. [11])

as important, a predictive genetic result can clarify the risk status of *their* first-degree relatives, including children.

As a consequence of the increase in genetic testing of families with HCM, a new clinical spectrum of individuals has arisen, i.e. those who carry a specific causative gene mutation but have not yet developed a detectable clinical phenotype. This new clinical subgroup, referred to as *genotype positive-phenotype negative*, has arisen directly as a result of genetic testing, and subsequent predictive genetic testing in at-risk family relatives [13, 14]. These patients are effectively "gene carriers", and very little is known regarding how to best manage these asymptomatic patients, e.g. participation in competitive sports. Early studies suggest those who are HCM gene carriers and reach adulthood with no clinical signs of HCM have a generally favorable outcome with a low chance of developing clinical disease [15]. Nevertheless, these individuals represent a fascinating subgroup, likely to increase significantly as more genetic testing in HCM is performed, and may be an ideal subgroup to initiate preventative therapies before the development of clinical disease.

While genetic testing in HCM does not currently guide therapy, there is growing evidence that "gene dose" may predict those patients with more severe clinical outcomes [16]. Human HCM studies have shown that up to 5 % of families carry two or more pathogenic HCM mutations [17, 18]. Collectively, these multiple mutation patients have earlier age of disease onset, have more severe hypertrophy, have a higher rate of sudden death events, and are more likely to develop heart failure symptoms [19]. These findings support the notion that "gene dose" may be a marker of disease progression and prognosis in HCM.

Multidisciplinary Specialized Clinic Model of Care in HCM

A genetic diagnosis in the HCM proband has major implications for family relatives. In all situations where HCM is identified, appropriate clinical and genetic screening is indicated. The clear goal of both clinical and genetic screening of family members is to identify those with clinical evidence of HCM or those who may carry the same pathogenic mutation as the proband, but do not express a clinical phenotype. As discussed previously, early identification of these at-risk individuals provides opportunities to initiate early therapies aimed at preventing disease complications.

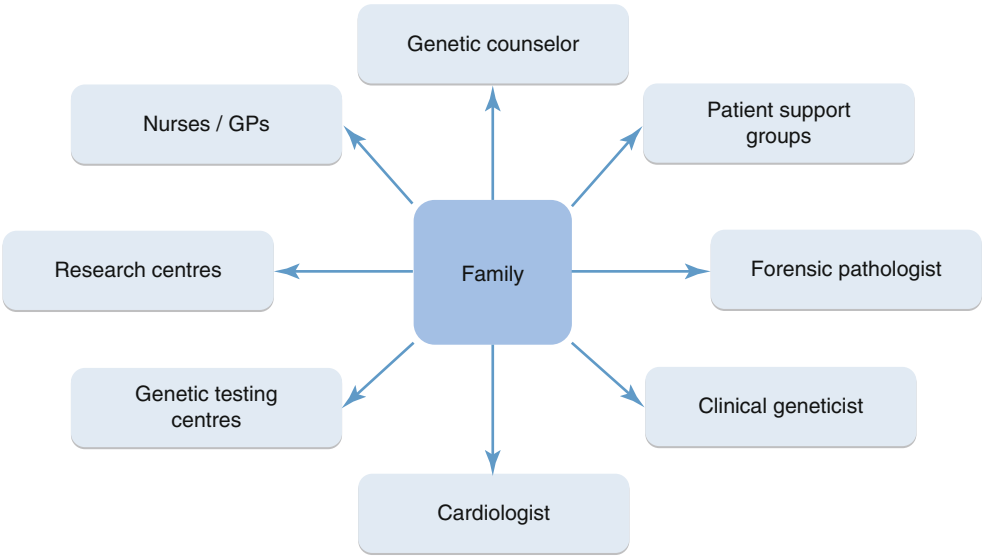

Fig. 6.4 Key role of the specialized multidisciplinary clinic in the evaluation of families with HCM. *GP* general practitioner (Adapted from Ingles et al. [10])

The management of families with HCM is therefore complex. HCM is a challenging clinical and genetic disease. There are many different issues to consider, such as clinical evaluations and management, coordination of services including genetic counseling and testing, patient education and support, and awareness of the psychological, social and potential legal issues. These services are offered in a sensitive environment, with the knowledge that the families may experience a range of emotions, particularly where there has been a sudden death of a loved one. As a consequence the ideal model of care is the cardiologist-led specialized multidisciplinary cardiac genetic clinic (Fig. 6.4) [10, 20]. Expertise from a number of health professionals is drawn upon, including cardiologists, genetic counselors, clinical geneticists, psychologists, as well as services such as patient support groups and research centers. This type of multidisciplinary model has been shown to improve psychosocial outcomes of patients with genetic heart diseases, specifically showing less worry and reduced levels of anxiety [21].

Ethical, Legal and Societal Implications

The ethical, legal, and societal implications of genetic testing in HCM are beyond the scope of this Chapter and are influenced strongly by government regulations, societal views, and cultural considerations. There do exist some common issues, such as timing of genetic testing. Should children at risk of HCM have genetic testing? Comprehensive guidelines exist for genetic testing in children, which take into account many factors related to the child, the parents and family, and the medical circumstances of the underlying genetic heart disease. Genetic testing in HCM can be offered in both the prenatal setting (i.e. in early pregnancy), as well as at conception, referred to as pre-implantation genetic diagnosis. Such approaches are based on identifying embryos that carry the HCM gene mutation and then implanting only those that are unaffected. While available currently, prenatal and pre-implantation approaches need to be discussed extensively with families, appropriate counseling provided, and decisions made in an informed manner. The complexities of such issues, which span clinical, social, psychological, ethical, and moral boundaries, further highlights the importance of multidisciplinary teams in the care of families with HCM. If the attending cardiologist is not equipped to discuss these issues, further discussion should be offered in partnership with genetic counselors, and/or clinical geneticists. Such a multidisciplinary approach will help serve the needs of the patients and their families more comprehensively, and will facilitate open and informed discussion about the ethical, legal and societal implications of genetic testing. It is therefore important that pre-genetic test counseling, genetic testing, and the interpretation of genetic test results be performed in centers experienced in the genetic evaluation and family-based management of HCM families.

Future Directions

With the emergence of newer genetic technologies coupled with a greater understanding and appreciation of the clinical complexities of HCM, the coming years will represent very exciting times. Defining the other 50 % of HCM individuals where current studies do not find a gene mutation will be a focus of great importance. Whether these individuals have mutations in other as yet unknown genes, or harbor different types of mutations (insertions, deletions, copy number variations) in currently known genes, or whether some of these patients actually do not have HCM but other HCM phenocopies, remains unclear. Expanding our knowledge base in terms of genotype-phenotype correlations in larger cohorts, and identifying other genetic and environmental modifiers

which may influence clinical outcomes, will be instrumental as we move towards gene- or mutation- based, personalized therapies. In this respect, the greatest excitement lies in the potential to not only define the precise genetic causes of HCM, but to develop specific mutation-targeted molecular therapies such as small RNA silencing molecules which may ultimately lead to development of effective curative strategies in HCM.

Conclusions

Major advances have been made in our understanding of the genetic causes of HCM. The widespread commercial availability of genetic testing has facilitated the steady introduction of genetic testing for HCM into clinical cardiology practice. Overall, the greatest utility of HCM genetic testing is in the screening and diagnosis of at-risk relatives through predictive genetic testing. Currently, there is little utility of a HCM genetic mutation in guiding therapy or prognosis.

Most exciting are the amazing advances in genetic technologies. These advances have emerged from next generation sequencing technologies, which provide the platforms for sequencing many DNA segments, rapidly and extensively, across many genes at once. Indeed, whole exome or genome sequencing, whereby all the 23,000 genes that make up the human body can be sequenced in one test, will revolutionize our understanding of the genetic basis of many medical diseases, including HCM. Clearly having the appropriate bioinformatics strategies to identify the key DNA variants from background genetic noise, and understanding the functional consequences of these DNA changes, will all be essential as we move forward in developing more comprehensive genetic testing strategies in HCM.

Clinical Pearls

- Always take a thorough and detailed family history
- Presence of a family history of HCM or sudden death may increase chances of finding a causative gene mutation in the proband
- Never order a genetic test without thorough clinical evaluation of the patient
- Always provide genetic counseling to all HCM patients both pre- and post- genetic testing
- Don't always accept the findings of the genetic reports for HCM – check the pathogenicity of the variant thoroughly
- Provide close clinical surveillance in families where multiple (2 or more) causative gene mutations have been identified

References

1. Teare D. Asymmetrical hypertrophy of the heart in young adults. Br Heart J. 1958;20:1–8.
2. Seidman J, Seidman C. The genetic basis for cardiomyopathy: from mutation identification to mechanistic paradigms. Cell. 2001;104:557–67.
3. Nabel EG. Cardiovascular disease. N Engl J Med. 2003;349: 60–72.
4. Maron BJ, Maron MS, Semsarian C. Genetics of hypertrophic cardiomyopathy after 20 years: clinical perspectives. J Am Coll Cardiol. 2012;60:705–15.
5. Ingles J, Sarina T, Yeates L, Hunt L, Macciocca I, McCormack L, Winship I, McGaughran J, Atherton J, Semsarian C. Clinical predictors of genetic testing outcomes in hypertrophic cardiomyopathy. Genet Med. 2013;15(12):972–7.
6. Watkins H, Rosenzweig A, Hwang DS, Levi T, McKenna W, Seidman CE, Seidman JG. Characteristics and prognostic implications of myosin missense mutations in familial hypertrophic cardiomyopathy. N Engl J Med. 1992;326:1108–14.
7. Niimura H, Bachinski LL, Sangwatanaroj S, Watkins H, Chudley AE, McKenna W, Kristinsson A, Roberts R, Sole M, Maron BJ, Seidman JG, Seidman CE. Mutations in the gene for cardiac myosin-binding protein c and late-onset familial hypertrophic cardiomyopathy. N Engl J Med. 1998;338:1248–57.
8. Semsarian C, Yu B, Ryce C, Lawrence C, Washington H, Trent RJ. Sudden cardiac death in familial hypertrophic cardiomyopathy: are "benign" mutations really benign? Pathology. 1997;29: 305–8.
9. Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H, Camm AJ, Ellinor PT, Gollob M, Hamilton R, Hershberger RE, Judge DP, Le Marec H, McKenna WJ, Schulze-Bahr E, Semsarian C, Towbin JA, Watkins H, Wilde A, Wolpert C, Zipes DP. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Heart Rhythm. 2011;8:1308–39.
10. Ingles J, Yeates L, Semsarian C. The emerging role of the cardiac genetic counselor. Heart Rhythm. 2011;8:1958–62.
11. Das KJ, Ingles J, Bagnall RD, Semsarian C. Determining pathogenicity of genetic variants in hypertrophic cardiomyopathy: importance of periodic reassessment. Genet Med. 2013;16(4): 286–93.
12. Ingles J, McGaughran J, Scuffham PA, Atherton J, Semsarian C. A cost-effectiveness model of genetic testing for the evaluation of families with hypertrophic cardiomyopathy. Heart. 2012;98(8): 625–30.
13. Maron BJ, Semsarian C. Emergence of gene mutation carriers and the expanding disease spectrum of hypertrophic cardiomyopathy. Eur Heart J. 2010;31:1551–3.
14. Maron BJ, Yeates L, Semsarian C. Clinical challenges of genotype positive (+)-phenotype negative (−) family members in hypertrophic cardiomyopathy. Am J Cardiol. 2011;107:604–8.
15. Gray B, Ingles J, Semsarian C. Natural history of genotype positive-phenotype negative patients with hypertrophic cardiomyopathy. Int J Cardiol. 2011;152:258–9.
16. Kelly M, Semsarian C. Multiple mutations in genetic cardiovascular disease: a marker of disease severity? Circ Cardiovasc Genet. 2009;2:182–90.
17. Ingles J, Doolan A, Chiu C, Seidman J, Seidman C, Semsarian C. Compound and double mutations in patients with hypertrophic cardiomyopathy: Implications for genetic testing and counselling. J Med Genet. 2005;42:e59.
18. Richard P, Charron P, Carrier L, Ledeuil C, Cheav T, Pichereau C, Benaiche A, Isnard R, Dubourg O, Burban M, Gueffet JP, Millaire A, Desnos M, Schwartz K, Hainque B, Komajda M. Hypertrophic cardiomyopathy: distribution of disease genes, spectrum of

mutations, and implications for a molecular diagnosis strategy. Circulation. 2003;107:2227–32.
19. Maron BJ, Maron MS, Semsarian C. Double or compound sarcomere mutations in hypertrophic cardiomyopathy: a potential link to sudden death in the absence of conventional risk factors. Heart Rhythm. 2012;9:57–63.
20. Ingles J, Semsarian C. Sudden cardiac death in the young: a clinical genetic approach. Intern Med J. 2007;37:32–7.
21. Ingles J, Lind JM, Phongsavan P, Semsarian C. Psychosocial impact of specialized cardiac genetic clinics for hypertrophic cardiomyopathy. Genet Med. 2008;10:117–20.

Assessment of Heart Failure: Invasive and Non-invasive Methods

7

Michael A. Fifer and Aaron L. Baggish

Abstract

The symptoms of hypertrophic cardiomyopathy (HCM) result from a combination of high filling pressures ("backward" heart failure) and low cardiac output ("forward" heart failure). The mainstay of noninvasive testing in symptomatic patients with HCM is transthoracic echocardiography. The detection of concomitant coronary artery disease (CAD) as a cause of symptoms may be difficult by clinical assessment and exercise testing; cardiac computerized tomographic angiography (CTA) has emerged as perhaps the most useful noninvasive test for the assessment of potentially ischemic symptoms due to CAD. Cardiac catheterization is useful for documenting right-sided pressures and cardiac output; determining whether a left ventricular outflow tract (or midcavity) gradient is present at rest or with provocation; separating aortic valvular from subvalvular and supravalvular gradients; determining whether CAD is present; and excluding other pathologic causes of left ventricular thickening. Cardiopulmonary exercise testing provides quantification of functional capacity and distinguishes between cardiac and pulmonary contributions to symptoms.

Keywords

Cardiac catheterization • Cardiopulmonary exercise testing • Exercise testing • Gradient • Heart failure • Hemodynamics • Hypertrophic cardiomyopathy • Hypertrophic obstructive cardiomyopathy

Key Points

- The symptoms of hypertrophic cardiomyopathy (HCM) result from a combination of high filling pressures ("backward" heart failure) and low cardiac output ("forward" heart failure); sudden drops in cardiac output may result in syncope.
  When present, elevated right atrial pressure and right ventricular (RV) end-diastolic pressures are often associated with RV hypertrophy, which may result from pulmonary hypertension due to left heart failure or may be a primary manifestation of HCM.

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- The symptoms of coronary artery disease (CAD) overlap those of HCM. The diagnosis of CAD by conventional testing may be inconclusive in patients with HCM. Cardiac computed tomographic angiography is a reliable means of detecting concomitant CAD in patients with HCM.
- In HCM patients with concomitant lung disease, cardiopulmonary exercise testing or right and left heart cardiac catheterization is useful for determining whether symptoms are due to a cardiac or pulmonary limitation.

Heart failure is perhaps the most common manifestation of HCM in adulthood, especially for those in the middle or later years of life. The diagnosis of heart failure in these patients may be especially difficult, as diastolic dysfunction is the main finding in the vast majority and has typically been slowly progressive over years to decades. Accordingly, patients typically fail to notice acute declines in function, and may attribute their insidious symptoms to a natural decline in functional status as they age, or to a gradual increase in weight and associated morbidities. In addition, few patients have signs or symptoms of congestion until late in the disease process, with the majority of early symptoms being those of "forward" heart failure, or an inappropriately low cardiac output in response to exercise, resulting primarily in fatigue and dyspnea on exertion.

Once the diagnosis of HCM is firm and heart failure is clinically evident, it may be quite difficult in some cases to elucidate and prioritize the various components of a patient's heart failure syndrome, especially as patients age and accumulate multiple comorbidities. This chapter will discuss the various causes of heart failure in patients with HCM and provide insights into how to determine the main causes in individual patients and tailor therapies accordingly.

Heart Failure in HCM

"Backward" vs. "Forward" Manifestations of Heart Failure

"Backward" symptoms of heart failure in HCM include dyspnea, orthopnea, PND, and, less commonly, vascular congestion and edema, whereas "forward" symptoms include fatigue, dyspnea, lightheadedness, and even frank syncope (Fig. 7.1). Exertional dyspnea may reflect elevation of pulmonary venous (and left atrial) pressure (a manifestation of "backward" failure) or limitation of cardiac output available to exercising muscle (a manifestation of "forward" failure); in many cases, forward and backward failure coexist. Alternatively, exertional

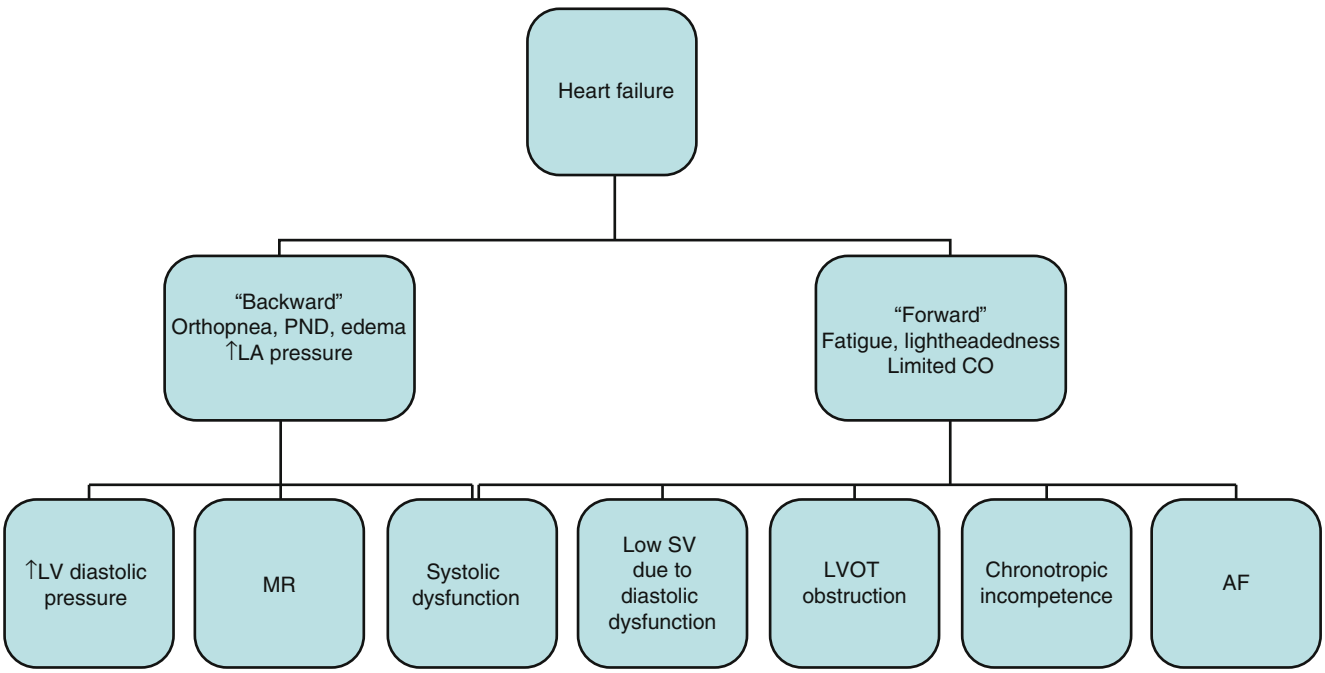

Fig. 7.1 Schematic representation of mechanisms of "backward" and "forward" manifestations of heart failure in patients with hypertrophic cardiomyopathy. *AF* atrial fibrillation, *CO* cardiac output, *LA* left atrial, *LV* left ventricular, *LVOT* left ventricular outflow tract, *MR* mitral regurgitation, *PND* paroxysmal nocturnal dyspnea, *SV* stroke volume

dyspnea may be due to myocardial ischemia ("anginal equivalent") resulting from inadequacy of coronary blood flow to the hypertrophied myocardium or, in patients with LVOT obstruction, high myocardial wall stress; both forward and backward heart failure may be present in these cases.

Elevation of pulmonary venous pressure in HCM may result from (1) abnormal diastolic left ventricular (LV) function associated with hypertrophy and, in some patients, fibrosis; (2) mitral regurgitation (MR) associated with systolic anterior motion (SAM) of the mitral valve and left ventricular outflow tract (LVOT) obstruction and/or intrinsic abnormalities of the mitral valve associated with HCM; or, much less commonly, (3) abnormal systolic left ventricular LV function. Limitation of cardiac output in HCM may result from LVOT obstruction; rarely, systolic dysfunction; or, perhaps most commonly, low LV end-diastolic volume and stroke volume due to diastolic dysfunction. Low cardiac output may also result from chronotropic incompetence or, in patients with atrial fibrillation, from loss of atrial transport. Finally, low cardiac output may result from secondary pulmonary hypertension.

Exertional lightheadedness and even syncope may result from inadequate augmentation of cardiac output with exercise, particularly in the presence of volume depletion. Alternatively, these symptoms may result from autonomic dysfunction with abnormal peripheral vasodilation [1] or from exercise-induced ventricular tachyarrhythmias. Exercise-induced hypotension may occur in the presence or absence of LVOT obstruction. Patients with HCM may be particularly prone to orthostatic hypotension and to postprandial splanchnic shunting, with consequent effective intravascular volume depletion. The systemic vasodilation associated with certain systemic illnesses, such as sepsis and systemic immune response syndrome, may also bring out the hemodynamic manifestations of HCM.

Right Heart Failure

Manifestations of right heart failure, such as jugular venous distention, ascites, and edema, are unusual in HCM. Patients with longstanding HCM and left heart failure, however, often manifest a component of pulmonary hypertension and right heart failure. When present, elevated right atrial pressure and (RV) end-diastolic pressure are often associated with RV hypertrophy, which may result from pulmonary hypertension due to left heart failure or may be a primary manifestation of HCM [2]. In the latter case, the hypertrophied septum may impinge on RV outflow, causing obstructive pathophysiology similar to that more commonly seen within the LV; this finding is more common in childhood and young adulthood in patients with massive septal hypertrophy.

Importantly, patients with HCM may have comorbidities affecting the pulmonary vasculature and RV, the most common of which are chronic obstructive pulmonary disease and sleep apnea; when present, these diseases contribute to right-sided heart congestion and reduced cardiac output.

Intrinsic Mitral Valve Disease

Posterolaterally directed MR regularly accompanies SAM of the anterior leaflet of the mitral valve in patients with LVOT obstruction. HCM may also be associated with intrinsic abnormalities of the mitral valve (in which case the regurgitant jet may not be posterolaterally directed), including papillary muscle malposition, leaflet elongation and thickening, and prolapse [3]. Finally, older patients with HCM may develop age-related mitral annular calcification, degenerative mitral valve disease, or other diseases that affect the mitral valve, contributing to mitral regurgitation or stenosis that is independent of underlying HCM. Such pathologies contribute to the manifestations of heart failure in some patients with HCM.

Intrinsic Aortic Valve Disease

Patients with HCM may also develop intrinsic pathology of the aortic valve, most commonly aortic stenosis due to calcific degeneration in older patients [4]. Valvular obstruction may occur concurrently or in the absence of subvalular obstruction due to HCM. When present, the valvular stenosis contributes to hypotension, diastolic dysfunction, and elevation of myocardial wall stress with associated myocardial ischemia, in turn contributing to both forward and backward manifestations of heart failure, including syncope.

Assessment of Heart Failure in HCM

In patients with HCM, symptoms attributable to heart failure range from mild to severe. In general, the goal of management is to make patients asymptomatic or at least reduce symptoms to the level of New York Heart Association Class II. In order for the clinician to accomplish this goal, it is necessary to determine the pathophysiologic underpinning of the symptoms. After a careful history and physical examination, noninvasive and in some cases invasive testing may be necessary. If edema and other overt signs of congestion are present, a cautious trial of diuretic therapy may be warranted.

Noninvasive Testing (Table 7.1)

The mainstay of the noninvasive assessment of heart failure in patients with HCM is transthoracic echocardiography, generally with the Valsalva maneuver and sometimes with exercise to elicit an LVOT gradient. Transesophageal echocardiography is useful in selective patients for delineating intrinsic abnormalities of the mitral valve apparatus and, on occasion, for detecting a subaortic membrane (particularly in the presence of aortic regurgitation) [5] or supravalvular AS. Mitral regurgitation (MR) caused by SAM is invariably associated with a posteriorly directed jet; if regurgitation is not posteriorly directed, the mitral apparatus should be examined with particular care for conditions including prolapse, excessive leaflet prolongation, calcification, and anomalous papillary muscle position.

Routine treadmill exercise testing yields a quantitative measure of exercise tolerance, data on heart rate (for chronotropic response) and blood pressure response (for exercise-induced hypotension), and the occurrence of exercise-induced arrhythmias. Cardiac magnetic resonance imaging provides global visualization of the left ventricular myocardium for assessment of wall thickness and presence and extent of fibrosis.

Holter monitoring may be utilized to detect arrhythmias that contribute to or cause heart failure symptoms [6]. In select cases with more intermittent symptoms, an event monitor or implantable loop recorder may be considered. A chest X-ray and pulmonary function tests are useful in selected patients to elicit pulmonary rather than cardiac causes of dyspnea. Similarly, sleep studies may help determine the presence and severity of concomitant obstructive or central sleep apnea.

Table 7.1 Investigations for heart failure symptoms in patients with HCM

Test	Data obtained
Transthoracic echocardiogram	Extent and pattern of hypertrophy Resting and provoked LVOT (and midcavity) gradient Abnormalities of mitral apparatus Estimation of RV systolic pressure Concomitant valvular and other abnormalities
Transesophageal echocardiogram	Abnormalities of mitral apparatus Subaortic membrane or supravalvular AS
Treadmill exercise test	Quantitative measure of exercise tolerance Chronotropic response Blood pressure response Exercise-induced arrhythmias
Cardiac magnetic resonance	Extent of hypertrophy Presence and extent of fibrosis
Holter, event, or loop monitoring	Arrhythmias contributing to heart failure symptoms
Cardiac chest tomographic angiography	Concomitant CAD
Chest X-ray, pulmonary function tests	Pulmonary disease as alternative cause of dyspnea
Sleep study	Obstructive or central sleep apnea
Cardiac catheterization	Right heart, pulmonary arterial, and pulmonary capillary wedge pressures Resting and provoked gradients Exercise hemodynamics Concomitant CAD HCM mimics

Detection of Concomitant CAD

The symptoms of CAD may mimic or contribute to those of heart failure in patients with HCM who are "old enough" to have CAD. Noninvasive diagnosis of CAD may be challenging in patients with HCM. Exercise-induced electrocardiographic changes are nonspecific in this patient population. Moreover, stress radionuclide perfusion imaging may show fixed or reversible defects in patients with HCM in the absence of CAD [7]. In addition, regional differences in wall thickness may cause apparent differences in tracer uptake that do not reflect abnormalities in perfusion. Exercise echocardiography to detect wall motion abnormalities has not been validated in patients with HCM. Cardiac computerized tomographic angiography (CTA) is a high-sensitivity test for the presence of CAD, and has emerged as perhaps the most useful noninvasive test for the assessment of potentially ischemic symptoms in due to CAD, especially in younger patients. In contrast, cardiac catheterization may be helpful in older patients, in whom CTA may be equivocal.

Cardiac Catheterization

In patients with HCM, cardiac catheterization may be useful for (1) documenting right atrial, RV, pulmonary arterial (PA), and pulmonary capillary wedge (PCW) pressures, cardiac output, and pulmonary vascular resistance (PVR); (2) determining whether a LVOT (or midcavity) gradient is present at rest or with provocation; (3) separating aortic valvular from subvalular and supravalvular gradients (Table 7.2);

Table 7.2 LVOT obstruction: differential diagnosis

	Site of gradient	Aortic regurgitation	Brockenbrough sign
Valvular AS	LV → Ao	Often present	Absent
HOCM	LV → LV	Generally absent	Present
Subaortic membrane	LV → LV	Often present	Absent
Supravalvular AS	Ao → Ao	Generally absent	Absent

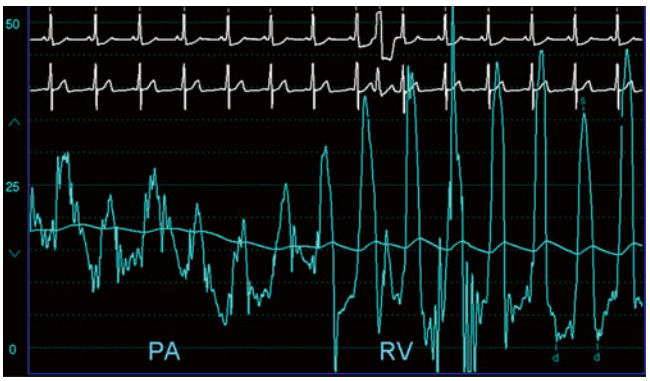

Fig. 7.2 Right heart catheter "pullback" from pulmonary artery (*PA*) to right ventricle (*RV*) in a patient with a 30 mmHg RV outflow tract gradient

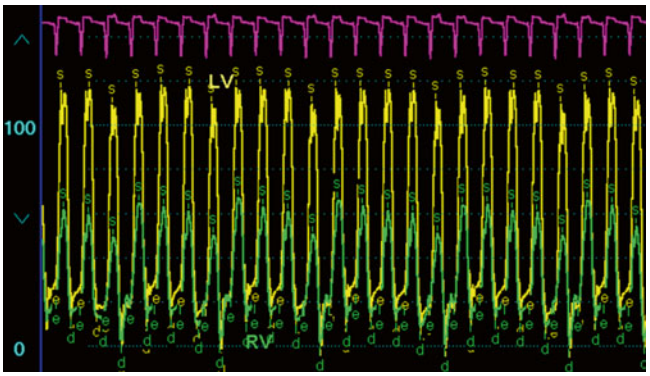

Fig. 7.3 Simultaneous right ventricular (*RV*) and left ventricular (*LV*) pressure tracings from a patient with HCM and "congestive" or "backward" heart failure symptoms and signs. Diastolic pressures are elevated in both ventricles. Systolic pressures are concordant with respect to the respiratory cycle, indicating that pericardial disease is absent

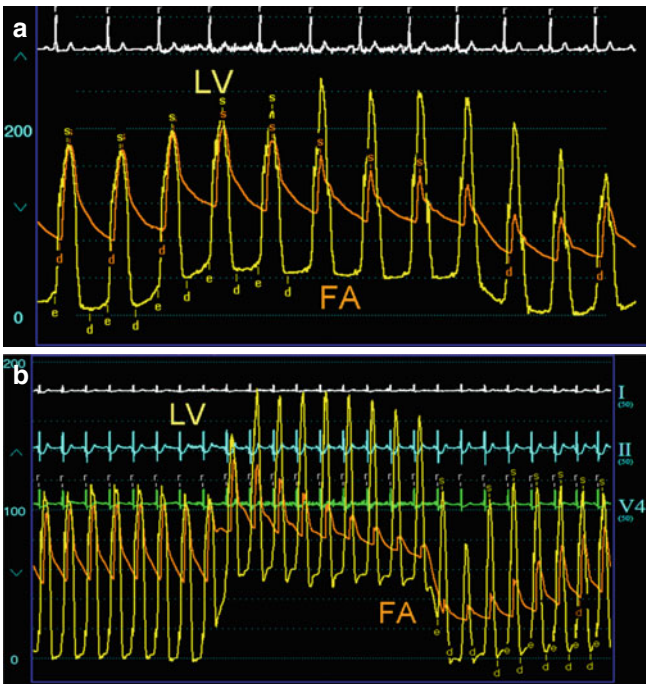

Fig. 7.4 Simultaneous left ventricular (*LV*) and femoral arterial (*FA*) pressures from two patients with HOCM. During the Valsalva maneuver, left ventricular diastolic pressure, which reflects intrathoracic pressure, increases. An LVOT gradient is absent (panel **a**) or present (panel **b**) at rest. During the Valsalva maneuver, the gradient (and, presumably, the systolic murmur) appears (panel **a**) or increases (panel **b**). In the patient whose pressures are depicted in panel (**b**), the systolic systemic arterial pressure falls to 40 mmHg, an illustration of the importance of asking patients with HOCM to perform the maneuver only when supine

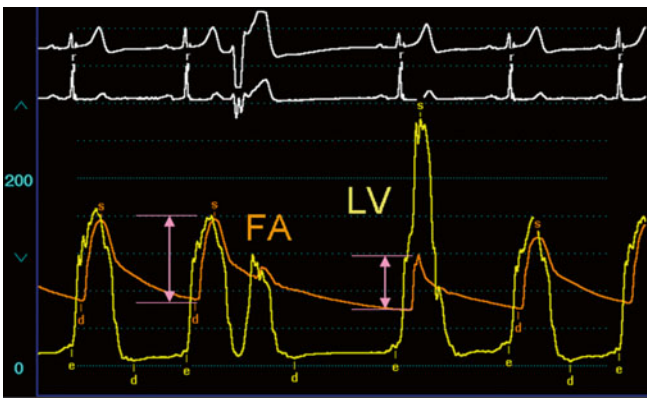

Fig. 7.5 Simultaneous left ventricular (*LV*) and femoral arterial (*FA*) pressure tracings from a patient with HOCM. There is only a small resting LVOT gradient. In the beat after a ventricular premature beat, there is a large gradient. In addition, there is a decrease in the systemic arterial pulse pressure in the postextrasystolic beat (Brockenbrough sign)

(4) determining whether concomitant CAD is present; and (5) excluding, as indicated, other causes, such as amyloid, of thickening of the left ventricular wall. Since much of the hemodynamic data may be obtained from echocardiography, delineation of coronary anatomy has become the most common indication for cardiac catheterization in patients with HCM. In difficult cases of heart failure refractory to optimal medical management, however, invasive assessment of hemodynamics may be indispensable.

Pressures on "pullback" from PA to RV in a patient with RV outflow tract obstruction are shown in Fig. 7.2. RV and LV pressure tracings from a patient with bisided heart failure are shown in Fig. 7.3.

In the cardiac catheterization laboratory, LVOT gradients may be provoked with the Valsalva maneuver (Fig. 7.4) or by inducing ventricular premature beats (VPBs, as by mechanical stimulation with a catheter in the RV; Fig. 7.5). Production of VPBs during the Valsalva maneuver provides a particularly sensitive mean of eliciting a gradient when no gradient is found with either maneuver alone. It is critical to distinguish between LVOT and midcavity gradients. Whereas the presence or absence of an LVOT gradient determines whether, for example, treatment with

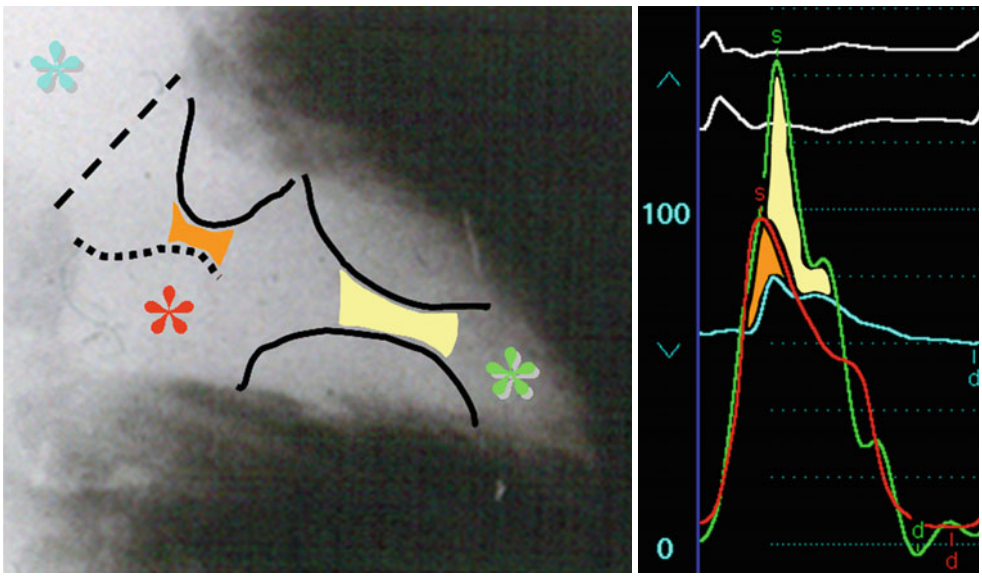

Fig. 7.6 Simultaneous left ventricular apical (*green*), left ventricular inflow (*red*), and systemic arterial (*blue*) pressure tracings from a patient with both LVOT (*orange*) and midcavity (*yellow*) gradients. The left ventricular inflow pressure was obtained in this case via the transseptal technique, but may also be obtained via manipulation of a catheter passed in retrograde fashion through the aortic valve

disopyramide or septal reduction therapy is appropriate, the significance of a midcavity gradient is much less clear. It is possible to distinguish between the two during either transseptal or retrograde LV catheterization (Fig. 7.6). An intracavitary gradient between catheters in the LV apex and aorta (or other systemic artery) may originate from the LVOT or the midcavity (or both). An intracavitary gradient between the LV inflow region and aorta (or other systemic artery) must originate from the LVOT. The mitral inflow area may be reached via the transseptal technique or by manipulating a retrograde catheter to that region. Figure 7.6 illustrates a case in which both LVOT and midcavity gradients are present.

During cardiac catheterization, one may determine whether a Brockenbrough sign (perhaps the least well understood sign in cardiology) is present (Fig. 7.5) [8]. A Brockenbrough sign is defined as a failure of the systemic arterial pulse pressure to increase after a ventricular premature beat (*not*, as is often mistakenly believed, an increase in the LVOT gradient), representing diminished stroke volume resulting from exacerbation of LVOT obstruction [8]. Since the gradients of valvular aortic stenosis and hypertrophic obstructive cardiomyopathy (HOCM) both increase in a postextrasystolic beat, the increase does not distinguish between the two conditions. Since the pulse pressure increases after a postextrasystolic beat in valvular aortic stenosis (Fig. 7.7), it is the decrease after a postextrasystolic beat in HOCM (the Brockenbrough sign) that distinguishes the two conditions. The fact that it is the systemic arterial pulse pressure rather than the LVOT gradient that defines the Brockenbrough sign is brought home by the point that it is actually possible to observe a Brockenbrough sign without placing a catheter in the LV (Fig. 7.8). A "spike and dome" waveform in the aortic pressure tracing (Fig. 7.8), either

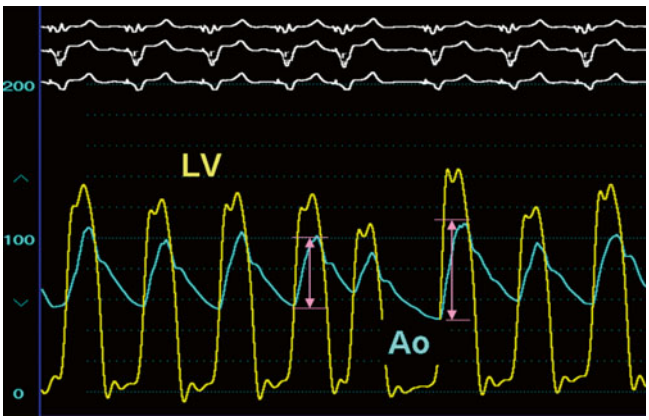

Fig. 7.7 Simultaneous left ventricular (*LV*) and aortic (*Ao*) pressure tracings from a patient with valvular aortic stenosis. In the beat following a pause, there is an increase in the transvalvular gradient *and* in the aortic pulse pressure (*arrows*); thus, the Brockenbrough sign is absent

fixed or variable, is highly specific for outflow tract obstruction.

In patients with HOCM, left ventriculography in the cranially-angulated left anterior oblique projection demonstrates the pathoanatomic features of LVOT obstruction (Fig. 7.9). A "pullback" from LV to aorta in a patient with LVOT obstruction is shown in Fig. 7.10; there is no gradient across the aortic valve. A similar finding occurs in the rare adult with a subaortic membrane (Fig. 7.11). In this case, the Brockenbrough sign is absent and the membrane may be visualized by left ventriculography in the cranial left anterior oblique projection (Fig. 7.11).

Supine exercise testing in the cath lab may be useful for understanding exertional symptoms in patients with HCM. Exercise parameters of interest include heart rate, PA and PCW pressures, and cardiac output. Exercise testing

Fig. 7.8 Aortic (*Ao*) pressure tracing from a patient with HOCM. The Brockenbrough sign (a fall in the systemic arterial pulse pressure in the postextrasystolic beat) is present. Furthermore, the "spike and dome" morphology typical of HOCM is accentuated, a sign of great obstruction to left ventricular outflow, in the postextrasystolic beat

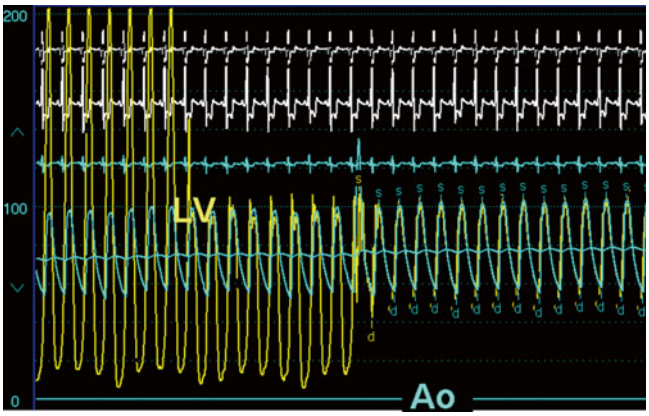

Fig. 7.10 Catheter "pullback" from LV (*LV*) to aorta (*Ao*) from a patient with HOCM. LV systolic pressure drops from approximately 200 to 100 mmHg within the LV cavity, indicating that the pressure gradient is within the cavity. There is no change in systolic pressure as the catheter is withdrawn across the aortic valve, indicating that valvular aortic stenosis is absent

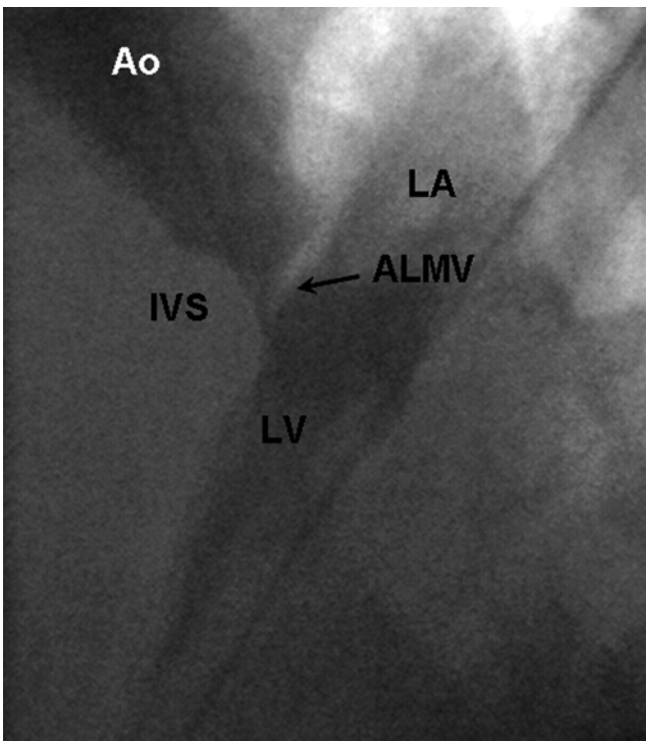

Fig. 7.9 Left ventriculogram in the cranially angulated left anterior oblique projection from a patient with HOCM. There is SAM of the anterior leaflet of the mitral valve (*ALMV*), which is in apposition to the interventricular septum (*IVS*). The LV (*LV*) has contracted down to a low end-systolic volume. There is contrast in the left atrium (*LA*), reflecting MR. (*AO*) aorta

may be accomplished with the use of a cycle or, alternatively, alternating active leg raising in patients with internal jugular or upper extremity access; or with active single leg raising in patients with femoral access. Exertional dyspnea may be explained, for example by an exercise-induced increase in PCW pressure, by absence of an appropriate increase in cardiac output, or by a combination of the two. Alternatively, exercise-induced pulmonary hypertension with abnormal (or increasing) PVR implicates a separate pulmonary process as the cause of dyspnea.

On occasion, right (or left) ventricular endomyocardial biopsy may be useful for detecting the presence of Fabry disease or amyloidosis (Fig. 7.12). In the latter case, we recommend that an abdominal fat pad biopsy (which has lower sensitivity but also lower morbidity) and/or cardiac MRI be done prior to consideration of endomyocardial biopsy.

Cardiopulmonary Exercise Testing (CPET)

CPET is a safe and often valuable diagnostic modality in patients with HCM. CPET, typically performed on a treadmill or upright cycle ergometer, integrates graded exercise to volitional peak effort or symptom limited test termination with simultaneous measurement of ventilatory gas exchange and systemic arterial oxygen saturation and continuous 12-lead electrocardiography. Comprehensive reviews of CPET technical performance and diagnostic capabilities are available for the interested reader [9, 10].

Among patients with suspected or confirmed HCM, CPET provides the most accurate and reproducible quantification of functional capacity and proves useful for establishing the diagnosis, determining the relative contributions to symptoms of cardiac and pulmonary diseases, estimating prognosis, determining suitability for heart transplantation, and assessing response to therapy. Despite theoretical concerns about the risk of intense exercise among patients with

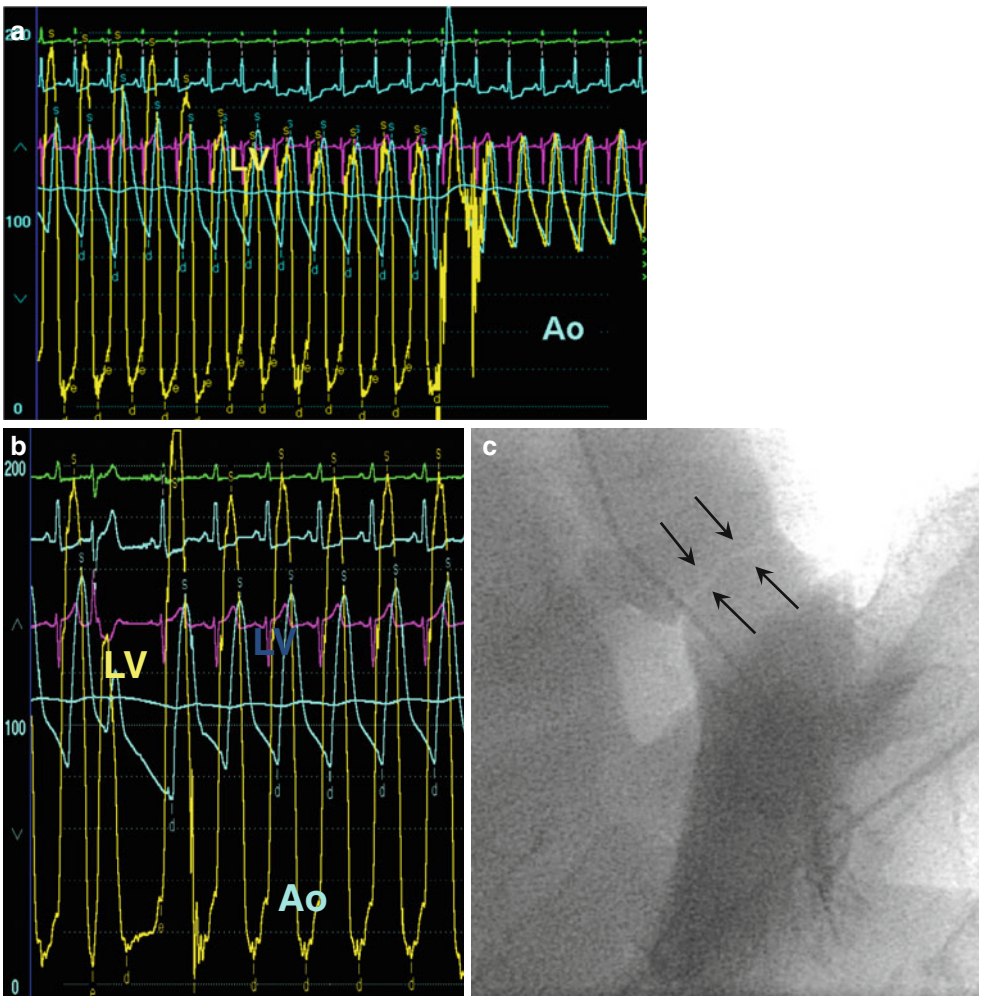

Fig. 7.11 Panel (**a**), catheter "pullback" from LV (*LV*) to aorta (*Ao*) from a patient with a subaortic membrane. LV systolic pressure drops from approximately 180 to 140 mmHg within the LV cavity, indication that the pressure gradient is within the cavity. There is no change in systolic pressure as the catheter is withdrawn across the aortic valve, indication that valvular aortic stenosis is absent. Panel (**b**), simultaneous LV and FA pressure tracings. The systemic arterial pulse pressure increases in the postextrasystolic beat, indicating that the Brockenbrough sign is absent. Panel (**c**), left ventriculogram in the cranially angulated left anterior oblique projection, showing the thin subaortic membrane (*arrows*)

high risk cardiovascular disease, including HCM, the safety of CPET has been demonstrated, with adverse event rates among a large series ambulatory patients of less than 0.2 % [11]. The primary outcome variable obtained from CPET is peak oxygen uptake (peak VO_2). Peak VO_2 is the most accurate determinant of functional capacity and is a powerful predictor of prognosis in patients with cardiovascular disease [12].

CPET facilitates management of patients with suspected or confirmed HCM in several ways. First, peak VO_2 can be used to assist in differentiating physiologic, exercise-induced LV hypertrophy from mild forms of pathologic HCM. In a small but illustrative series, Sharma et al. demonstrated striking differences in oxygen kinetics between trained athletes with LV hypertrophy and patients with mild phenotypic HCM [13]. These investigators suggested a peak VO_2 cut-point of >120% age/gender predicted maximum for differentiating athletic cardiac remodeling from HCM. An example comparing CPET results from a healthy athlete with physiologic LVH and an age-matched asymptomatic athletic patient with nonobstructive HCM is shown in Fig. 7.13.

Second, CPET is useful for determining whether symptoms such as dyspnea or subjective exercise intolerance are attributable to a central cardiovascular limit (i.e. caused by HCM) or by a primary, perhaps underappreciated, pulmonary process. This distinction is critical in patients with HCM and concomitant lung disease, such as older patients with chronic obstructive lung disease or younger patients with asthma.

Third, CPET can be used to assess response to therapy among patients with symptomatic HCM. This evaluation is particularly useful in patients with LVOT obstruction treated with negative inotropic medications who fail to respond to therapy. In some cases, the benefits of negative inotropy afforded by beta blockers or nondihydropyridine calcium channel blockers may be outweighed by undesired reductions in achievable heart rate. Additionally,

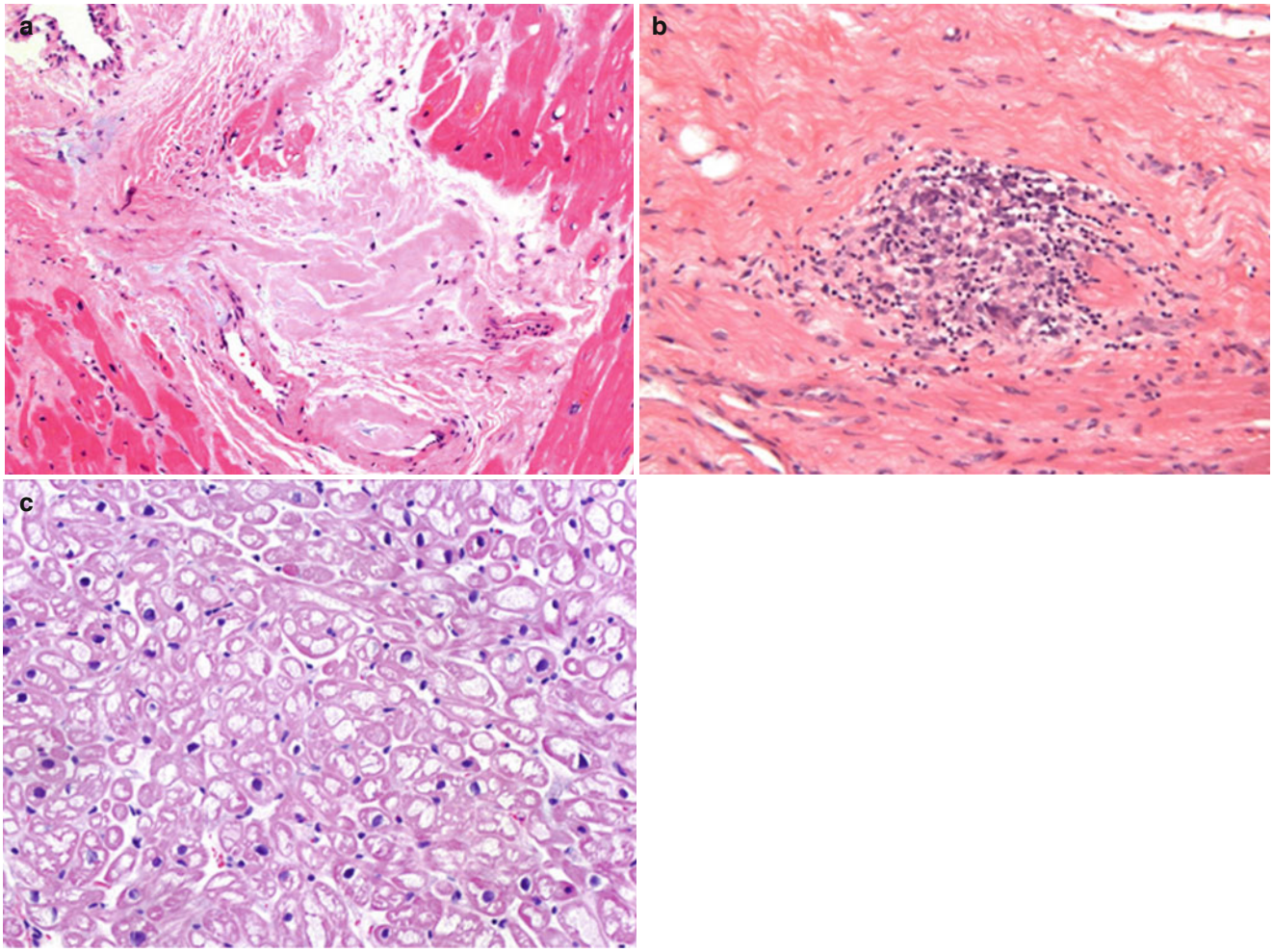

Fig. 7.12 Pathology specimens from three patients presenting with cardiac symptoms and signs indistinguishable from those of HCM. Panel (**a**), amyloidosis; panel (**b**), sarcoidosis; panel (**c**), Fabry disease. The Fabry specimen was obtained by RV endomyocardial biopsy, while the other two are septal myectomy specimens

peak VO_2 is inversely related to the degree of LVOT obstruction and improves significantly with septal reduction therapy [14]. Finally, as in other heart failure populations, CPET in patients with HCM and advanced heart failure is a key determinant of eligibility for cardiac transplantation.

Illustrative Cases

Symptomatic LVOT Obstruction

A 62 year old woman was referred to our HCM Program with exertional dyspnea, chest pain, and lightheadedness. She had been treated with metoprolol, with partial improvement. Heart rate was 60 and blood pressure 105/80. There was a grade II systolic ejection murmur. Electrocardiogram (ECG) showed normal sinus rhythm, left atrial enlargement, and T wave inversion in leads I, II, III, $_aV_F$, and $V_{2–6}$. Echocardiography demonstrated an LVOT gradient of 34 mmHg at rest and 84 mmHg with Valsalva maneuver. We placed her on disopyramide in a controlled-release preparation, and her symptoms resolved [15, 16].

Heart Failure in Nonobstructive HCM

A 38 year old man was referred to our HCM Program with exertional dyspnea. Heart rate was 75 and blood pressure 120/55. He had no murmur. ECG showed normal sinus rhythm and apicolateral ST and T wave abnormalities

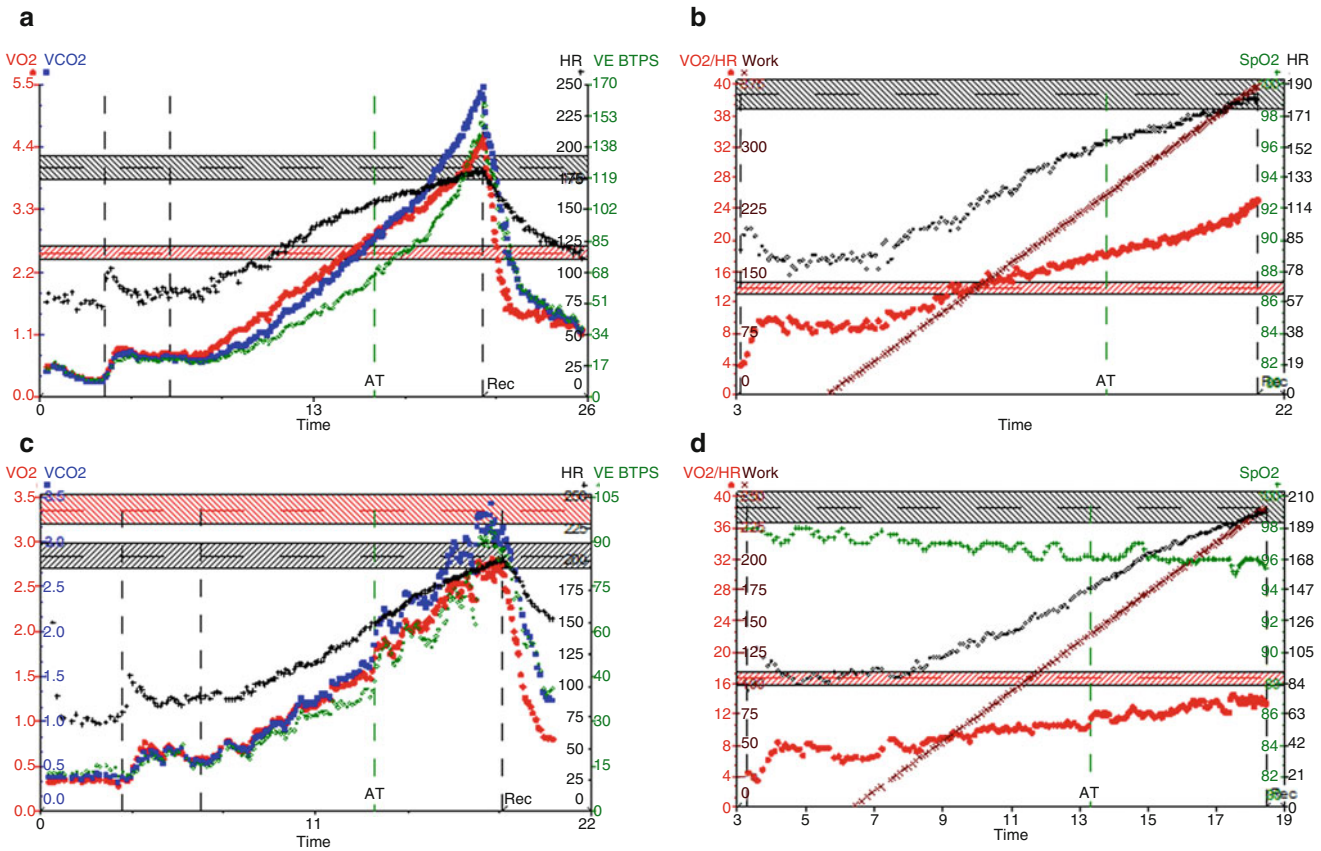

Fig. 7.13 Cardiopulmonary exercise test (CPET) data from a healthy 24 year old rower with mild LVH detected during a research study (**a** and **b**) and a 21 year old rower found to have mild phenotypic nonobstructive HCM during pre-participation screening (**c** and **d**). Panel (**a**) depicts a normal linear heart rate response to graded exercise (*black line*) coupled with normal VO_2 kinetics (*red line*) and a peak VO_2 of roughly 170 % predicted. Panel (**b**) demonstrates a normal progressively increasing oxygen pulse (*red line*), reflecting normal stroke volume augmentation [O_2 pulse = stroke volume × $C(a-v)O_2$] during exercise. In contrast, panel (**c**) depicts blunted peak VO_2, despite reaching an appropriate peak heart rate, coupled with reduced O_2 pulse (panel **d**), indicating impaired exercise capacity due to a primary cardiovascular limit

consistent with strain. Echocardiography showed septal thickness 19 mm, posterior wall thickness 9 mm, ejection fraction 0.55, no LVOT gradient at rest or during Valsalva maneuver, biatrial enlargement, and estimated RV systolic pressure 48 mmHg. He exercised for 3 min, 31 s of a Bruce protocol, with heart rate increasing from 85 to 150 and blood pressure from 128/70 to 144/68. He had dyspnea and fatigue without chest discomfort. There were occasional atrial and ventricular premature beats, with an atrial triplet in early recovery. There were no ST segment changes. Cardiac catheterization showed right atrial pressure 14 mmHg, pulmonary arterial systolic pressure 54 mmHg and mean pressure 40 mmHg, pulmonary capillary wedge pressure 33 mmHg, cardiac output 4.4 l/min, cardiac index 1.6 l/min/m^2, and minimal coronary atherosclerosis. He was treated with furosemide with resolution of dyspnea.

Heart Failure with Intrinsic Mitral Valve Pathology and Atrial Fibrillation

A 52 year old man was referred to our HCM Program for evaluation and follow-up of HCM and mitral valve prolapse. He had no cardiac symptoms. There was a grade III systolic murmur with wide radiation, including to the axilla; with Valsalva maneuver, it became harsher in quality. ECG showed sinus rhythm and left atrial enlargement. Echocardiography showed left ventricular end-diastolic dimension 56 mm, septal thickness 15 mm, posterior wall 12 mm, ejection fraction 0.75, LVOT gradient 18 mmHg at rest and 47 mmHg with Valsalva maneuver, SAM, prolapse of the posterior mitral leaflet with moderate to severe regurgitation, left atrial enlargement, RV systolic pressure 48 mmHg, mild tricuspid regurgitation, and right atrial enlargement. There were two jets of MR, one posteriorly

directed and one anteriorly directed, with the latter predominating. He had a family history of sudden cardiac death and had ventricular tachycardia on Holter monitoring, and received an implantable cardioverter defibrillator.

He developed mild exertional dyspnea. He had an episode of atrial fibrillation, and warfarin and disopyramide were added to atenolol. At age 56, echocardiography showed LVOT gradient 11 mmHg at rest and 22 mmHg with Valsalva maneuver, severe MR with a flail posterior leaflet, and RV systolic pressure 50 mmHg. Cardiac catheterization demonstrated pulmonary capillary wedge pressure 24 mmHg with large v waves and mild CAD. In the operating room, there was flail of the P1, P2, and P3 segments of the mitral valve, as well as marked elongation of the chordae tendineae. He underwent mitral valve replacement, septal myectomy, maze procedure, and left atrial appendage amputation.

Conclusions

Manifestations of heart failure in HCM result from a combination of LVOT obstruction, diastolic dysfunction, and MR, as well as secondary problems including pulmonary hypertension and atrial fibrillation. The clinical presentation may be complicated by concomitant intrinsic valvular disease, CAD, or pulmonary disease. While MR regularly accompanies LVOT obstruction and SAM in patients with HOCM, careful echocardiographic assessment of the mitral valve for intrinsic pathology is essential. Whereas the results of conventional exercise testing may be ambiguous, coronary CTA and cardiac catheterization are reliable means of detecting concomitant CAD. CPET is often useful for the distinction between HCM and pulmonary disease as the cause of dyspnea. While not a component of the routine evaluation of patients with HCM, cardiac catheterization often provides critical additional information.

Clinical Pearls

- Patients with HCM may be particularly prone to orthostatic hypotension and to postprandial splanchnic shunting, and may experience symptoms only after meals.
- In patients with hypotension, the Valsalva maneuver may result in hypotension. Therefore, the patients should be placed in the supine position before the maneuver is elicited.
- When MR results from LVOT obstruction with SAM of the anterior leaflet, the jet is directed posterolaterally. The presence of a jet oriented in another director should prompt a search for an intrinsic abnormality of the valve.
- The Brockenbrough sign is a decrease in the systemic arterial pulse pressure (*not an increase in LVOT gradient*) in the beat following a ventricular premature beat.
- Left ventricular outflow tract (LVOT) gradients may be distinguished from midcavity gradients by careful manipulation of the catheter within the LV.
- The presence of aortic regurgitation should lead to careful evaluation for a subaortic membrane as a mimic of HOCM.

References

1. Frenneaux MP, Counihan PJ, Caforio AL, Chikamori T, McKenna WJ. Abnormal blood pressure response during exercise in hypertrophic cardiomyopathy. Circulation. 1990;82(6):1995–2002. 617-782-6674.
2. Maron MS, Hauser TH, Dubrow E, et al. Right ventricular involvement in hypertrophic cardiomyopathy. Am J Cardiol. 2007;100(8):1293–8.
3. Kaple RK, Murphy RT, DiPaola LM, et al. Mitral valve abnormalities in hypertrophic cardiomyopathy: echocardiographic features and surgical outcomes. Ann Thorac Surg. 2008;85(5):1527–35, 35 e1–2.
4. Gupta RM, Weiner RB, Baggish AL, Fifer MA. Still a kid at heart: hypertrophic cardiomyopathy in the elderly. Circulation. 2011;124(7):857–63.
5. Ahn KT, Lee YD, Choi UL, et al. Flail subaortic membrane mimicking left ventricular outflow tract obstruction in hypertrophic cardiomyopathy. J Cardiovasc Ultrasound. 2013;21(2):90–3.
6. Olivotto I, Cecchi F, Casey SA, Dolara A, Traverse JH, Maron BJ. Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. Circulation. 2001;104(21):2517–24.
7. O'Gara PT, Bonow RO, Maron BJ, et al. Myocardial perfusion abnormalities in patients with hypertrophic cardiomyopathy: assessment with thallium-201 emission computed tomography. Circulation. 1987;76(6):1214–23.
8. Brockenbrough EC, Braunwald E, Morrow AG. A hemodynamic technic for the detection of hypertrophic subaortic stenosis. Circulation. 1961;23:189–94.
9. Balady GJ, Arena R, Sietsema K, et al. Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. Circulation. 2010;122(2):191–225.
10. American Thoracic Society; American College of Chest Physicians. ATS/ACCP statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med. 2003;167(2):211–77.
11. Skalski J, Allison TG, Miller TD. The safety of cardiopulmonary exercise testing in a population with high-risk cardiovascular diseases. Circulation. 2012;126(21):2465–72.
12. Stelken AM, Younis LT, Jennison SH, et al. Prognostic value of cardiopulmonary exercise testing using percent achieved of predicted peak oxygen uptake for patients with ischemic and dilated cardiomyopathy. J Am Coll Cardiol. 1996;27(2):345–52.

13. Sharma S, Elliott PM, Whyte G, et al. Utility of metabolic exercise testing in distinguishing hypertrophic cardiomyopathy from physiologic left ventricular hypertrophy in athletes. J Am Coll Cardiol. 2000;36(3):864–70.
14. Kim JJ, Lee CW, Park SW, et al. Improvement in exercise capacity and exercise blood pressure response after transcoronary alcohol ablation therapy of septal hypertrophy in hypertrophic cardiomyopathy. Am J Cardiol. 1999;83(8):1220–3.
15. Fifer MA, Vlahakes GJ. Management of symptoms in hypertrophic cardiomyopathy. Circulation. 2008;117(3):429–39.
16. Rothman RD, Baggish AL, O'Callaghan C, et al. Management strategy in 249 consecutive patients with obstructive hypertrophic cardiomyopathy referred to a dedicated program. Am J Cardiol. 2012;110(8):1169–74.

Assessment of Syncope

8

Nickolaos Michelakis and Todd J. Cohen

Abstract

Patients with hypertrophic cardiomyopathy can manifest syncope during the course of their disease. This chapter reviews three etiologies of syncope in these patients: arrhythmogenic causes (bradycardia and tachycardia), left ventricular outflow tract obstruction, and neurocardiogenic causes. An approach to the evaluation of the syncope in terms of etiology, diagnosis, and recommended treatment is presented.

Keywords

Adrenergic beta-1 receptor antagonists • Autonomic nervous system diseases • Cardiac arrhythmias • Catheter ablation • Hypertrophic cardiomyopathy • Implantable defibrillators • Left ventricular outflow obstruction • Neurocardiogenic syncope • Sudden cardiac arrest • Sudden cardiac death • Syncope • Ventricular tachycardia

Key Points

- Hypertrophic cardiomyopathy is associated with syncope via three major mechanisms: arrhythmias, left ventricular outflow tract obstruction, and autonomic dysfunction.
- Major risk factors for sudden cardiac arrest in hypertrophic cardiomyopathy include: an area of thickened myocardium exceeding 3 cm, sustained ventricular tachycardia, a family history of sudden cardiac arrest in someone <50 years of age with a known diagnosis of hypertrophic cardiomyopathy, a history of recurrent, unexplained syncope, and finally a history of cardiac arrest.
- Work up of syncope includes a history, a physical exam, a baseline ECG, and non-invasive testing; invasive testing may be necessary in a subset of patients.
- Mainstay of therapy includes beta-1-selective blockade for those with obstructive physiology, implantable cardioverter-defibrillator implantation for high-risk SCD candidates or those with documented malignant arrhythmias, and cardiac catheter ablation for those with recurrent and refractory, symptomatic ventricular tachycardia.

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Introduction

Syncope (from the Greek: "syn" -thoroughly and "koptein"- to cut.) can be defined as a complete loss of consciousness. It is not an infrequent condition in hypertrophic cardiomyopathy, and indeed the anatomic structure, function, and geometry of the heart in patients with hypertrophic cardiomyopathy may result in the propensity to syncopize. In particular, myocardial disarray in hypertrophic cardiomyopathy, neurologic innervation of the myocardium, and/or anatomy of left ventricular outflow tract obstruction may all contribute to the development of syncope, and should be fully evaluated.

This chapter reviews three distinct, and potentially interrelated, etiologies of syncope in patients with hypertrophic cardiomyopathy: arrhythmogenic causes (bradycardia and tachycardia), left ventricular outflow tract obstruction, and neurocardiogenic causes, including autonomic dysfunction. The chapter discusses the etiology, presentation and pathophysiology of these etiologies, focusing on the first two as they are the most common. The chapter also reviews an approach to the workup and recommended treatment of syncope in the affected population.

Arrhythmogenic Causes

Arrhythmogenic causes of syncope in patients with hypertrophic cardiomyopathy may be the most life-threatening, but fortunately the most amenable to therapy. The presentation of this type of syncope may be either without warning signs or with premonitory symptoms of lightheadedness and dizziness (presyncope), syncope, and/or palpitations. Occasionally, patients may feel other hemodynamic effects of arrhythmia and complain of chest pressure and shortness of breath. Table 8.1 lists the arrhythmias which may be potential causes of syncope in hypertrophic cardiomyopathy: (1) bradycardias, such as sinus node, AV nodal disease, and other forms of conduction disorders (including disease in the His-Purkinje system) and (2) tachycardias, including supraventricular and ventricular forms. Supraventricular tachycardia (such as atrial fibrillation) may be highly symptomatic and, in those with significant left ventricular outflow tract obstruction, may result in syncope either from a rapid ventricular response or a loss of atrial kick. Non-sustained ventricular tachycardia in and of itself may be a marker for sudden death but is oftentimes asymptomatic in this population. Non-sustained ventricular tachyarrhythmias might also be symptomatic and result in lightheadedness and dizziness (pre-syncope), especially when prolonged or when there is profound diastolic dysfunction. When identified, non-sustained ventricular tachycardia and/or ventricular tachycardia may be harbingers of subsequent sudden cardiac death ("SCD"), especially when combined with other SCD risk factors. Sustained ventricular tachycardia in particular may be poorly tolerated due to an elevated rate and the associated loss of atrial component to late diastolic filling, and also may degenerate to ventricular fibrillation and sudden cardiac death. Fortunately, once ventricular tachycardia and/or a confluence of associated risk factors are identified, device-based treatment with an implantable defibrillator can effectively prevent sudden death.

Table 8.1 Arrhythmias contributing to syncope

1. Bradycardia
(a) Conduction Disease
(b) Sinus node dysfunction
(c) Tachy-brady Syndrome
2. Tachycardias
(a) Atrial Fibrillation
(b) Ventricular tachycardia
(c) Ventricular Fibrillation

The micro- and macroscopic anatomic substrate, together with the superimposed stress and strain of the hypertrophied myocardium's contraction may predispose the affected population to arrhythmia and syncope. On a microscopic level, the substrate's inherent myocardial disarray may create the amount of differential electrical conduction (anisotropy) needed for bidirectional conduction and unidirectional block (a prerequisite for reentrant tachycardia). This anisotropy may be a basic requirement for a circus rhythm tachycardia or reentry in patients with hypertrophic cardiomyopathy. Reentry is a principal mechanism in both ventricular and supraventricular tachyarrhythmias. Spirito and colleagues [1] have shown that the thicker myocardium in patients with hypertrophic cardiomyopathy, in particular left ventricular septal thickness of greater than 3 cm, places patients at a higher risk for sudden death; whether the thickness is a surrogate for the extent of disarray and potential for re-entrant arrhythmias remains unknown, but scar density appears to track with thickness at least in some. In addition, several other markers may lead to an increased propensity to sudden death, including the presence of outflow tract obstruction. Thus, at a macroscopic level, the outflow tract obstruction makes a patient more susceptible to the hemodynamic consequences of arrhythmias that may be better tolerated in those with more normal hearts, while at the microscopic level both diastolic dysfunction and the propensity to reentrant arrhythmias are evident. Jensen et al. [2] and Orme et al. [3] have found that the treatment of hypertrophic cardiomyopathy with alcohol septal ablation and/or surgical septal myectomy may result in a reduction in either sudden death (in the former) or syncope (in the latter). This shows the interrelationship between myocardial disarray, left ventricular outflow tract gradient, and arrhythmogenic causes of sudden death. Table 8.2 lists the risk factors for sudden death in patients with hypertrophic cardiomyopathy.

Table 8.2 Major risk factors for sudden cardiac death

1. Thickened myocardium > 3 cm in any location
2. Family with history of sudden death in HCM patient < 40–50 years of age
3. Sustained ventricular tachycardia
4. Sustained ventricular fibrillation/cardiac arrest
5. History of recurrent, unexplained and recent syncope

Spirito and colleagues [4] investigated syncope and sudden death in over 1,500 patients with hypertrophic cardiomyopathy. In this patient population, 40 % had experienced syncope. The relative risk of sudden death in the population was 1.78. Importantly, a recent syncopal event occurring within 6 months was associated with a five-fold increased risk of sudden death as compared to those who did not experience syncope. Moreover, patients with distant syncopal episodes did not show an increased risk of sudden death. Importantly, syncope in and of itself is not a major risk factor; rather, refractory and unexplained syncope is a harbinger of sudden cardiac death. If the syncope cannot be explained by bradycardia, autonomic dysfunction or outflow tract gradient, then malignant arrhythmia is the most likely etiology by exclusion and warrants implantable cardioverter-defibrillator placement.

Bradycardia as an etiology of syncope in patients with hypertrophic cardiomyopathy is relatively rare. Bradycardia may be due to excessive beta-blocker or other AV nodal blocking agents, particularly in elderly patients with some degree of degenerative conduction disease, or in patients with atrial fibrillation with slow ventricular response; alternatively, conduction disease for any number of reasons is also possible, although it is a rare occurrence in this disease. Nonetheless, such bradyarrhythmias can potentiate syncope, and necessitate treatment with a permanent pacemaker. In some patients, prior surgical myectomy or alcohol septal ablation may mitigate the occurrence of syncope from outflow tract obstruction but result in intermittent or permanent conduction disease and bradycardia-induced syncope instead. Such patients also benefit from permanent pacemaker placement, with resolution of syncope.

Left Ventricular Outflow Obstruction

Left ventricular outflow obstruction is a major cause of syncope in hypertrophic cardiomyopathy patients. The dynamic nature of obstruction may cause dizziness and syncope in patients who are dehydrated or who are under physical stress. Physical stressors may include climbing stairs, rising from a seated position, or even walking briskly or running briefly from a standing position. Certain medications may precipitate syncope in hypertrophic cardiomyopathy patients, especially those that either reduce preload and/or afterload. Angiotensin converting enzyme inhibitors, angiotensin-receptor inhibitors, and systemic vasodilators in particular can reduce the afterload. Drugs that vasodilate the systemic periphery include phosphodiesterase-5 inhibitors used for either erectile dysfunction or pulmonary hypertension, such as sildenafil and tadalafil. Drugs that reduce the preload include venodilators such as nitroglycerin and loop diuretics such as furosemide.

Patients can also develop pre-syncopal or syncopal episodes in post-prandial states. Splanchnic blood flow is augmented, and may be greater after large meals. Blood is shunted to the gut to increase absorption of food content. This reduces available blood for left ventricular preload, effectively "dehydrating" the hypertrophic cardiomyopathy patient and promoting the development of syncope. Accordingly, post-prandial exacerbation of dyspnea and/or syncope is a commonplace complaint among symptomatic obstructive patients with HCM.

The syncope related to a significant outflow tract gradient may be abrupt, without warning signs, similar to that traditionally ascribed to arrhythmogenic syncope. Although most patients notice premonitory symptoms, including a flushed sensation or lightheadedness, traumatic syncope can and does occur in the absence of an arrhythmia and should not automatically implicate an arrhythmogenic etiology.

Autonomic Dysfunction and Neurocardiogenic Syncope

The autonomic nervous system consists of myelinated parasympathetic and unmyelinated sympathetic nerve fibers innervating the myocardium. Stretch receptors present in the carotid bodies and aortic arch sense fluctuations in blood pressure on a beat-to-beat basis and the response to these fluctuations leads to the regulation of the heart rate and peripheral vascular resistance, known as the baroreceptor reflex [5]. Delicate control of blood pressure and heart rate are dependent on the baroreceptor reflex function. The baroreceptor reflex mechanisms involve the integration of afferent signals from the carotid baroreceptors (via the glossopharyngeal nerve) and the aortic arch baroreceptors, as well as the left ventricular mechanoreceptors (via the vagus nerve), which sense changes in preload [6]. The central nervous system integrates the afferent mechanical stretch information and then responds with efferent flow to the heart and peripheral vessels [7]. These relationships are depicted in Fig. 8.1.

These efferent signals flow along the vagus and sympathetic nerves, innervating the SA and AV nodes, as well as the atrial and ventricular myocardium. The sympathetic efferent flow to the arterial resistance and venous capacitance

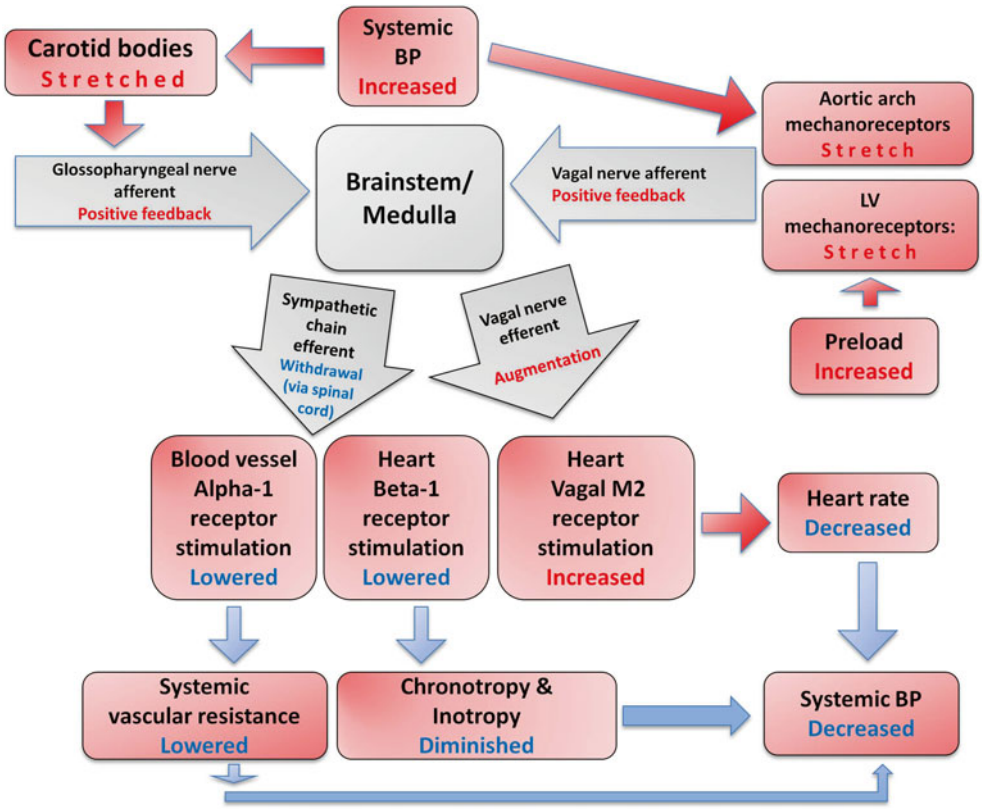

Fig. 8.1 Normal individual profile

vessels adjusts the peripheral vascular tone according to the prevailing extent of baroreceptor stretch. For example, with increased carotid baroreceptor and left ventricular mechanoreceptor stretch, there is decreased peripheral vascular tone, thereby maintaining hemodynamic homeostasis.

In general, activation of the baroreceptor reflex leads to withdrawal of sympathetic tone and prolongs ventricular re-polarization and refractoriness [8]. There is decreased sympathetic efferent flow to the peripheral vascular smooth muscle (alpha-mediated vasoconstriction) and cardiac tissue (beta-1-mediated tachycardia), thereby exerting a negative feedback effect on the hemodynamic status, i.e., decrease in systemic vascular resistance and decrease in heart rate [9].

The distribution of autonomic fibers highlights the heterogeneity of autonomic tone in the heart, both from apex-to-base and transmurally, from epicardium to endocardium. When viewed from base to apex, the sympathetic fibers run along the sub-epicardial surface of the left ventricle. The parasympathetic fibers, however, start subepicardially at the left ventricular base, course towards the subendocardial surface at the left ventricular base and then continue along the subendocardial surface to terminate in the left ventricular apex [10]. This autonomic nervous system distribution underscores the importance of vagal tone in the subendocardial region of the left ventricular outflow tract, located at the septal base of the left ventricle.

In hypertrophic cardiomyopathy patients, the afferent limb of the baroreflex mechanism may be defective, as evidenced by a dampened forearm vascular resistance, which measures the dampened alpha-mediated vasoconstriction response to reduced left ventricular preload [6] (see Fig. 8.2). The impaired afferent flow from the left ventricular mechanoreceptors to the brainstem may be secondary to the disorganized myocyte arrangement characteristic of patients with hypertrophic cardiomyopathy. With increased left ventricular preload and left ventricular outflow tract obstruction, the left ventricular mechanoreceptors are stimulated, but they do not send vagal afferent signals to the brain stem. Concurrently, the aortic arch and carotid bodies are not stretched due to the overall reduced stroke volume from the left ventricular outflow tract obstruction. This leads to an overall sustained sympathetic tone to the vascular alpha-1 and cardiac beta-1 receptors, along with a lack of vagal tone augmentation to the left ventricular basal septal subepicardial and subendocardial surfaces. The overall effect is heightened sympathetic tone to the left ventricular myocardium, causing an augmented inotropic and chronotropic left ventricular response. This leads to an exacerbation of the left ventricular outflow tract obstruction and perpetuation of the fall in cardiac output characteristically seen in hypertrophic cardiomyopathy patients.

Prasad and colleagues [11] have shown that approximately a third of patients with hypertrophic cardiomyopathy

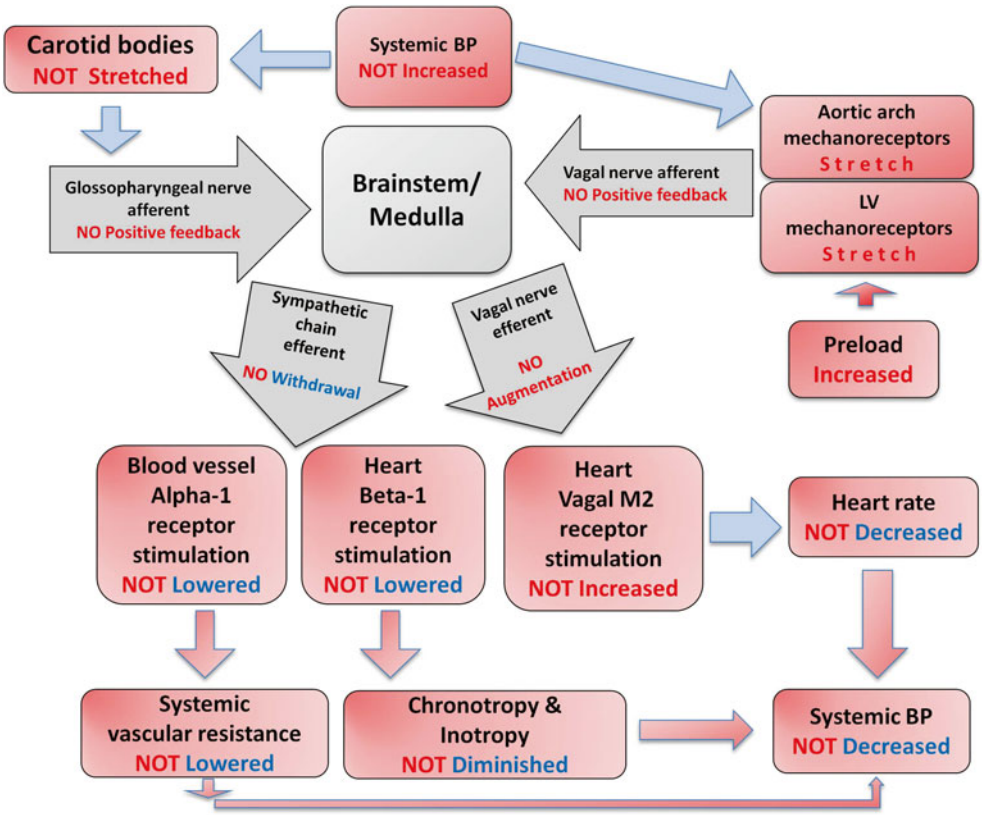

Fig. 8.2 HCM patient profile

have an abnormal blood pressure response during peak exercise. This has been attributed to an exaggerated decrease in the systemic vascular resistance as well as the development of outflow tract obstruction in some. They attributed the former to an abnormality in the activation of mechanoreceptor C-fibers found in the left ventricle. More recently, they have implicated this mechanism as a potential cause for syncope in patients with hypertrophic cardiomyopathy, and a risk factor for sudden cardiac death in some patients. They examined a total of 29 patients and found vascular instability as a cause of syncope or pre-syncope in 8 of the 18 patients who reported symptomatic impairment of consciousness (syncope or pre-syncope).

Table 8.3 Syncope work-up

1. History
2. Physical exam
3. ECG
4. Non-invasive tests
(a) Holter monitor
(b) Event/loop recorder
(c) Echocardiogram
(d) Exercise stress test
5. Other imaging studies
6. Invasive testing
(a) Cardiac catheterization
(b) Electrophysiology testing

Syncope Workup in Hypertrophic Cardiomyopathy

The workup of syncope in hypertrophic cardiomyopathy is very similar to that of syncope in general (see Table 8.3). It begins with a history, paying attention to the type of presentation, the presence of premonitory symptoms, and the abruptness of the presentation. Patients with hypertrophic cardiomyopathy may have abrupt syncope, frequently leading to trauma, regardless of the underlying etiology, and presumably because of the interplay and potentiation of multiple potential mechanisms once the cycle begins. This is unlike the presentation in the general population, where traumatic syncope is almost always due to brady -or tachy- arrhythmias. Palpitations and their association to lightheadedness or dizziness (pre-syncope) may still indicate an arrhythmogenic cause, however. In contrast, a more gradual, somewhat posturally-related syncopal presentation may tend more towards neurocardiogenic syncope and/or autonomic dysfunction. Syncope related to dehydration, non-compliance with medications, or new medications (especially vasodilators) may lead to exacerbation of the pre-existing left ventricular outflow obstruction physiology as the causative mechanism. And, finally, syncope on exertion may be due to

any of the three mechanisms, outflow tract obstruction, arrhythmia or autonomic dysfunction.

After a thorough history, a complete physical examination should be performed. Patients may often have the typical physiologic findings of hypertrophic cardiomyopathy and examination with and without Valsalva is often useful to elicit the outflow tract physiology. An S4 gallop may further implicate diastolic dysfunction. An electrocardiogram may be helpful with specific attention to a long rhythm strip, looking for evidence of heart block and/or supraventricular/ventricular arrhythmias.

A non-invasive workup of syncope asks whether LVOT obstruction is present. Evaluation of the cardiac substrate by two-dimensional echocardiography includes assessment of the degree of myocardial thickness, the left ventricular cavity dimensions, and the presence of outflow tract obstruction. The degree of provoked outflow tract obstruction could also be identified before and after the Valsalva maneuver, while 2D echocardiography images are obtained. Cardiac MRI imaging may be useful in evaluating the scar and/or thickness of the myocardium, as well as look for other potential anatomic causes of obstruction, such as supravalvar and valvar aortic stenosis. Coronary angiography may be useful in confirming the absence of coronary artery disease and the level or severity of outflow tract obstruction. The Brockenbrough-Braunwald-Morrow sign is elicited by provoking a premature ventricular contraction to produce a diminished pulse pressure in the next contraction, thereby assessing if the LVOT obstruction exceeds 30 mmHg or is severe.

When LVOT obstruction is absent and electrocardiographic monitoring for arrhythmias has not yielded any cause for the syncope, then stress testing is indicated to both further rule out obstructive physiology and help determine an abnormal blood pressure response that might indicate a primary autonomic dysfunction issue. Assessment of the potential for LVOT obstruction with activity can be done utilizing exercise/treadmill stress echocardiography. Symptoms may not be present at rest, so elicitation of the obstructive symptoms with treadmill stress testing can help elicit these symptoms. Treadmill testing is well suited to determine the exertional LVOT gradients as well as any occurrence of abnormal blood pressure response (due to underlying autonomic dysfunction) during exercise. Arrhythmogenic causes can also be evaluated during exercise and/or immediately in recovery. A myocardial exercise stress test may also be useful in defining the presentation of syncope as it is helpful to rule out ischemia in this population, which although a rare cause of syncope may be the culprit in some.

If the LVOT obstructs, then the appropriate therapy should be implemented. This includes hydration and lifestyle modification to prevent abrupt drops in preload, which can worsen the LVOT obstruction. Use of long-acting beta-1-selective blockers as first-line agents is indicated. Second- and third-tier choices for medical therapy include non-dihydropyridine calcium-channel blockers and disopyramide. Finally, surgical myectomy or alcohol septal ablation should be considered in severely symptomatic patients. Importantly, patients with recurrent, refractory syncope due to left ventricular outflow tract obstruction may be candidates for invasive therapies, either surgical myectomy or alcohol septal ablation, even when they do not meet NYHA Class 3 or 4 symptoms of heart failure. Elderly patients may also be candidates for a trial of dual chamber pacing to reduce outflow tract obstruction, especially when the use of such devices will allow higher doses of beta-blocker therapy.

In parallel with asking the question whether LVOT obstruction is present, loop recorder monitoring for arrhythmias should be undertaken. If a brady-arrhythmia is present, which is determined to be a contributing factor to syncope, then a pacemaker is indicated. If risk factors for sudden cardiac arrest are present in such a patient, especially if NSVT is also found, then an ICD should be implanted instead. If a tachy-arrhythmia is present, its chamber origin should be determined first. SVTs and AF warrant rate control, anticoagulation, and rhythm control if rate control does not ensure adequate diastolic filling time of the LV. VT warrants ICD implantation, although recurrent VT episodes necessitate anti-arrhythmic therapy and/or possibly catheter-based ablation of the VT foci in addition to ICD implantation.

If no arrhythmia is found during routine 30-day loop recorder monitoring, and the patient continues to have syncope refractory to medications, then the LVOT should be reassessed for obstruction if none has been previously determined to be present. This may warrant invasive testing such as right and left heart catheterization in the awake patient (no sedation). If obstruction is finally determined, the above-described approach for managing LVOT obstruction should be pursued. If there is no LVOT obstruction, then a tilt-table test and/or repeat exercise stress testing with the patient off of their medications may help in determining the presence (or absence) of autonomic dysfunction. With exercise and tilt-table testing, the periphery vasodilates, so maintenance of blood pressure depends on an adequate preload, augmented contractility, and heart rate response.

Adequate hydration and lifestyle modification are necessary to prevent autonomic dysfunction-mediated and LVOT obstruction-mediated syncope. Medications such as beta-blockers with intrinsic sympathomimetic activity may help prevent systemic vasodilatation during tachycardic episodes. If syncope recurs despite adequate hydration, lifestyle modification, and appropriate medication administration, an ICD is indicated. Although this does not treat autonomic dysfunction, the theory is that an arrhythmic focus may still be at play in such patients and simply not uncovered. Given the high risk of SCD in such patients with refractory recurrent syncope and a negative workup, ICD implantation is indicated by consensus opinion. A systematic process to syncope evaluation and treatment in HCM patients is shown in Fig. 8.3a, b.

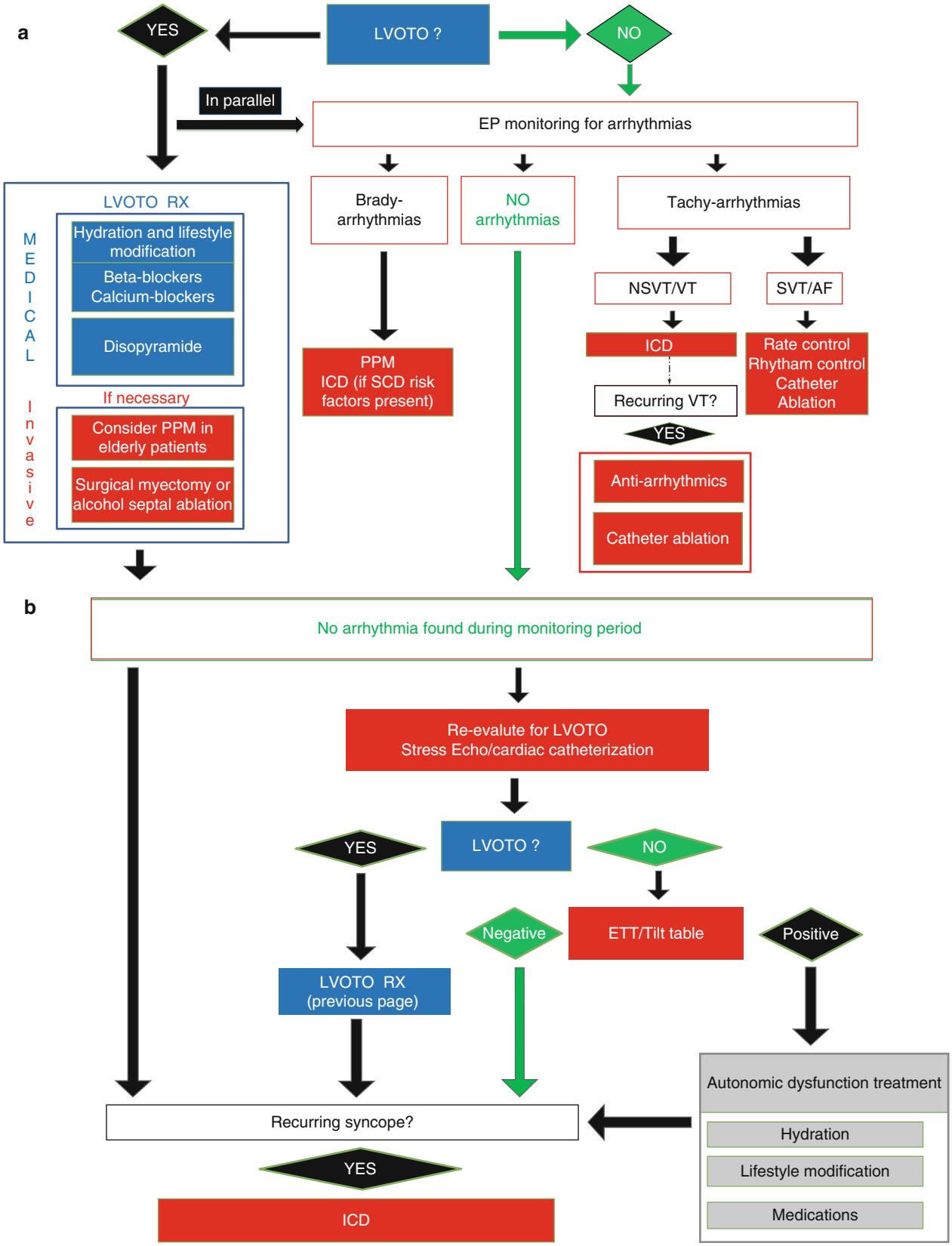

Fig. 8.3 (**a**, **b**) Syncope treatment

The Role of Electrophysiology Testing

The role for invasive electrophysiology testing in hypertrophic cardiomyopathy is not entirely clear. In particular, the finding of inducible ventricular arrhythmias may be nonspecific in this population and does not automatically warrant ICD implantation. However, electrophysiologic testing is useful in confirming the presence or absence of significant conduction disease. It can also be helpful at ruling out supraventricular etiologies that may be treatable via catheter ablation. This includes a variety of paroxysmal supraventricular tachycardias such as atrioventricular reentry (i.e., Wolf Parkinson White syndrome) or atrioventricular nodal reentry. In addition, atrial tachycardia and atrial flutter might be highly symptomatic in this population, but also curative via catheter ablation. The presence or absence of inducible ventricular tachyarrhythmias is not as helpful in this population as in other populations with ischemic cardiomyopathy/coronary artery diseases. In addition, a Holter monitor may be useful, but the implantation of an implantable cardiac monitor and/or implantable loop recorder may be particularly helpful by providing long-term monitoring in order to elucidate the true etiology of syncope.

Treatment

The treatment of syncope depends on the reported etiology (see Table 8.4). It is critical to identify cardiac arrhythmogenic causes in order to treat them accordingly. If the patient presents with cardiac arrest and/or documented sustained ventricular tachycardia and ventricular fibrillation, the treatment must include an implantable cardioverted-defibrillator. If the patient has risk factors placing the patient at high risk for sudden death, such as recurrent, unexplained syncope after a thorough evaluation or severe thickness > 3 cm, an implantable cardioverter-defibrillator must also be considered. The utility of the electrophysiology study in determining and ruling in or out inducible sustained ventricular arrhythmias is less useful in this population, and therefore given a Class III indication in the 2011 ACC/AHA Guidelines on the Diagnosis and Treatment of Hypertrophic Cardiomyopathy [12]. If the patient has the risk factors outlined in Table 8.2, an implantable cardioverter-defibrillator may be useful. However, its implantation might not prevent the exact etiology of syncope which brought the patient to the physician's attention in the first place. However, recurrent syncope with an ICD showing no arrhythmias is a powerful sign that outflow tract gradient or autonomic dysfunction is the etiology. Certain patients who have symptomatic supraventricular arrhythmia such as atrial fibrillation and/or atrial flutter may benefit from pharmacologic therapy, such as amiodarone, disopyramide, or metoprolol succinate. In addition, atrial fibrillation ablation therapy or general cardiac ablation therapy may be useful in treating the supraventricular arrhythmias in this population.

Table 8.4 Treatments

1. Lifestyle modification
2. Pharmacologic
3. Cardiac electrophysiologic ablation
4. Coronary revascularization
5. Invasive therapies for outflow tract obstruction
(a) Surgical myectomy
(b) Alcohol septal ablation
6. Implantable devices
(a) Dual chamber pacing
(b) Antitachycardiac devices (ICDs)

With respect to neurocardiogenic syncope and/or autonomic dysfunction, treating the patient with significant hydration, support/compression stockings may be useful. These are useful measures in all patients with hypertrophic cardiomyopathy who are euvolemic, and especially those with outflow tract obstructive physiology. Use of metoprolol succinate twice daily prolongs the diastolic filling time and increases the left ventricular preload. An implantable loop recorder can be useful in patients who are not at high risk for sudden death and in whom the etiology of recurrent syncope remains a mystery. This relatively innocuous subcutaneous implantable device can be left in place for up to 3 years and can help rule out cardiac arrhythmias as an etiology for the syncope.

The treatment of left ventricular outflow obstruction is twofold: medical and invasive. Lifestyle modification to limit dehydration is important: decreased alcohol intake and decreased caffeine consumption. Beta-1 selective blockers can mitigate the left ventricular outflow obstruction by prolonging the diastolic filling time and reducing contractility, and are the first-line pharmacotherapy. Drugs such as dihydropyridine calcium-channel blockers should be avoided as they can reduce the afterload. Verapamil, a non-dihydropyridine calcium-channel blocker has been used for its negative inotropic, negative chronotropic, and negative dromotropic effects. At high doses, however, systemic afterload reduction may negate the beneficial effect of reduced heart rate and reduced contractility of the left ventricle.

Disopyramide has been used with variable efficacy in reducing the left ventricular outflow obstruction. It is not considered a first-line agent in hypertrophic cardiomyopathy patients with left ventricular outflow obstruction, however, and must be combined with other AV nodal blocking agents.

Importantly, however, disopyramide may reduce both resting and provocable gradients in a subset of patients and thus may be useful. More information on the treatment of outflow tract obstruction is found in the Medical Therapy chapter.

When medical therapy does not successfully improve the left ventricular outflow obstruction and recurrent syncope remains, and when the left ventricular outflow obstruction exceeds 50 mmHg at rest or on provocation, surgical or percutaneous alleviation of the obstruction may be considered regardless of the NYHA heart failure class. This is especially important for patients who continue to pass out despite the absence of significant atrial or ventricular arrhythmias which could explain the syncopal episodes. This subset of patients often demonstrates the interplay between left ventricular outflow obstruction and neurocardiogenic causes. Elimination of the left ventricular outflow obstruction gradient effectively mitigates the interplay between obstruction and the neurocardiogenic-mediated mechanisms for syncope.

Therefore, recurrent non-arrhythmic (due to outflow tract obstruction) syncope despite medical therapy in patients with hypertrophic cardiomyopathy is an indication for advanced invasive therapies despite lack of significant NYHA class 3 or 4 heart failure symptoms.

The efficacy of dual chamber pacing has been a controversial topic in the treatment of hypertrophic cardiomyopathy. Studies have shown disparate results regarding the efficacy in consistently reducing the left ventricular outflow tract obstruction gradient and improving symptoms. In theory, pacing the right ventricle alone with its associated abnormal myocardial depolarization can result in less isotropy and a decrease in gradient. The entire impact of dual chamber pacing is at best controversial, but may be helpful on a case by case basis. Most recently, Yue-Cheng and colleagues [13] presented the results of their long-term follow-up study of dual-chamber pacing in those with hypertrophic obstructive cardiomyopathy. They closely followed 37 patients for up to 4 years and specifically found a benefit from this kind of therapy which translated into what they called improved "cardiac structural reconstruction." However, it is important to note that dual-chamber pacing parameters needed to be adjusted (i.e., AV delay and pacing rate) in order to achieve a very high rate of ventricular pacing in this study. If pacing is to be employed, every opportunity should be taken to ensure that the ventricular pacing feature is utilized almost all of the time.

The decision to proceed with advanced invasive therapy to alleviate the left ventricular outflow obstruction has to involve a detailed discussion of the advantages and disadvantages of both surgical and percutaneous approaches to therapy. Factors such as degree of septal hypertrophy, anterior displacement of the anterior mitral valve papillary muscle, chordal tendon and anterior mitral valve leaflet redundancy extent will be taken into consideration in the joint decision between patient and clinician in determining the optimal course of advanced therapy. The significant experience of the operator with surgical myectomy or alcohol septal ablation plays an obvious role in determining the safer choice of therapy for the patient. The patient's age and comorbid conditions will also determine the patient's suitability for either surgical myectomy or alcohol septal ablation. Finally, the patient's preference for advanced invasive therapy may trump all other considerations for alleviating the patient's left ventricular outflow obstruction. More information on the choice of invasive therapy for outflow tract obstruction may be found in the chapter on "Indications for and Individualization of Septal Reduction Therapy."

Conclusions

Arrhythmogenic, neurocardiogenic syncope/autonomic dysfunction and left ventricular outflow tract obstruction etiologies in hypertrophic cardiomyopathy have been described. In reality, there is interplay between all three of these etiologies, with one or two dominating in any given hypertrophic cardiomyopathy patient with syncope. Arrhythmogenic causes tend to be associated with a worse prognosis, especially if left untreated. Metoprolol succinate may attenuate the risk for ventricular arrhythmias, although this has not been proven, but does prolong the diastolic filling time, reduce contractility, and re-upregulate the post-synaptic myocardial beta-1 adrenoceptor density. Medications also reduce left ventricular outflow tract obstruction, and thus improve syncope in patients with significant recurrent obstructive physiology. Treatment with implantable devices is reserved for patients with documented ventricular arrhythmias, those who meet high risk SCD criteria, and those with recurrent syncope despite optimal control of outflow tract obstruction. When obstruction is felt to be the dominating lesion, augmented medications, permanent pacemaker implantation and/or other invasive therapies may be required, with pacemaker therapy typically reserved for elderly patients. There is no specific treatment for neurocardiogenic syncope, which of the three etiologies is the rarest to exist in isolation; thus, patients with autonomic dysfunction may be best treated by hydration and elimination of outflow tract obstruction. When no defined etiology can be found, and recurrent syncope occurs despite optimal medical management, patients should proceed to defibrillator for primary prevention.

Clinical Pearls

- Patients with left ventricular outflow tract obstruction gradients exceeding 30 mmHg at rest or with provocation should be kept hydrated, unless signs of hypervolemia are present and avoid dehydrating agents as well as agents that increase contractility.
- Preload- and afterload-reducing drugs should be avoided whenever possible in hypertrophic cardiomyopathy patients with outflow tract obstruction physiology.
- Patients should be screened for high risk features predisposing them to sudden cardiac arrest and referred early for ICD implantation; syncope is a major risk factor for sudden cardiac death if recurrent and unexplained, despite optimal medical therapy.
- Those with symptomatic left ventricular outflow tract obstruction and recurrent syncope should be considered for alleviation of the obstruction, either with alcohol septal ablation or with septal myectomy, if optimal medical therapy does not control symptoms.
- Syncope in hypertrophic cardiomyopathy is frequently traumatic, and does not in and of itself implicate an arrhythmogenic cause; outflow tract obstruction may lead to traumatic syncope in a subset of patients.

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References

1. Spirito P, Autore C, Rapezzi C, Bernabo P, Badagliacca R, Maron MS, Bongioanni S, et al. Syncope and risk of sudden death in hypertrophic cardiomyopathy. Circulation. 2009;119(13):1703–10.
2. Jensen MK, Prinz C, Horstkotte D, van Buuren F, Bitter T, Faber L, Bundgaard H. Alcohol septal ablation in patients with hypertrophic obstructive cardiomyopathy; low incidence of sudden cardiac death and reduced risk profile. Heart. 2013;99(14):1012–7.
3. Orme NM, Sorajja P, Dearani JA, Schaff HV, Gersh BJ, Ommen SR. Comparison of surgical septal myectomy to medical therapy alone in patients with hypertrophic cardiomyopathy and syncope. Am J Cardiol. 2013;111(3):388–92.
4. Spirito P, Chiarella F, Carratino L, Berisso MZ, Bellotti P, Vecchio C. Clinical course and prognosis of hypertrophic cardiomyopathy in an outpatient population. N Engl J Med. 1989;320(12):749–55.
5. Kirchheim HR. Systemic arterial baroreceptor reflexes. Physiol Rev. 1976;56:100–77.
6. Thomson HL, Morris-Thurgood J, Atherton J, Frenneaux M. Reduced cardiopulmonary baroreflex sensitivity in patients with hypertrophic cardiomyopathy. J Am Coll Cardiol. 1998;31:1377–82.
7. Miura M, Reis DJ. The role of the solitary and paramedian reticular nuclei in mediating cardiovascular reflex responses from carotid baro- and chemoreceptors. J Physiol. 1972;223:525–48.
8. Martins JB. Carotid sinus baroreflex influence on electrophysiologic properties of the canine atrioventricular node and ventricle. Am J Cardiol. 1984;54:431–6.
9. de Boer RW, Karemaker JM, Strackee J. Hemodynamic fluctuations and baroreflex sensitivity in humans: a beat-to-beat model. Am J Physiol. 1987;253:H680–9.
10. Zipes DP, Inoue H. Autonomic neural control of cardiac excitable properties. In: Kulbertus HE, Franck G, editors. Neurocardiology. New York: Futura Publishing; 1988. p. 787–96.
11. Prasad K, Williams L, Campbell R, Elliott PM, McKenna WJ, Frenneaux M. Episodic syncope and hypertrophic cardiomyopathy: evidence for inappropriate vasodilation. Heart. 2008;94(10):1312–7.
12. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naidu SS, Nishimura RA, Ommen SR, Rakowski H, Seidman CE, Towbin JA, Udelson JE, Yancy CW. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2011;58:e212–60.
13. Yue-Cheng H, Zuo-Cheng L, Xi-Ming L, Yuan DZ, Dong-Xia J, Ying-Yi Z, Hui-Ming Y, Hong-Liang C. Long-term follow-up impact of dual-chamber pacing on patients with hypertrophic obstructive cardiomyopathy. Pacing Clin Electrophysiol. 2013;36(1):86–93.

Pediatric Diagnosis and Management

9

Steven D. Colan

Abstract

Hypertrophic cardiomyopathy in children manifests important differences with regard to the causes, manifestations, response to therapy, and outcomes compared to this disease in adults. Management and diagnosis in infants and young children in particular are associated with unique considerations. Etiology is an important determinant of survival, particularly in the youngest patients, and pursuit of the specific cause is therefore requisite. Diagnosis is more challenging because of a variety of metabolic and syndromic disorders that present with the hypertrophic cardiomyopathy phenotype in infancy. Diagnostic criteria commonly used in adults must be scaled to body size in children. There is considerable clinical value in genetic characterization in children with hypertrophic cardiomyopathy and the resulting cost-benefit ratio for genetic testing is therefore far more favorable than in adults. Most of the available information concerning response to therapy and potential methods of preventing sudden death has been developed in adult patients, but management of children requires consideration of the differences in age-specific risk-to-benefit ratios such as higher complication rates for implantable defibrillators. Sports participation is a particularly challenging issue in adolescents because of the high percentage of participation and the important social role of these activities. These young patients experience high rates of adverse psychological response to both exercise restrictions and defibrillator implantation. Overall, both diagnosis and therapy require age-stratification.

Keywords

Cardiomyopathy • Hypertrophic cardiomyopathy • Sudden death • Pediatrics • Children • Infants

Abbreviations

ACEi	Angiotensin-converting enzyme inhibitor
AED	Automated external defibrillator
CMR	Cardiac magnetic resonance
CPR	Cardiopulmonary resuscitation
DHE-MRI	Delayed hyper-enhancement on CMR
FHCM	Familial hypertrophic cardiomyopathy
G+P–	Genotype positive phenotype negative
HCM	Hypertrophic cardiomyopathy
ICD	Implantable cardioverter defibrillator
LV	Left ventricle
LVH	Left ventricular hypertrophy
NSVT	Non-sustained ventricular tachycardia

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Introduction

Cardiomyopathy is a rare (about 1/100,000 children) but serious condition in infants and children [1]. Hypertrophic cardiomyopathy accounts for about 40 % of cardiomyopathy

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cases in children and is an unusually heterogeneous group of disorders during childhood. Pediatric hypertrophic cardiomyopathy encompasses conditions with diverse genetic origins and clinical phenotypes, including associations with inborn errors of metabolism, mitochondrial defects, neuromuscular disorders, and malformation syndromes. Few data are available to predict which patients with pediatric hypertrophic cardiomyopathy will experience congestive heart failure or sudden cardiac death. Morbidity and mortality are higher in the first year of life by a factor of ten compared with the remainder of childhood. This discussion will focus primarily on issues related to diagnosis and management of these children.

Diagnosis of Hypertrophic Cardiomyopathy in Children

Hypertrophic cardiomyopathy (HCM) is defined as the presence of a hypertrophied, non-dilated ventricle in the absence of a hemodynamic disturbance that is capable of producing the existent magnitude of wall thickening, such as hypertension, aortic valve stenosis, catecholamine-secreting tumors, hyperthyroidism, and other disorders. Physiologic hypertrophy secondary to intense athletic participation is also excluded from this definition. In contrast to the practice in adult cardiology, the criteria for the magnitude of wall thickness that can be considered diagnostic of HCM in children require adjustment for body size. A left ventricular (LV) wall thickness of 14–15 mm wall thickness is considered diagnostic of HCM in adults [2], corresponding to a value that is 5–6 standard deviations above the normal adult mean. In contrast, Z-scores relative to body surface area are used to adjust the size of cardiovascular structures for body size in children, where the z-score is the number of standard deviations from the mean [3]. The adult criteria therefore correspond to a z-score range of 5–6, while typically a wall thickness z-score >4 is used as the diagnostic criterion in children. A graph of the normal range and the 4 z-score cutoff value using data from our echocardiographic laboratory is provided in Fig. 9.1. Even if this z-score threshold is not achieved, substantial isolated regional variation in wall thickness (asymmetry), typically defined as delimited areas with >1.5 times the prevailing wall thickness at that position in the base-to-apex distance, is often accepted as a diagnostic criterion. It should be noted that a progressive fall in wall thickness from base to apex is normal. Similar to diagnostic criteria based on wall thickness alone, this discriminating value for magnitude of asymmetric hypertrophy may overlap with changes seen in physically active individuals [4].

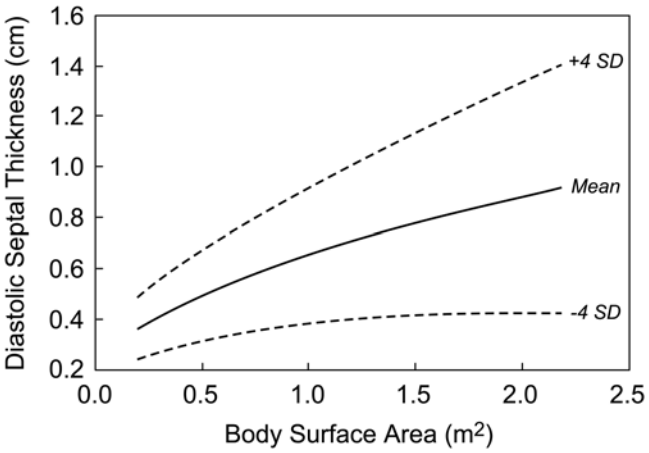

Fig. 9.1 Graph of normal end-diastolic interventricular septal thickness (cm) as a function of body surface area (m^2) with the z-score values of +/−4 standard deviations (*SD*) indicated with interrupted lines

Nomenclature Issues in Hypertrophic Cardiomyopathy

It should be noted that the foregoing definition, based on the presence of non-hemodynamically induced hypertrophy, is derived from the original World Health Organization recommendations on the nomenclature of the cardiomyopathies and is preferentially used in the pediatric cardiology community and forms the basis for the terminology used in this chapter (Table 9.1) [5, 6]. This nomenclature and classification scheme is also in alignment with the position paper published by the European Society of Cardiology [7, 8]. However, the advent of genetic characterization of the disease has resulted in an effort to include the genetic basis of the disease in the definition. The ACCF/AHA guidelines, although in agreement with the phenotypically-based definition provided here, has recommended a narrower use of the term "hypertrophic cardiomyopathy", restricting it to patients with (1) left ventricular hypertrophy (LVH), (2) overt disease restricted to the heart, and (3) either a sarcomeric mutation or unknown mutation [2]. Notably, the ACCF/AHA guidelines mark as hypertrophic cardiomyopathy only those disorders that fit these criteria, whereas within the pediatric population multiple disease states may present with the broader definition of hypertrophic cardiomyopathy; that is, the presence of non-hemodynamically induced hypertrophy from any cause. Alternative terms that have been used for this subset of patients with HCM are familial HCM (FHCM) and sarcomeric HCM. In contrast to this recommendation to narrow the definition beyond the original phenotypically-based terminology, some groups favor a broader definition of the disease that includes carriers of HCM-associated sarcomeric

Table 9.1 Phenotypically-based classification of hypertrophic cardiomyopathy

Familial hypertrophic cardiomyopathy
Sarcomeric hypertrophic cardiomyopathy
Maternally-inherited hypertrophic cardiomyopathy syndromes
Syndromic hypertrophic cardiomyopathy
Noonan's syndrome
Beckwith-Wiedemann syndrome
Cardiofacialcutaneous syndrome
Costello syndrome
Multiple lentiginosis syndrome
Neuromuscular disease
Friedreich's Ataxia
Metabolic disorders
Anabolic steroid therapy and abuse
Carnitine deficiency (carnitine palmitoyl transferase II deficiency, carnitine-acylcarnitine translocase deficiency)
Fucosidosis type 1
Glycogenoses type 2, 3 and 9 (Pompe disease, Forbes disease, Phosphorylase kinase deficiency)
Glycolipid lipidosis (Fabry disease)
Glycosylation disorders
I-Cell disease
Infant of diabetic mother
Congenital generalized lipodystrophy
Lysosomal disorders (Danon disease)
Mannosidosis
Mitochondrial disorders (multiple forms)
Mucopolysaccharidoses type 1, 2 and 5 (Hurler syndrome, Hunter syndrome, Scheie syndrome)
Pre and postnatal corticosteroid therapy
Selenium deficiency

gene mutations, even if LVH is absent. These genotype positive, phenotype negative (G+P−) individuals have also been labeled as preclinical HCM, subclinical HCM, presymptomatic HCM, HCM mutation carriers, and HCM without hypertrophy [9]. Equating the presence of the gene with the presence of the disease is quite controversial, however, particularly in children, since an increased risk of sudden death or other adverse outcomes has not been identified when LVH is absent. There is also a substantial experience indicating incomplete penetrance for these mutations, making the use of the term problematic since some of these patients may never experience clinical manifestations. The pediatric cardiology community has been resistant to expanding the definition of HCM to include gene carriers without hypertrophy, in this case a position that is in agreement with the ACCF/AHA Guidelines [2]. The purpose of this nomenclature discussion is not to attempt to assert which is the "correct" nomenclature but to clarify for the purposes of the ensuing discussion that in this chapter: (1) the term HCM is used to encompass the full spectrum of non-hemodynamically induced hypertrophy represented in Table 9.1, and (2) the presence of other clinically detectable manifestations of gene carriage, collectively referred to as biomarkers for genetic predisposition, are not taken to represent "disease" in the absence of hypertrophy.

Diagnostic Testing for Hypertrophic Cardiomyopathy in Children

The diagnosis of HCM in children is nearly always based on echocardiography due to the excellent images that can typically be obtained in this age group, although cardiac magnetic resonance (CMR) imaging is occasionally required in patients with poor echocardiographic access or when apical HCM is suspected based on family history or failure to image the left ventricular apex on echocardiography. A variety of other morphologic, electrophysiologic [10], and hemodynamic manifestations of the disease have been described in children with the HCM phenotype that are similar to the findings in adult populations, including dynamic LV outflow tract obstruction, mitral regurgitation, abnormal tissue Doppler velocities, elevated end-diastolic pressure, and left atrial dilation. In addition, in infants it is not uncommon to observe right ventricular outflow tract obstruction secondary to direct septal impingement, unrelated to tricuspid valvar motion. Although these additional findings may have important implications for management and prognosis, ultimately the diagnosis of HCM remains dependent on the finding of hypertrophy. For example, dynamic LV outflow tract obstruction can be seen in morphologically variant mitral valves and even in normal hearts in the absence of HCM [10]. The presence and severity of myocardial hypertrophy remains the fundamental diagnostic criteria and is an important predictor of outcome.

Morphologic Variants of Hypertrophic Cardiomyopathy in Children

Several patterns of myocardial and ventricular morphology are encountered in HCM. The majority of children have reduced cavity volume that is near or below the normal range for body size in conjunction with hyperdynamic systolic function, similar to the pattern that is characteristic of adult populations, a pattern that can be referred to as typical or "pure HCM". There are subsets of children with mixed phenotype disease who, in addition to ventricular hypertrophy, have marked ventricular dysfunction (hypokinetic HCM) or severe restrictive physiology (restrictive HCM), patterns found in 6 and 5 % of cases, respectively [11]. These patterns

are of importance as they tend to be associated with specific etiologies and outcomes. In contrast to the transition to dilated cardiomyopathy that is seen as an end-stage manifestation of HCM in adult populations and is occasionally but rarely encountered in children, the hypokinetic HCM phenotype is generally seen in infants as a primary disease (i.e., no preceding phase of typical HCM) and is not characterized by wall thinning and ventricular dilation. Finally, the mixed phenotype of HCM with noncompaction can be encountered, but the frequency of this pattern is less well characterized, in part because of its rarity but also related to the diagnostic uncertainty associated with noncompaction [12].

Diagnosis of Hypertrophic Cardiomyopathy in Pediatric Athletes

The challenge related to differentiation of HCM from physiologic hypertrophy in young adults who participate in high level athletics and in enlisted military personnel has been well documented. The issue rarely arises prior to puberty, but should be considered in any adolescent with the combination of relatively mild hypertrophy and high levels of exercise participation. The potential consequences of the diagnosis or at times even the suspicion of the diagnosis can have a marked impact on the educational, career, and financial opportunities for these athletes, escalating the gravity of the decision [13]. Specific activities (wrestling, weight lifting, football, basketball) are more often represented in these athletes, and anabolic steroid use may further confound the situation. Generally, wall thickness up to a z-score of 5 or 6 can occasionally be encountered, and this is the area of overlap that creates the greatest diagnostic uncertainty. A number of characteristics of the phenotype can help differentiate pathologic from physiologic hypertrophy. Findings such as a family history of HCM or sudden death increase the probability of HCM. Symptoms such as diminished exercise tolerance are uncommon in athletes. Syncope is very common in the general population, including athletes, and should not be presumed to tilt the balance towards HCM. Generally, syncope following exercise is a more likely to be related to hyperthermia, hypovolemia, or neurally-mediated syncope, whereas patients with hypertrophy who experience syncope during exercise must generally be presumed to have HCM until proven otherwise. Extensive effort has been devoted to testing electrocardiographic methods for screening for hypertrophic cardiomyopathy but it is clear that there is broad overlap with the changes induced by intense training and this is not a reliable method for discriminating the two [14]. Physiologic remodeling is more frequently associated with symmetric hypertrophy, larger LV chamber size, normally ellipsoidal LV shape, left atrial dilation proportional to left ventricular dilation, normal diastolic function indices, absence of outflow track obstruction, and absent delayed enhancement on CMR. When all these parameters are normal HCM is quite unlikely, but ultimately some cases will remain ambiguous. The strongest evidence of physiologic hypertrophy is significant reduction in hypertrophy in response to detraining, often requiring at least 6 months of relative inactivity. Some of these individuals have great difficulty adequately restricting their level of exertion, but functionally this activity restriction is equivalent to presuming HCM is present until proven otherwise. Therefore, exclusion from competitive sports participation is required and is likely the only intervention that would be undertaken for an asymptomatic HCM with mild hypertrophy.

Diagnosis of Hypertrophic Cardiomyopathy in Children with Structural Congenital Heart Disease

The coexistence of HCM in the setting of structural congenital heart disease is sometimes suspected, particularly in infants, and can present a particularly difficult dilemma. The presence of asymmetric septal hypertrophy is commonly seen in right ventricular outflow tract obstruction such as valvar pulmonary stenosis, tetralogy of Fallot, or double chambered right ventricle [15], and is not uncommonly observed in complete atrioventricular septal defects. In addition, there are patients who manifest ventricular hypertrophy that appears excessive for the severity of the hemodynamic disturbance. This represents a diagnostic dilemma insofar as the coincidence of both diseases may complicate management. There is generally no satisfactory method for untangling the two other than eliminating the hemodynamic overload and seeing if regression of hypertrophy takes place, similar to the approach in suspected athletic heart syndrome. Complete elimination of the hemodynamic burden related to the congenital heart disease is often not possible, resulting in a persistent diagnostic dilemma. Efforts to differentiate on the basis of histopathology have also not been successful [16]. Identification of a known pathogenic mutation via genetic testing will heighten the probability of HCM and aid in exclusion of other genetic syndromes with cardiac manifestations but cannot be considered definitive due to the variable age of onset of the disease.

Diagnosis of Etiology in Hypertrophic Cardiomyopathy

In contrast to the relatively homogeneous etiologic profile seen in adults, where the overwhelming majority of patients have

FHCM, in which the disease is usually noted in a pedigree and the responsible gene mutation is generally in a sarcomeric protein, the HCM phenotype in children is etiologically diverse and outcomes tend to be highly dependent on etiology. A classification is presented in Table 9.1 based on groupings of familial, syndromic, neuromuscular, and metabolic (storage disease and mitochondrial disorders) disorders [6]. A number of other classification schemes are commonly used, including division into primary and secondary forms, where the primary form is devoid of findings outside of the heart, and the secondary forms include diseases such as Friedreich ataxia [17] where ventricular hypertrophy is common but is not the dominant clinical manifestation and others, such as glycogen storage disease type IX [18], in which a systemic disorder has primarily or exclusively cardiac manifestations.

The importance of etiologic diagnosis relates to the fact that management and outcome in pediatric HCM are highly dependent on etiology. The Pediatric Cardiomyopathy Registry, a multicenter observational study of pediatric cardiomyopathies, was initiated in 1995, and in 2003 we reported that HCM was found to account for 42 % of childhood cardiomyopathy, has an incidence of 0.5/100,000 children, is significantly more common in males, occurs at ten times the rate of that in older children in subjects < 1 year old, and is significantly more common in blacks than in whites or Hispanics. Subsequently, the distribution of etiologies and the etiology-specific HCM survival in 849 children was reported [19]. We found a nearly equal distribution between inborn errors of metabolism (9 %), malformation syndromes (9 %), and neuromuscular disorders (8 %), with idiopathic and FHCM comprising the remaining 75 %. Patients in the inborn errors of metabolism and malformation syndrome groups were diagnosed at a mean age <6 months with a significantly older age at diagnosis in the other groups. This is also the reason why by the time subjects reach adulthood, the familial/idiopathic group is the dominant form, and genetic testing or a search for alternate etiologies is less productive. Survival was also found to be etiology- and age-specific, as illustrated in Fig. 9.2 [11]. For patients with FHCM, the survival rate is similar to contemporary reports in adults. Both survival and management are highly etiology-specific. In 2007 we found that based on data from the preceding 15 years, about 50 % of HCM cases under age 1 remained idiopathic [19]. This study excluded infants with HCM secondary to maternal diabetes, who are generally more readily diagnosed and are characterized by spontaneous resolution of the HCM. More recent data of this type are not available but the pace of advances in genetic and metabolic diagnostics has quickened and the expectation that a specific diagnosis can be achieved has improved substantially in recent years. Many states have expanded the range of disorders screened on the neonatal blood spot screening as well and consequently the underlying metabolic disorder may be known prior to the recognition of cardiomyopathy.

Children presenting with the HCM phenotype in the presence of a family history of HCM are typically presumed to have FHCM, a diagnosis that can be confirmed by testing for a familial mutation if this has been or can be identified. Presentation in infancy is rare and further evaluation is justified to ensure the absence of multiple causes, which includes both multiple pathogenic sarcomeric mutations and coexistent syndromic HCM such as Noonan Syndrome, both of which have been reported. The presence of multiple pathogenic sarcomeric gene mutations in infants has resulted in the hypothesis of a genetic "dosage" effect accounting for the early presentation. The presence of a coexistent syndromic or metabolic disorder may be clinically occult during infancy, impeding early diagnosis and appropriate management,

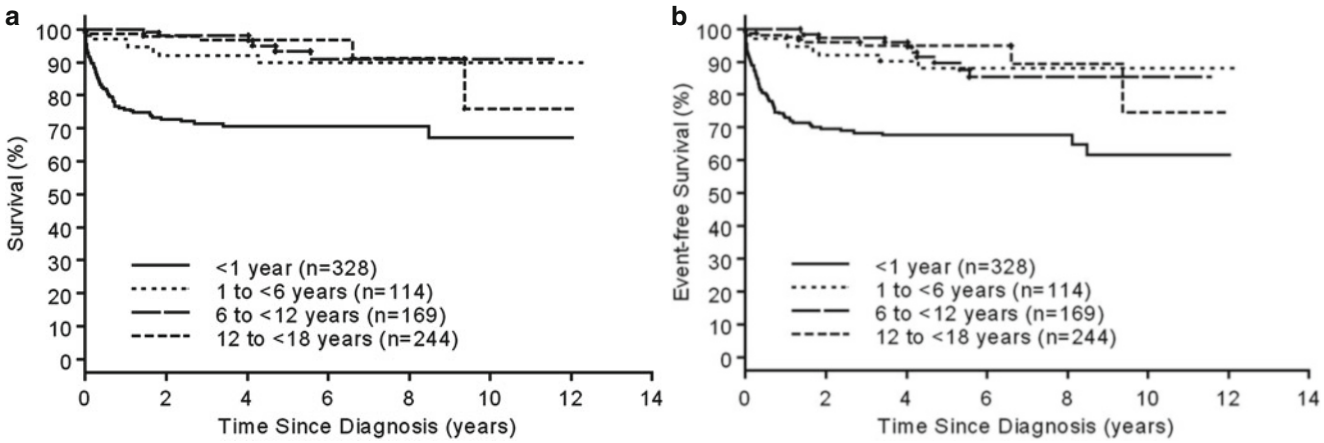

Fig. 9.2 Survival rates from diagnosis of cardiomyopathy to (**a**) death (logrank P<0.001); and (**b**) death or transplant (logrank P<0.001) in the combined prospective and retrospective cohorts (N=855) by age at diagnosis (<1 year, 1 to <6 years, 6 to <12 years and 12 to <18 years) [19]

justifying a more extensive and comprehensive diagnostic evaluation of the newborn with HCM.

Children presenting with the HCM phenotype in the absence of a family history of HCM require consideration of the associated metabolic, syndromic, and neuromuscular disorders presented in Table 9.1. Depending on age, they may require a wide ranging diagnostic evaluation to assure absence of an underlying disorder. Although finding of sarcomeric HCM in children who do not have a family history of HCM may represent a new mutation, there is also a well-documented incidence of incomplete penetrance in sarcomeric HCM, and therefore gene testing in these children is recommended for the reasons discussed in detail below, followed by gene testing the parents and other family members when appropriate; clinical correlation with cascading cardiac (echocardiographic) testing of gene positive individuals may reveal a familial disease.

Association of HCM with numerous disorders other than FHCM has been described and in many instances these case reports likely represent coincidence, but there are several for which HCM is seen with sufficient frequency to indicate that it is an intrinsic element of the disease (Table 9.1). Patients with Friedreich ataxia have a >50 % incidence of HCM that rarely presents prior to the onset of neurologic symptoms, tend to manifest symmetric hypertrophy without outflow obstruction, and do not appear to be at significant risk for sudden death [19]. HCM is seen in up to 20–30 % of patients with Noonan's syndrome [20] and other RASopathies (Costello syndrome, cardiofaciocutaneous syndrome, multiple lentigines syndrome, and neurofibromatosis) [21]. The cardiac findings in the RASopathies are similar to FHCM with myocardial disarray, asymmetric hypertrophy, dynamic LV outflow obstruction, and risk of sudden death. These patients may present with congestive heart failure and recognition of the associated syndrome is often delayed due to incomplete phenotypic expression in infancy. In infants, the risk of congestive heart failure with HCM associated with Noonan syndrome is more common than in infants with FHCM, and those who experience heart failure at <6 months of age have only a 33 % 1 year survival, with nearly all of the childhood deaths occurring within the first 2 years [22]. Infants of diabetic mothers and neonates exposed to corticosteroids often have transient biventricular hypertrophy, sometimes with outflow tract obstruction, and occasionally causing symptoms, but invariably experience spontaneous resolution of hypertrophy over a period of weeks.

Generally, HCM in infants presents unique problems in differential diagnosis. In various series, diseases other than FHCM have accounted for 30–70 % of HCM cases in patients <2 years of age [23]. Amongst those patients for whom a defined etiology is identified, a few disorders (Pompe disease, Noonan syndrome, and FHCM) account for the majority of cases with the remainder caused by a broad range of rare disorders. From the cardiac perspective, the association of particular patterns of the cardiac phenotype with specific etiologies has been an area of considerable interest because of the potential to guide the evaluation and management. For example, the finding of a hypertrophic, hypokinetic LV is rare in FHCM but has been frequently associated with mitochondrial defects [24] and inborn errors of metabolism, as has severe concentric hypertrophy in patients under 2 years of age. Myocardial biopsy is often necessary to distinguish among these disorders, is recommended in all patients under the age of 2 years, and can be particularly helpful in children with symmetric hypertrophy or depressed function who have no family history of HCM [24, 25]. Biventricular outflow tract obstruction is more common in Noonan syndrome than in other forms of infantile HCM. Asymmetric patterns of hypertrophy are more commonly seen in syndromic and familial HCM than in inborn errors of metabolism. Although these sorts of observations can provide some guidance, for most infants with HCM early referral for multi-specialty evaluation including specialists in cardiology, neurology, genetics, and metabolism is warranted. Finally, differentiation between physiologic hypertrophy secondary to athletic participation and pathologic hypertrophy in FHCM is a frequent and an important problem in adolescents and young adults, and is dealt with separately in this volume.

Genetic Diagnosis of Hypertrophic Cardiomyopathy in Children

The routine use of genetic testing in the HCM population remains controversial and many insurers deny coverage, in part related to a perceived lack of clinical utility because management of the index case is generally not affected by the results. However, this view is short-sighted because it fails to recognize the benefits to other family members, particularly for children, who face the highest probability of new-onset HCM. Because development of the phenotype can be noted at any age, current practice is to periodically screen first and second degree relatives of individuals with familial or idiopathic HCM because of the associated risk of gene carriage of 50 and 25 %, respectively. If DNA from phenotypically positive family members is available, identification of a pathogenic familial gene within the pedigree allows the other family members who prove to be genotype negative to avoid longitudinal evaluation for development of hypertrophy, markedly reducing the overall cost of care, in addition to anxiety reduction and elimination of concerns about exercise participation. Phenotype negative relatives who prove to be genotype positive are appropriately evaluated periodically for development of disease and also for eligibility for trials of interventions to prevent or attenuate development of the phenotype. The potential to prevent the onset of hypertrophy remains an unproven hypothesis in

humans although animal models have provided proof of concept for this theory. A mouse model of myosin heavy chain HCM treated prior to the onset of hypertrophy with diltiazem had less hypertrophy, fibrosis, and myocyte disarray than placebo-treated mice [26], and rapamycin has been reported to reverse the cardiac hypertrophy in a mouse model of multiple lentigines syndrome associated with a PTPN11 mutation [27].

Diagnosis of Genotype Negative Status

A definitive genetic diagnosis cannot be achieved through currently available commercial genetic testing in 40–50 % of HCM phenotype positive individuals. As discussed above, accurate identification of which of these relatives do not have a genetic predisposition permits exclusion of these individuals from a lifelong requirement for periodic evaluation. The availability of genotyped pedigrees has permitted evaluation of whether gene positive individuals can be distinguished from gene negative individuals based on standard electrocardiographic and echocardiographic testing, with early studies [28] demonstrating reasonable specificity but poor sensitivity to genotype positive status [29]. More recently, a variety of potential biomarkers for genetic predisposition have been reported. Reduced early diastolic tissue Doppler velocities were found to correlate with gene carriage by several different groups [9, 30–32]. The specific velocity value that has had optimal positive predictive value for at risk individuals has varied but has generally been <10 cm/s in several studies, corresponding to the lower limits of normal in adults <40 years old [33]. However, early diastolic velocities are age-dependent, as illustrated in Fig. 9.3, and the discriminatory power could undoubtedly be improved by use of age-adjusted z-scores. Findings on CMR

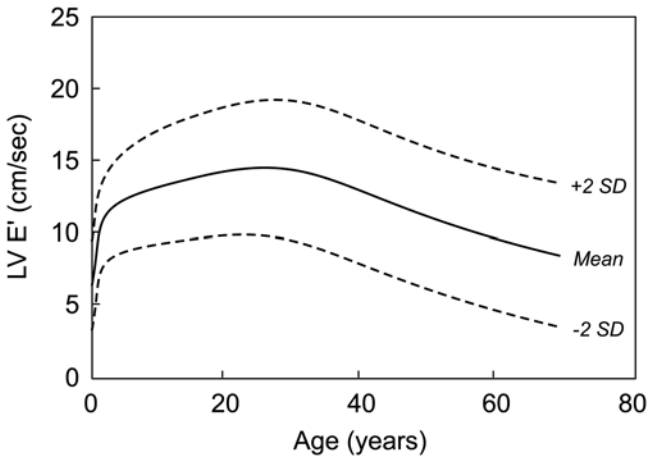

Fig. 9.3 Composite graph of the normal values for septal peak early diastolic tissue Doppler values as a function of age based on data from Boston Children's Hospital (18 years and younger) and adult values from Dalen et al. [33] The male and female values from Dalen et al. were averaged and the mid-position of the age range was used for each data point

that have been reported as potentially useful in the detection of G+P– individuals include late gadolinium enhancement [34], increased extracellular myocardial volume [35], and myocardial crypts [36]. Left atrial and LV dimensions, torsion, strain, and strain rate have been reported to have different mean values in G+P– individuals compared to a control population [37, 38]. Thus far, similar to the electrocardiographic patterns in this population, although many of these biomarkers have a higher prevalence in gene carriers, they fail to definitively segregate gene positive from gene negative individuals, even in combinations [38].

The exploration of these biomarkers was initially performed primarily to enable the detection of genotype positive status because genetic testing was both expensive and not widely available, a situation that is gradually improving. Identification of biomarkers in G+P– has interesting potential implications for pathogenesis of the disease but ultimately the ability of these methods to identify the genotype negative subjects (i.e. the negative predictive value) is likely of equal or more value than the positive predictive value. Management of phenotype negative first and second degree relatives who are genotype positive is not different from those with unknown gene status in terms of the need for longitudinal evaluation for new onset hypertrophy. However, those who can be proved to be genotype negative can be dismissed from further evaluation. If clinical testing with electrocardiography, imaging, biomarkers, or other non-genetic testing could reliably identify which members of the pedigree do not carry a familial HCM genetic mutation, they would benefit from being excluded from longitudinal evaluation, whereas the individuals for whom this clinical testing was either ambiguous or predicted presence of the mutation would have no change in management. Work to date has centered primarily on positive predictive value and it is likely that some biomarkers that perform poorly in this regard would nevertheless have strong negative predictive value. Similar to disease expression (i.e., onset of hypertrophy), there is potential for age dependence of these biomarkers, a factor that has not been investigated. The accuracy of negative predictive capacity that is required to exclude family members from longitudinal assessment would only need to achieve 90 % to exceed the current practice of evaluating only first and second degree relatives (third degree relatives remain at 12.5 % risk of mutation carriage).

In theory, the issues concerning optimal methods for biomarker-based identification of genotype negative individuals can be addressed in future studies, but ultimately there is an important issue that may render these efforts futile. Development of these methods of genetic stratification is based on studies performed on populations with known genotypes. However, these potential biomarkers of G+P– status can be mutation specific, as has been noted for abnormal tissue Doppler velocities [32]. Extrapolation of the predictive capacity of these biomarkers to individuals with

an unknown genetic predisposition could fail because association between mutation carriage and any specific biomarker may not be generalizable.

Management of HCM in Children

The goals of therapy in this disorder are to improve quality of life and prolong survival, goals that at times may conflict. Management of symptomatic HCM is commonly an issue in infants and occasionally in other age groups and is discussed in this section, but the majority of children are symptom free. Implantable cardioverter-defibrillator (ICD) therapy remains the only therapeutic option that is unequivocally accepted as effective for improved survival in high risk groups by reducing the incidence of sudden death, and the issues concerning ICD implantation in children are discussed in more detail below.

Management of Symptoms Related to Hypertrophic Cardiomyopathy in Children

Similar to management in adult patients, digitalis is not helpful and is usually contraindicated in the absence of ventricular systolic dysfunction or atrial fibrillation, both of which are quite rare in pediatrics. Diuretic therapy is usually not helpful in alleviating dyspnea and may increase symptoms by reducing cardiac output and increasing the outflow gradient due to reductions in both arterial pressure and ventricular volumes. Outflow tract obstruction and mitral regurgitation are frequently seen together and play an important role with regard to symptom status in HCM. The clinical importance of outflow obstruction has been highly controversial over the years, as recently recounted in some detail [39]. Patients with outflow tract obstruction are at greater risk for symptoms and progression to heart failure and death [40], but the impact on the risk of sudden death remains controversial.

Some reports have found that relief of outflow tract obstruction, in addition to symptomatic relief and potentially averting progression to congestive heart failure, may indeed reduce the incidence of sudden death in adults [41, 42]. However, a recent large study in adults found that although invasively managed LV outflow tract obstruction had improved survival compared with medically managed patients, the difference related to death from non-cardiac causes with no significant improvement in HCM-related mortality [43]. The variability of these results accounts for the continued controversy as to whether pharmacologic or interventional reduction of LV outflow tract obstruction should be considered in the absence of symptoms [2]. Although there are no independent data in children to contribute to this decision, pharmacologic therapy of outflow obstruction is nearly universal in infants and young children, related to both the difficulty in early detection of symptom such as growth failure and the excellent safety profile of beta-blockers and calcium channel blockers.

Exercise-induced or exacerbated outflow tract obstruction is both common and associated with a higher risk of symptoms [44]. Reduction in outflow tract obstruction is one of the primary targets of therapy for symptomatic patients. In some patients outflow obstruction is present only with provocation such as inotropic stimulation, vasodilation, or exercise, and often demonstrates marked spontaneous lability [45]. Although provocation of latent outflow obstruction with maneuvers such as amyl nitrate and Valsalva maneuver has been recommended, the clinical significance of gradients elicited in this fashion remains uncertain, in part due to the difficulty in standardization, and is typically not performed in children.

In general, HCM-related symptoms have been considered the primary indication for other medical or surgical interventions in children. Similar to management of adults with HCM [46], a stepwise approach is taken, first using medical therapy (beta blocker, calcium channel blocker, and/or disopyramide), reserving surgical myectomy or alcohol septal ablation for patients with symptomatic LV outflow obstruction unresponsive to medical therapy. However, data have accumulated indicating that, although the risk of sudden death may not be higher in the presence of outflow tract obstruction, overall survival is nonetheless reduced due to an increased risk of congestive heart failure. Data supporting the concept that improved overall survival can be achieved from interventions to reduce LV outflow tract obstruction have begun to accumulate [43]. The mortality rate in HCM is sufficiently low (1–3 % in most series) that large cohorts and substantial length of follow-up are needed to detect such a benefit, and no pediatric-specific data are available. Heart failure in children with HCM is quite rare after the first year of life, making it unlikely that any sort of benefit from presymptomatic intervention for outflow obstruction will be detectable during childhood. At present, interventions specifically targeted to relief of outflow tract obstruction in children are generally reserved for symptomatic patients. However, any cumulative contribution of the pressure overload associated with outflow tract obstruction to the progressive diastolic dysfunction in HCM could render this approach short-sighted. Indeed, an argument can be made that a more aggressive approach to gradient reduction might improve long-term outcomes. As for most issues related to late outcomes in children, such questions are very difficult to address because of the extended time horizons, low disease incidence, and continuous evolution of disease management. It is therefore almost certain that management will continue to be based on first principles and extrapolation of data from adult studies.

Management of Symptoms in Children with HCM

Beta-Blockers

Beta-adrenergic blockaders are the most common form of pharmacologic therapy in FHCM. Although chest pain and dyspnea are often reduced, improved exercise capacity is less common. The response appears to be dose dependent, and very high dosage levels have been tested. Use of these agents in children have been associated with a high incidence of side effects such as fatigue, depression, sleep disorders, and impaired school performance. Despite early improvement, symptoms often recur, and may not respond to dose escalation. Studies of the impact of beta-blocker therapy on survival in adults and children have invariably been uncontrolled but generally have not identified a measurable effect on survival. In a single report of an uncontrolled observational study in children, a small number of pediatric patients in each of two geographically distinct areas were compared, with only one of the centers treating all HCM patients with high dose propranolol. Unusually high mortality (52 % 10 year survival) was found in the untreated cohort compared with no mortality in the treated cohort [47]. These findings stand in stark contrast with many prior, larger studies that failed to identify a survival benefit from propranolol. The high mortality in the untreated group is also difficult to reconcile with large pediatric studies that have found a 10 year survival of 80 % in unselected HCM populations [19]. The results of this report may be in part related to the well-known confounder that stratification based on geographic location is often associated with genetic stratification, particularly for autosomal dominant diseases where multiple family members of individual pedigrees segregate to the same cohort.

Calcium Channel Blockers

Calcium channel blockers in general and verapamil in particular have been used extensively in patients with FHCM. Sustained improvement in diastolic relaxation is generally noted in response to verapamil administration with secondary reduction in diastolic pressure and mean left atrial pressure [48, 49], resulting in a reduction in dyspnea and increase in exercise capacity. Improved distribution of subendocardial blood flow and diminished inducible ischemia have been noted as well [50]. Although verapamil may exacerbate congestive heart failure in older patients, pediatric tolerance has been excellent, even in neonates [23]. In stark contrast to the beta blockers, adverse effects of calcium channel blockers in children are almost never encountered.

Disopyramide

Disopyramide is a type Ia antiarrhythmic agent with negative inotropic properties that has been advocated to be used in combination for patients with FHCM unresponsive to beta-blocker or verapamil. The potent negative inotropic effect of this drug diminishes LV outflow obstruction and mitral regurgitation, and has been associated with variable results, with clinical improvement in some but not all patients. Several uncontrolled case series have found reduced obstruction at both rest and provocation and symptomatic improvement in up to 2/3 of patients who remained symptomatic on standard therapy [51, 52]. The experience in adults has not identified a significant incidence of proarrhythmic effects and the vagolytic side effects can be managed with concomitant cholinesterase inhibitor therapy when needed [53]. The published experience in pediatrics consists primarily of case reports, although the safety profile appears acceptable based on the experience in adults and on the pediatric experience using this drug for neurocardiogenic syncope [54]. Symptomatic LV outflow obstruction can be a particularly difficult issue in the first 2 years of life, a time period when recurrence of obstruction after effective myectomy is particularly common. Dosing in small children may require monitoring of plasma concentrations as therapeutic levels often require much higher dosing than in older patients [55].

Angiotensin Converting Enzyme Inhibitors (ACEi)

Inhibition of the renin-angiotensin system has a favorable impact on LVH and diastolic function in secondary hypertrophy, but has rarely been used in FHCM. Patients with dynamic LV outflow tract obstruction respond negatively to ACEi with a fall in cavity size and increase in outflow gradient, as well as impaired LV relaxation and compliance [56]. The potential for exacerbation of outflow obstruction has generally led to the conclusion that these as well as other systemic vasodilators are contraindicated in HCM. However, more recent data have noted a significant role for aldosterone [57] and the renin-angiotensin system in general [58] in modulating the phenotypic manifestations of HCM, and it is possible that blocking this system might reduce hypertrophy and fibrosis in patients with HCM [59]. Conclusive data are not available and there is no reported experience in children with HCM.

Asynchronous Pacemaker Therapy

Asynchronous ventricular pacing for treatment of symptoms in patients with LV outflow tract obstruction has largely fallen into disfavor. Results in small cohorts of children with outflow obstruction described symptomatic improvement, reduced outflow obstruction, reduced LVH, and improved exercise tolerance [60–62]. However, subsequent controlled studies found that only about 60 % of subjects improved and in 2/3 of these the benefit appeared to reflect placebo effect with an adverse response in 5 % [63]. The significant placebo effect has been seen in other studies [64], providing a

plausible explanation for persistent symptom relief after pacing termination [65], an effect not confirmed in later studies [66]. We consider surgical or transcatheter septal reduction as first line therapy in patients with obstructive FHCM who are symptomatic despite maximum medical therapy and would only consider asynchronous pacing if other interventions are not possible.

Alcohol Septal Ablation

Septal infarction following transcatheter infusion of absolute alcohol directly into septal coronary perforators can result in a reduction in septal thickness and relief of LV outflow tract obstruction, with symptomatic improvement and increased exercise tolerance. Procedural complications are higher than for surgical myectomy, primarily related to a ten-fold higher incidence of permanent complete heart block [67–69] Success is highest when obstruction is related to basilar septal hypertrophy, whereas patients with intrinsic mitral valve abnormalities or obstruction that is more apical are poor candidates, limiting the number of patients that are candidates for this intervention. Results to date indicate septal ablation may represent a reasonable alternative to surgery for relief of outflow tract obstruction in selected patients [70]. Coil occlusion of these vessels has been reported as an alternative method of inducing controlled infarction [71]. There is almost no reported experience with these techniques in children, in part related to the smaller coronary vessels in younger children and concerns about the lifetime consequences of a large septal infarction. Accordingly, the ACCF/AHA guidelines currently advise against routine utilization of alcohol septal ablation in childhood and young adulthood [1].

Surgical Myectomy

In symptomatic subaortic stenosis, septal myotomy-myectomy results in symptomatic improvement in nearly all patients and most contemporary studies have documented a high success rate, near zero mortality, and few complications with the procedure in adults, when performed by high volume, experienced surgeons [72–75]. Results in children have been similar to those reported in adults [76, 77]. Mitral regurgitation often improves in response to myectomy due to improved intraventricular flow patterns and surgery permits concomitant mitral valve repair in patients with underlying mitral valve abnormalities. Although recurrence of obstruction is rare in older patients (2 % [78]), it is common in neonates and infants, likely due to continued growth as well as associated disease states, when present, in these age groups. In our experience, despite complete relief of LV outflow tract obstruction, recurrence to pre-intervention gradients is seen within a year in up to 50 % of children under age 2, in particular.

Management of Sudden Death Risk in Children with HCM

Exercise Restriction

Avoidance of high intensity exercise is generally recommended for patients with FHCM. The rationale for this restriction is based on the observation that even though sudden death in HCM occurs less frequently during exercise, when adjusted for the amount of time spent exercising sudden death has a higher than expected association with exercise [79]. Nevertheless, the basis for this recommendation has several serious weaknesses [80]. The true incidence of FHCM in athletes who experience sudden death is uncertain since genetic confirmation is rarely available and diagnosis is based on morphologic criteria that may not unequivocally differentiate FHCM from physiologic hypertrophy. It is clear that some patients with FHCM tolerate intense, competitive athletic participation without symptoms or sudden death [81]. Population studies have documented the apparent paradox that although there is a transient increase in the risk for sudden death during intense exercise in patients with coronary artery disease who regularly participate in low and high level exertion, these individuals experience an overall reduction in the risk for sudden death [82, 83]. Additionally, individuals who do not exercise regularly have an exaggerated risk of sudden death during exercise [84]. In fact, it is precisely those individuals with cardiovascular risk factors who derive the largest risk reduction from regular participation in moderate to intense exercise [84]. There are no data to substantiate improved survival in HCM related to either exercise exclusion or inclusion, and indeed this is an experiment that is almost impossible to perform.

In view of the fact that the risk versus benefit ratio of exercise restriction is unknown, the adverse impact of exclusion from exercise participation should be considered when making recommendations to young patients with FHCM. Several population studies have now documented that exercise and sports participation during childhood are predictive of activity level in adults [85]. Detraining and social stigmatization are particularly difficult problems for the adolescent who is excluded from the usual school activities and peer interactions. It is common for the adolescent athlete who is abruptly excluded from sports participation to experience significant adverse psychological reactions resulting in social withdrawal, impaired school performance, and depression that may in some cases require hospitalization. Balancing the potential risks and benefits of exercise restriction is one of the most challenging aspects of providing care to the adolescent newly diagnosed with FHCM. Competitive team sports elicit an emotional overlay that appears to increase the risk associated with participation, in addition to demanding more intense exercise, and

can therefore be justifiably proscribed. Certain activities, such as weight lifting, are associated with high levels of circulating catecholamines that can predispose to arrhythmias and elicit a marked stimulus to eccentric cardiac hypertrophy. However, in patients who do not manifest high grade arrhythmias or exercise-induced arrhythmias or hypotension, there is little evidence to indicate that moderate aerobic-type exercise represents a significant risk and it does provide measurable hemodynamic and psychological benefits. Although it would be highly desirable to define an unequivocal line demarcating the level of exercise participation that provides the optimum division between risk and benefit, this is a decision that must be individualized and is associated with huge uncertainties.

Antiarrhythmics

Although most instances of sudden death in FHCM are arrhythmic events, prophylactic antiarrhythmic therapy has not proven effective [86]. Amiodarone was initially reported to reduce the incidence of sudden death in certain high-risk subgroups, but subsequent studies indicated an increased risk of sudden death [87]. Furthermore, the pediatric experience with amiodarone therapy for FHCM is very limited due to the toxicity associated with chronic therapy. The promising experience with ICDs has resulted in a shift to recommending an ICD for patients with ventricular tachycardia on Holter monitor or resuscitated cardiac arrest [88].

ICD Implantation

The incidence of sudden death in HCM is less than 1 % per year in both adults and children and ICDs are not without hazard [89], including depression, anxiety, inappropriate discharges, and overall reduced quality of life. Even in adults, the annualized frequency of inappropriate ICD intervention rate exceeds the appropriate discharge rate (4.8 % versus 3.3 %). "Appropriate discharges" occur at a much higher rate than the expected rate of sudden death by at least two-fold, supporting the interpretation that not all of the arrhythmias that trigger ICD discharge would be otherwise fatal and suggesting that less that 25 % of discharges are actually life-saving. Nonetheless, the data concerning efficacy of ICDs in HCM derive primarily from studies reporting the frequency with which "appropriate discharges" take place, an event that is used as a surrogate for aborted sudden death [41]. In general, the minimum requirement for consideration of ICD implantation is the potential for a reduced risk of sudden death, which generally means identification of subpopulations at higher risk for sudden death. For purposes of risk stratification, a number of risk factors for sudden death in adults with FHCM have been proposed. The 2011 ACCF/AHA guidelines [2] recognized aborted sudden death and sustained ventricular tachycardia as established, independent risk factors for sudden death warranting an ICD. Several other potential risk factors are of less certain significance, including family history of sudden death in a first degree relative, recent unexplained syncope, non-sustained ventricular tachycardia, extreme hypertrophy, and abnormal exercise blood pressure. The list of potential risk factors continues to evolve, such as the findings on a recent meta-analysis of data in adults with HCM indicating that positive delayed hyper-enhancement on CMR (DHE-MRI) correlates with all-cause mortality and demonstrates a trend towards significance for sudden death [90]. The data on many of these risk factors are characterized by reports both in favor and against their significance, oversampling of populations with multiple reports evaluating overlapping cohorts, and identification of risk factors on univariate analysis with insufficient power to evaluate their significance on multivariate analysis. Some groups have reported that risk is higher in the presence of multiple risk factors but this also remains controversial. The overall limitations of these data for risk stratification in adults are discussed at some length in the ACCF/AHA guidelines [2], but there is no discussion of the specific issues that arise in children and the potential need for age-stratification of these guidelines for application in pediatrics.

It is clear that even in adults, current methods for risk stratification for appropriate ICD use remain inadequate insofar as, based on current ICD utilization rates after implantation in high risk subjects and an anticipated device lifespan of 5 years, 83 % of devices will be not be used prior to replacement [91]. This dilemma is further compounded in children, for whom the risk-benefit ratio for the use of ICD's is less favorable than in adults. In a recent review, 28 % of children experienced appropriate, potentially life-saving ICD discharges, 25 % experienced inappropriate discharges, and there was a 21 % incidence of lead failure [92]. Children are also at higher risk for device-related infections and adverse psychosocial impact than adults. Therefore, although potentially life-saving, pediatric-specific implantation indications must be developed and tested before this technology will achieve its full potential in children.

Aborted sudden death and sustained ventricular tachycardia are generally accepted as indications for ICD implantation in children, but the other proposed risk factors are controversial. Identification of risk factors is problematic in the young because of the rarity of the disease in children and the low rate of sudden death. For example, in one of the few studies to include children, unexplained syncope (that is, excluding neurally mediated syncope) was identified as a risk factor for sudden death in children with a hazard ratio of 7.8 [93], but the small number of children and adolescents in

this series who experienced syncope seriously limits the strength of this conclusion. Similarly, NSVT is uncommon in children with HCM and in one series [94] was not associated with sudden death, although confidence is seriously limited due to a small number of events in a single study. Similarly, one investigation of exercise blood pressure response in children found that it was predictive of non-sudden death but not of sudden death [95], but the study sample is too small to exclude an association. Although severity of hypertrophy has been reported as risk factors for sudden death in children in some reports [96], other reports have found it to be only a risk factor for non-sudden death [95]. In a provocative report of a relationship between sudden death and the presence of myocardial bridging in children with FHCM [97], Yetman et al. reported that surgical unroofing of the coronary can prevent sudden death, whereas other investigations in children have reported that myocardial bridging is not a risk factor for sudden death [98]. Most of the more recently reported potential risk factors such as DHE-MRI have not been investigated in children. Overall, the data available concerning risk factors for sudden death in children with HCM are not adequate to justify differentiation from adults. However, given the age-related risk of ICD implantation in children, our institution has adopted an age-adjusted management approach. Aborted sudden death is considered an indication for ICD regardless of age. An ICD is recommended for adolescents with sustained ventricular tachycardia or with two or more of the other accepted risk factors (family history of sudden death due to HCM in 1st degree relative, abnormal blood pressure response to exercise, syncope, non-sustained ventricular tachycardia, or extreme hypertrophy). For pre-adolescents, additional evidence of risk is required before primary prevention is considered.

Conclusions

This review emphasizes issues concerning diagnosis and management of the diverse set of disorders that fall within the clinical phenotype of HCM in children with a focus on the differences in the disease between children and adults, emphasizing how certain of the management recommendations must be modified when applied to pediatric patients. In addition to issues that are typically addressed in reviews such as this, there are additional practical considerations in the care of these patients that are commonly encountered in practice, but are experientially based and are seldom discussed in academic presentations on the disease. Educating families concerning these practical issues is an important aspect of their care insofar as the medical and general community will often be unaware of the special considerations that can impact these patients. These observations can be summarized as clinical pearls as follows:

Clinical Pearls

- Anesthesia: Families and patients need to be aware that the hemodynamic response to anesthesia can present significant risks in patients with HCM and should be undertaken in facilities that have cardiac anesthesia support. Procedures such as oral surgery (third molar extraction, for example) that are often performed in office settings with light anesthesia require a more controlled setting with a dedicated anesthesiologist.
- Stimulant drug therapy is often prescribed for attention-deficit disorders. For children with HCM, approval of this therapy is often sought from the managing cardiologist. The proarrhythmic effects of exogenous catecholamines and intense exercise have led to particular concerns related to the use of these drugs in HCM. Indeed, in 2006 the Food and Drug Administration received contradictory advice from two advisory panels concerning the advisability of a black box warning for use of these medications in children, even in the absence of heart disease. Ultimately the warning was not issued, and in fact no verified association with sudden death has been documented. Although caution is undoubtedly warranted, these drugs have proven benefits in at least some of these patients. It is no doubt prudent to limit dosing to the minimally effective dose in conjunction with periodic Holter monitoring, and to continue use only in those who have clear improvement, but a categorical exclusion of these drugs is not advisable due to the positive risk/benefit ratio for their use.
- Stimulant drug abuse: Both prescribed and illicit stimulants are common recreational drugs and drugs of abuse. The cardiotoxic effects of acute and chronic cocaine use are well established but it is fundamentally impossible to study this issue in humans and therefore the information concerning the risks of other illegal stimulants in patients with HCM are limited to case reports. Open and non-accusatory discussions with teens, particularly those heading off to college and often separately from parental observation can alert them to the fact that the issues for them go well beyond the usual legal and social taboos.
- Dehydration: Adequate vigilance for dehydration in infants is always a challenge and gastroenteritis is common at this age. Similarly, active teenagers often do not realize when they are failing to keep up with fluid losses. Dehydration is poorly tolerated in HCM because of outflow tract obstruction and ventricular non-compliance, and although prevention is

the best option families need to seek help early in case of inadequate fluid intake or excess fluid loss.

- School activities: Institutions have variable policies concerning health-related risks and although they occasionally push children beyond their safety zone, more commonly they will impose activity restrictions on children with HCM that are excessive, resulting in significant social isolation and stigmatization. The physician frequently needs to intercede and assume responsibility for the decision to permit participation in school outings and other activities.
- Syncope: Adolescents should be counseled as to how to respond to sensations of faintness and palpitations. Most are not aware of the dangers of being held upright by their friends and underestimate the risk of injury with falling.
- Situational depression: Newly diagnosed adolescents and those who have recently had ICD implantation are at increased risk for depression, suicidality, social withdrawal, decreased school performance, and substance abuse. More frequent follow up and closer observation by parents and providers are required in the first year following either of these life-changing events.
- In-home automated external defibrillator (AED): Families frequently inquire as to whether they should purchase an external defibrillator for their home. Statistically, the odds of use of an in-home AED are limited by the average adverse event rate of ~1 %/year and are further reduced by the amount of time spent in the house. The final decision is clearly up to the family but in general patients who are felt to be at sufficient risk to justify continuous access to a defibrillator should have an ICD.
- In-school AED: Families frequently inquire as to whether they should insist that external defibrillators be available in schools. The benefits to availability of these devices in the school setting are well documented [99] and their availability and appropriate personnel training should certainly be encouraged as a general policy. However, for the same reasons as described for in-home AEDs, the probability of use for a specific child is quite low.
- Cardiopulmonary resuscitation (CPR) training: Patients and their families need to understand that in the case of an arrest, CPR should be undertaken regardless of whether an ICD has been placed, which is a common source of confusion on the part of non-medical personnel. CPR training is a useful skill in general and family members should be encouraged to undertake it.

Reference

1. Lipshultz SE, Sleeper LA, Towbin JA, Lowe AM, Orav EJ, Cox GF, et al. The incidence of pediatric cardiomyopathy in two regions of the United States. N Engl J Med. 2003;348(17):1647–55.
2. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011; 124(24):2761–96.
3. Colan SD. The why and how of Z scores. J Am Soc Echocardiogr. 2013;26(1):38–40.
4. Lee PT, Dweck MR, Prasher S, Shah A, Humphries SE, Pennell DJ, et al. Left ventricular wall thickness and the presence of asymmetric hypertrophy in healthy young army recruits: data from the LARGE heart study. Circ Cardiovasc Imaging. 2013;6(2):262–7.
5. Delius RE. Congenital heart surgery and database project: pediatric cardiomyopathies and end-stage congenital heart disease. Ann Thorac Surg. 2000;69:S180–90.
6. Colan SD. Classification of the cardiomyopathies. Prog Pediatr Cardiol. 2007;23(1–2):5–15.
7. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, et al. Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2008;29(2):270–6.
8. Elliott P. The 2006 American Heart Association classification of cardiomyopathies is not the gold standard. Circ Heart Fail. 2008; 1(1):77–9.
9. McTaggart DR. Tissue doppler imaging in hypertrophic cardiomyopathy without left ventricular hypertrophy. Heart Lung Circ. 2002;11(2):92–4.
10. Alhaj EK, Kim B, Cantales D, Uretsky S, Chaudhry FA, Sherrid MV. Symptomatic exercise-induced left ventricular outflow tract obstruction without left ventricular hypertrophy. J Am Soc Echocardiogr. 2013;26(5):556–65.
11. Lipshultz SE, Orav EJ, Wilkinson JD, Towbin JA, Messere JE, Lowe AM, et al. Risk stratification at diagnosis for children with hypertrophic cardiomyopathy: an analysis of data from the Pediatric Cardiomyopathy Registry. Lancet. 2013;2.
12. Saleeb SF, Margossian R, Spencer CT, Alexander ME, Smoot LB, Dorfman AL, et al. Reproducibility of echocardiographic diagnosis of left ventricular noncompaction. J Am Soc Echocardiogr. 2012; 25(2):194–202.
13. Bove AA. Making or breaking athletic careers. J Am Coll Cardiol. 2011;57(11):1297–8.
14. Steinvil A, Chundadze T, Zeltser D, Rogowski O, Halkin A, Galily Y, et al. Mandatory electrocardiographic screening of athletes to reduce their risk for sudden death proven fact or wishful thinking? J Am Coll Cardiol. 2011;57(11):1291–6.
15. Maron BJ, Edwards JE, Moller JH, Epstein SE. Prevalence and characteristics of disporportionate ventricular septal thickening in infants with congenital heart disease. Circulation. 1979;59(1): 126–33.
16. Somerville J, Becu L. Congenital heart disease associated with hypertrophic cardiomyopathy. Br Heart J. 1978;40(9):1034–9.
17. Dutka DP, Donnelly JE, Nihoyannopoulos P, Oakley CM, Nunez DJ. Marked variation in the cardiomyopathy associated with Friedreich's ataxia. Heart. 1999;81(2):141–7.
18. Regalado JJ, Rodriguez MM, Ferrer PL. Infantile hypertrophic cardiomyopathy of glycogenosis Type IX: isolated cardiac phosphorylase kinase deficiency. Pediatr Cardiol. 1999;20(4):304–7.
19. Colan SD, Lipshultz SE, Lowe AM, Sleeper LA, Messere J, Cox GF, et al. Epidemiology and cause-specific outcome of hypertrophic cardiomyopathy in children: findings from the Pediatric Cardiomyopathy Registry. Circulation. 2007;115(6):773–81.

20. Noonan J, O'Connor W. Noonan syndrome: a clinical description emphasizing the cardiac findings. Acta Paediatr Jpn. 1996;38(1):76–83.
21. Lin AE, Alexander ME, Colan SD, Kerr B, Rauen KA, Noonan J, et al. Clinical, pathological, and molecular analyses of cardiovascular abnormalities in Costello syndrome: a Ras/MAPK pathway syndrome. Am J Med Genet A. 2011;155A(3):486–507.
22. Wilkinson JD, Lowe AM, Salbert BA, Sleeper LA, Colan SD, Cox GF, et al. Outcomes in children with Noonan syndrome and hypertrophic cardiomyopathy: a study from the Pediatric Cardiomyopathy Registry. Am Heart J. 2012;164(3):442–8.
23. Moran AM, Colan SD. Verapamil therapy in infants with hypertrophic cardiomyopathy. Cardiol Young. 1998;8(3):310–9.
24. Goldstein JD, Shanske S, Bruno C, Perszyk AA. Maternally inherited mitochondrial cardiomyopathy associated with a C-to-T transition at nucleotide 3303 of mitochondrial DNA in the tRNA(Leu(UUR)) gene. Pediatr Dev Pathol. 1999;2(1):78–85. [Review] [14 refs].
25. Leatherbury L, Chandra RS, Shapiro SR, Perry LW. Value of endomyocardial biopsy in infants, children and adolescents with dilated or hypertrophic cardiomyopathy and myocarditis. J Am Coll Cardiol. 1988;12(6):1547–54.
26. Semsarian C, Ahmad I, Giewat M, Georgakopoulos D, Schmitt JP, McConnell BK, et al. The L-type calcium channel inhibitor diltiazem prevents cardiomyopathy in a mouse model. J Clin Invest. 2002;109(8):1013–20.
27. Marin TM, Keith K, Davies B, Conner DA, Guha P, Kalaitzidis D, et al. Rapamycin reverses hypertrophic cardiomyopathy in a mouse model of LEOPARD syndrome-associated PTPN11 mutation. J Clin Invest. 2011;121(3):1026–43.
28. McKenna WJ, Spirito P, Desnos M, Dubourg O, Komajda M. Experience from clinical genetics in hypertrophic cardiomyopathy: proposal for new diagnostic criteria in adult members of affected families. Br Heart J. 1997;77(2):130–2.
29. Charron P, Forissier JF, Amara ME, Dubourg O, Desnos M, Bouhour JB, et al. Accuracy of European diagnostic criteria for familial hypertrophic cardiomyopathy in a genotyped population. Int J Cardiol. 2003;90(1):33–8.
30. Ho CY, Sweitzer NK, McDonough B, Maron BJ, Casey SA, Seidman JG, et al. Assessment of diastolic function with Doppler tissue imaging to predict genotype in preclinical hypertrophic cardiomyopathy. Circulation. 2002;105(25):2992–7.
31. Nagueh SF, Bachinski LL, Meyer D, Hill R, Zoghbi WA, Tam JW, et al. Tissue Doppler imaging consistently detects myocardial abnormalities in patients with hypertrophic cardiomyopathy and provides a novel means for an early diagnosis before and independently of hypertrophy. Circulation. 2001;104(2):128–30.
32. Michels M, Soliman OI, Kofflard MJ, Hoedemaekers YM, Dooijes D, Majoor-Krakauer D, et al. Diastolic abnormalities as the first feature of hypertrophic cardiomyopathy in Dutch myosin-binding protein C founder mutations. JACC Cardiovasc Imaging. 2009;2(1):58–64.
33. Dalen H, Thorstensen A, Vatten LJ, Aase SA, Stoylen A. Reference values and distribution of conventional echocardiographic Doppler measures and longitudinal tissue Doppler velocities in a population free from cardiovascular disease. Circ Cardiovasc Imaging. 2010;3(5):614–22.
34. Rowin EJ, Maron MS, Lesser JR, Maron BJ. CMR with late gadolinium enhancement in genotype positive-phenotype negative hypertrophic cardiomyopathy. JACC Cardiovasc Imaging. 2012; 5(1):119–22.
35. Ho CY, Abbasi SA, Neilan TG, Shah RV, Chen Y, Heydari B, et al. T1 measurements identify extracellular volume expansion in hypertrophic cardiomyopathy sarcomere mutation carriers with and without left ventricular hypertrophy. Circ Cardiovasc Imaging. 2013;6(3): 415–22.
36. Maron MS, Rowin EJ, Lin D, Appelbaum E, Chan RH, Gibson CM, et al. Prevalence and clinical profile of myocardial crypts in hypertrophic cardiomyopathy. Circ Cardiovasc Imaging. 2012;5(4): 441–7.
37. Russel IK, Brouwer WP, Germans T, Knaapen P, Marcus JT, van der Velden J, et al. Increased left ventricular torsion in hypertrophic cardiomyopathy mutation carriers with normal wall thickness. J Cardiovasc Magn Reson. 2011;13(1):3.
38. Germans T, Russel IK, Gotte MJ, Spreeuwenberg MD, Doevendans PA, Pinto YM, et al. How do hypertrophic cardiomyopathy mutations affect myocardial function in carriers with normal wall thickness? Assessment with cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2010;12(1):13.
39. Maron BJ, Maron MS, Wigle ED, Braunwald E. The 50-year history, controversy, and clinical implications of left ventricular outflow tract obstruction in hypertrophic cardiomyopathy from idiopathic hypertrophic subaortic stenosis to hypertrophic cardiomyopathy: from idiopathic hypertrophic subaortic stenosis to hypertrophic cardiomyopathy. J Am Coll Cardiol. 2009;54(3):191–200.
40. Maron MS, Olivotto I, Betocchi S, Casey SA, Lesser JR, Losi MA, et al. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. N Engl J Med. 2003;348(4):295–303.
41. McLeod CJ, Ommen SR, Ackerman MJ, Weivoda PL, Shen WK, Dearani JA, et al. Surgical septal myectomy decreases the risk for appropriate implantable cardioverter defibrillator discharge in obstructive hypertrophic cardiomyopathy. Eur Heart J. 2007;28(21):2583–8.
42. Ommen SR, Maron BJ, Olivotto I, Maron MS, Cecchi F, Betocchi S, et al. Long-term effects of surgical septal myectomy on survival in patients with obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol. 2005;46(3):470–6.
43. Ball W, Ivanov J, Rakowski H, Wigle ED, Linghorne M, Ralph-Edwards A, et al. Long-term survival in patients with resting obstructive hypertrophic cardiomyopathy comparison of conservative versus invasive treatment. J Am Coll Cardiol. 2011;58(22):2313–21.
44. Shah JS, Esteban MT, Thaman R, Sharma R, Mist B, Pantazis A, et al. Prevalence of exercise-induced left ventricular outflow tract obstruction in symptomatic patients with non-obstructive hypertrophic cardiomyopathy. Heart. 2008;94(10):1288–94.
45. Kizilbash AM, Heinle SK, Grayburn PA. Spontaneous variability of left ventricular outflow tract gradient in hypertrophic obstructive cardiomyopathy. Circulation. 1998;97(5):461–6.
46. Williams LK, Rakowski H. Surgical myectomy for hypertrophic obstructive cardiomyopathy: the cut that heals. Circulation. 2013; 128(3):193–7.
47. Ostman-Smith I, Wettrell G, Riesenfeld T. A cohort study of childhood hypertrophic cardiomyopathy: improved survival following high-dose beta-adrenoceptor antagonist treatment. J Am Coll Cardiol. 1999;34(6):1813–22.
48. Posma JL, Blanksma PK, Van der Wall E, Lie KI. Acute intravenous versus chronic oral drug effects of verapamil on left ventricular diastolic function in patients with hypertrophic cardiomyopathy. J Cardiovasc Pharmacol. 1994;24(6):969–73.
49. Hartmann A, Schnell J, Hopf R, Kneissl G. Persisting effect of Ca(2+)-channel blockers on left ventricular function in hypertrophic cardiomyopathy after 14 years' treatment. Angiology. 1996; 47(8):765–73.
50. Gistri R, Cecchi F, Choudhury L, Montereggi A, Sorace O, Salvadori PA, et al. Effect of verapamil on absolute myocardial blood flow in hypertrophic cardiomyopathy. Am J Cardiol. 1994;74(4):363–8.
51. Musat D, Marineci S, Sherrid MV. Can pharmacologic gradient reduction decrease mortality in hypertrophic cardiomyopathy? Prog Cardiovasc Dis. 2012;54(6):535–42.
52. Sherrid MV, Shetty A, Winson G, Kim B, Musat D, Alviar CL, et al. Treatment of obstructive hypertrophic cardiomyopathy symptoms and gradient resistant to first-line therapy with beta-blockade or verapamil. Circ Heart Fail. 2013;6(4):694–702.
53. Sherrid MV, Barac I, McKenna WJ, Elliott PM, Dickie S, Chojnowska L, et al. Multicenter study of the efficacy and safety of disopyramide in obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol. 2005;45(8):1251–8.

54. Sokoloski MC. Evaluation and treatment of pediatric patients with neurocardiogenic syncope. Prog Pediatr Cardiol. 2001;13(2):127–31.
55. Siddoway LA, Woosley RL. Clinical pharmacokinetics of disopyramide. Clin Pharmacokinet. 1986;11(3):214–22.
56. Kyriakidis M, Triposkiadis F, Dernellis J, Androulakis AE, Mellas P, Kelepeshis GA, et al. Effects of cardiac versus circulatory angiotensin-converting enzyme inhibition on left ventricular diastolic function and coronary blood flow in hypertrophic obstructive cardiomyopathy. Circulation. 1998;97(14):1342–7.
57. Ortlepp JR, Vosberg HP, Reith S, Ohme F, Mahon NG, Schroder D, et al. Genetic polymorphisms in the renin-angiotensin-aldosterone system associated with expression of left ventricular hypertrophy in hypertrophic cardiomyopathy: a study of five polymorphic genes in a family with a disease causing mutation in the myosin binding protein C gene. Heart. 2002;87(3):270–5.
58. Tsybouleva N, Zhang LF, Chen SN, Patel R, Lutucuta S, Nemoto S, et al. Aldosterone, through novel signaling proteins, is a fundamental molecular bridge between the genetic defect and the cardiac phenotype of hypertrophic cardiomyopathy. Circulation. 2004;109(10):1284–91.
59. Yamazaki T, Suzuki J, Shimamoto R, Tsuji T, Ohmoto-Sekine Y, Ohtomo K, et al. A new therapeutic strategy for hypertrophic nonobstructive cardiomyopathy in humans. A randomized and prospective study with an Angiotensin II receptor blocker. Int Heart J. 2007;48(6):715–24.
60. Alday LE, Bruno E, Moreyra E, Amuchastegui LM, Juaneda E, Maisuls H. Mid-term results of dual-chamber pacing in children with hypertrophic obstructive cardiomyopathy. Echocardiography. 1998;15(3):289–95.
61. Rishi F, Hulse JE, Auld DO, McRae G, Kaltman J, Kanter K, et al. Effects of dual-chamber pacing for pediatric patients with hypertrophic obstructive cardiomyopathy. J Am Coll Cardiol. 1997;29(4):734–40.
62. Dimitrow PP, Podolec P, Grodecki J, Plazak W, Dudek D, Pieniazek P, et al. Comparison of dual-chamber pacing with nonsurgical septal reduction effect in patients with hypertrophic obstructive cardiomyopathy. Int J Cardiol. 2004;94(1):31–4.
63. Nishimura RA, Trusty JM, Hayes DL, Ilstrup DM, Larson DR, Hayes SN, et al. Dual-chamber pacing for hypertrophic cardiomyopathy: a randomized, double-blind, crossover trial. J Am Coll Cardiol. 1997;29(2):435–41.
64. Linde C, Gadler F, Kappenberger L, Rydén L, PIC Study Group. Placebo effect of pacemaker implantation in obstructive hypertrophic cardiomyopathy. Am J Cardiol. 1999;83(6):903–7.
65. Fananapazir L, Cannon III RO, Tripodi D, Panza JA. Impact of dual-chamber permanent pacing in patients with obstructive hypertrophic cardiomyopathy with symptoms refractory to verapamil and β-adrenergic blocker therapy. Circulation. 1992;85(6):2149–61.
66. Gadler F, Linde C, Rydén L. Rapid return of left ventricular outflow tract obstruction and symptoms following cessation of long-term atrioventricular synchronous pacing for obstructive hypertrophic cardiomyopathy. Am J Cardiol. 1999;83(4):553–7.
67. Togni M, Billinger M, Cook S, Hess OM. Septal myectomy: cut, coil, or boil? Eur Heart J. 2008;29(3):296–8.
68. Sorajja P, Valeti U, Nishimura RA, Ommen SR, Rihal CS, Gersh BJ, et al. Outcome of alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Circulation. 2008;118(2):131–9.
69. Sorajja P, Ommen SR, Holmes Jr DR, Dearani JA, Rihal CS, Gersh BJ, et al. Survival after alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Circulation. 2012;126(20):2374–80.
70. Kimmelstiel CD, Maron BJ. Role of percutaneous septal ablation in hypertrophic obstructive cardiomyopathy. Circulation. 2004;109(4):452–6.
71. Durand E, Mousseaux E, Coste P, Pilliere R, Dubourg O, Trinquart L, et al. Non-surgical septal myocardial reduction by coil embolization for hypertrophic obstructive cardiomyopathy: early and 6 months follow-up. Eur Heart J. 2008;29(3):348–55.
72. Woo A, Williams WG, Choi R, Wigle ED, Rozenblyum E, Fedwick K, et al. Clinical and echocardiographic determinants of long-term survival after surgical myectomy in obstructive hypertrophic cardiomyopathy. Circulation. 2005;111(16):2033–41.
73. Nishimura RA, Holmes Jr DR. Hypertrophic obstructive cardiomyopathy. N Engl J Med. 2004;350(13):1320–7.
74. Smedira NG, Lytle BW, Lever HM, Rajeswaran J, Krishnaswamy G, Kaple RK, et al. Current effectiveness and risks of isolated septal myectomy for hypertrophic obstructive cardiomyopathy. Ann Thorac Surg. 2008;85(1):127–33.
75. Desai MY, Bhonsale A, Smedira NG, Naji P, Thamilarasan M, Lytle BW, et al. Predictors of long-term outcomes in symptomatic hypertrophic obstructive cardiomyopathy patients undergoing surgical relief of left ventricular outflow tract obstruction. Circulation. 2013;128(3):209–16.
76. Minakata K, Dearani JA, O'Leary PW, Danielson GK. Septal myectomy for obstructive hypertrophic cardiomyopathy in pediatric patients: early and late results. Ann Thorac Surg. 2005;80(4):1424–9.
77. Menon SC, Ackerman MJ, Ommen SR, Cabalka AK, Hagler DJ, O'Leary PW, et al. Impact of septal myectomy on left atrial volume and left ventricular diastolic filling patterns: an echocardiographic study of young patients with obstructive hypertrophic cardiomyopathy. J Am Soc Echocardiogr. 2008;21(6):684–8.
78. Minakata K, Dearani JA, Schaff HV, O'Leary PW, Ommen SR, Danielson GK. Mechanisms for recurrent left ventricular outflow tract obstruction after septal myectomy for obstructive hypertrophic cardiomyopathy. Ann Thorac Surg. 2005;80(3):851–6.
79. Semsarian C, Richmond DR. Sudden cardiac death in familial hypertrophic cardiomyopathy: an Australian experience. Aust N Z J Med. 1999;29(3):368–70.
80. Shephard RJ. The athlete's heart: is big beautiful? Br J Sports Med. 1996;30(1):5–10.
81. Maron BJ, Klues HG. Surviving competitive athletics with hypertrophic cardiomyopathy. Am J Cardiol. 1994;73(15):1098–104.
82. Friedewald Jr VE, Spence DW. Sudden cardiac death associated with exercise: the risk- benefit issue. Am J Cardiol. 1990;66(2):183–8.
83. Kohl HW, Powell KE, Gordon NF, Blair SN, Paffenbarger RS. Physical activity, physical fitness, and sudden cardiac death. Epidemiol Rev. 1992;14(1):37–58.
84. Richardson CR, Kriska AM, Lantz PM, Hayward RA. Physical activity and mortality across cardiovascular disease risk groups. Med Sci Sports Exerc. 2004;36(11):1923–9.
85. Beunen GP, Lefevre J, Philippaerts RM, Delvaux K, Thomis M, Claessens AL, et al. Adolescent correlates of adult physical activity: a 26-year follow-up. Med Sci Sports Exerc. 2004;36(11):1930–6.
86. Tung R, Zimetbaum P, Josephson ME. A critical appraisal of implantable cardioverter-defibrillator therapy for the prevention of sudden cardiac death. J Am Coll Cardiol. 2008;52(14):1111–21.
87. Fananapazir L, Leon MB, Bonow RO, Tracy CM, Cannon III RO, Epstein SE. Sudden death during empiric amiodarone therapy in symptomatic hypertrophic cardiomyopathy. Am J Cardiol. 1991;67(2):169–74.
88. Melacini P, Maron BJ, Bobbo F, Basso C, Tokajuk B, Zucchetto M, et al. Evidence that pharmacological strategies lack efficacy for the prevention of sudden death in hypertrophic cardiomyopathy. Heart. 2007;93(6):708–10.
89. Schinkel AF, Vriesendorp PA, Sijbrands EJ, Jordaens LJ, ten Cate FJ, Michels M. Outcome and complications after implantable cardioverter defibrillator therapy in hypertrophic cardiomyopathy: systematic review and meta-analysis. Circ Heart Fail. 2012;5(5):552–9.
90. Green JJ, Berger JS, Kramer CM, Salerno M. Prognostic value of late gadolinium enhancement in clinical outcomes for hypertrophic cardiomyopathy. JACC Cardiovasc Imaging. 2012;5(4):370–7.
91. Maron BJ, Spirito P, Shen WK, Haas TS, Formisano F, Link MS, et al. Implantable cardioverter-defibrillators and prevention of

sudden cardiac death in hypertrophic cardiomyopathy. JAMA. 2007;298(4):405–12.
92. Alexander ME, Cecchin F, Walsh EP, Triedman JK, Bevilacqua LM, Berul CI. Implications of implantable cardioverter defibrillator therapy in congenital heart disease and pediatrics. J Cardiovasc Electrophysiol. 2004;15(1):72–6.
93. Spirito P, Autore C, Rapezzi C, Bernabo P, Badagliacca R, Maron MS, et al. Syncope and risk of sudden death in hypertrophic cardiomyopathy. Circulation. 2009;119(13):1703–10.
94. McKenna WJ, Franklin RCG, Nihoyannopoulos P, Robinson KC, Deanfield JE, Dickie S, et al. Arrhythmia and prognosis in infants, children and adolescents with hypertrophic cardiomyopathy. J Am Coll Cardiol. 1988;11(1):147–53.
95. Decker JA, Rossano JW, Smith EO, Cannon B, Clunie SK, Gates C, et al. Risk factors and mode of death in isolated hypertrophic cardiomyopathy in children. J Am Coll Cardiol. 2009;54(3):250–4.
96. Maron BJ, Spirito P, Ackerman MJ, Casey SA, Semsarian C, Estes III NA, et al. Prevention of sudden cardiac death with implantable cardioverter-defibrillators in children and adolescents with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2013;61(14):1527–35.
97. Yetman AT, McCrindle BW, MacDonald C, Freedom RM, Gow R. Myocardial bridging in children with hypertrophic cardiomyopathy – a risk factor for sudden death. N Engl J Med. 1998;339(17):1201–9.
98. Mohiddin SA, Begley D, Shih J, Fananapazir L. Myocardial bridging does not predict sudden death in children with hypertrophic cardiomyopathy but is associated with more severe cardiac disease. J Am Coll Cardiol. 2000;36(7):2270–8.
99. Drezner JA, Rao AL, Heistand J, Bloomingdale MK, Harmon KG. Effectiveness of emergency response planning for sudden cardiac arrest in United States high schools with automated external defibrillators. Circulation. 2009;120(6):518–25.

Sudden Cardiac Death Risk Assessment

10

Katy E. Bockstall, Michael P. Gannon, Weijia Wang, and Mark S. Link

Abstract

Sudden cardiac death is a major issue in patients with HCM. The young are at particular risk for SCD, while those over 60 are less affected by SCD. There are five traditional risk factors for sudden cardiac death in patients with HCM, including: massively thick myocardium, unexplained syncope, family history of SCD due to HCM, nonsustained ventricular tachycardia, and hypotensive response to exercise. Currently, an ICD is recommended for resuscitated SCD and/or those with sustained ventricular tachycardia, and reasonable for those with massive hypertrophy (>3 cm), unexplained syncope and/or a family history of SCD, and also reasonable for patients with NSVT or abnormal blood pressure response to exercise, but usually when combined with other markers of heightened risk.

Keywords

Hypertrophic cardiomyopathy • Sudden Cardiac Death • Massive hypertrophy • Nonsustained ventricular tachycardia • Syncope

Key Points

- There are five traditional risk factors for sudden cardiac death in patients with HCM, in addition to prior episode of sustained ventricular tachycardia or SCD, including:
  Massively thick myocardium
  Unexplained syncope
  Family history of SCD due to HCM
  Nonsustained ventricular tachycardia
  Hypotensive response to exercise
- Evolving possible risk factors for SCD include:
  Extent of scarring seen at MRI
  End stage (burnt out) HCM
  Apical aneurysm
  LVOT obstruction
  High risk genetic mutations
  Impaired coronary flow reserve (myocardial ischemia)
- Currently, an ICD is recommended for resuscitated SCD and/or those with sustained ventricular tachycardia, reasonable for those with massive hypertrophy (>3 cm), unexplained syncope and/or a family history of SCD, and also reasonable for patients with NSVT or abnormal blood pressure response to exercise, but usually when combined with other markers of heightened risk
- There is no evidence that pharmacological therapy reduces the risk of SCD in HCM

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Sudden cardiac death is a major issue in patients with HCM [1, 2]. The young are at particular risk for SCD, while those over 60 are less affected by SCD [3]. Early reports of SCD mortality rates of 4–6 %/year were secondary to a referral bias to tertiary care centers of sicker individuals [4]. More recent community and non-referral based populations report an annual incidence of SCD at <1 %/year [1, 4–8].

Assessment of Risk for SCD: The Traditional Risk Factors

Because the risk of SCD is present over a patient's lifetime, and because the risk is oftentimes dissociated from the structural abnormality or severity of symptoms found in any given patient with HCM, a proactive approach to assessing risk and determining suitability for ICD implantation has become paramount. Accordingly, several major and minor risk factors have evolved through observational studies, and form the basis for recommendations on primary or secondary prevention.

Prior Cardiac Arrest or Sustained Ventricular Tachycardia

As in individuals with other structural heart diseases, a prior episode of sustained ventricular arrhythmia or SCD in the absence of a reversible cause is the strongest predictor of a subsequent SCD, with an annualized rate of recurrent events of 10 % per year [2, 9–11]. These individuals should be offered an implantable cardioverter defibrillator (ICD) as their lifelong risk of recurrent SCD is high.

Five Traditional Risk Factors

If you exclude individuals with SCD or sustained ventricular tachycardia, there are five traditional or historical risk factors for SCD [12]. It is likely that these five risk factors do not all convey equivalent risk. In fact in the latest HCM guidelines these five risk factors have been divided into major and minor risk factors (Fig. 10.1).

Family History of SCD

Individuals with a family history of SCD in a first degree relative under the age of 50 are at increased personal risk of SCD [13, 14]. In addition, patients with multiple individuals in their family sustaining SCD are likely at higher risk. It is probable that high risk genotypes and resultant phenotypes of the disease convey this risk, although there may be other factors such as environment, lifestyle, and genetic promoters of this malignant HCM phenotype [15–18].

Syncope

Syncope or presyncope occurs in 15–25 % of HCM, and may be due to left ventricular outflow tract obstruction, arrhythmia, or autonomic dysfunction, all of which occur to variable extent in this patient population. Unexplained syncope, especially when recent, recurrent or refractory to medical management, has been associated with a higher incidence of SCD, particularly in young patients [4, 19]. In a large HCM cohort, unexplained syncope had statistical significance as an independent predictor of sudden death. The effect was greater in patients with recent syncope within 6 months before initial evaluation, at a five-fold higher relative risk, and in patients <18 years of age [19]. No increased risk is seen in patients older than 40 years with distant episodes of syncope or with neurally mediated (vasovagal) syncope [19]. Importantly, unexplained syncope implies a presumed arrhythmic etiology, despite prolonged monitoring and treatment of outflow tract obstruction or autonomic dysfunction, if present. Thus, a comprehensive workup and management scheme is required prior to the determination that a patient fulfills criteria for unexplained syncope.

Extreme Left Ventricular Hypertrophy

Maximum LV thickness ≥30 mm in young patients has been predictive of SCD in a number of studies [20, 21] but not all [4]. One other found an increased risk in the subset of patients <18 years old [22]. LV wall thickness alone has low positive predictive accuracy and the number of additional risk factors present may be a better predictor of SCD [20, 21]. Maximum LV thickness <15 mm has consistently shown very low rates of SCD [20], however events can occur at all degrees of hypertrophy [20, 21].

Nonsustained Ventricular Tachycardia

Ventricular tachyarrhythmias are common in HCM patients. Premature ventricular contractions occur in 80–90 % of patients, ventricular couplets in 30–40 %, and nonsustained ventricular tachycardia (NSVT) in 20–25 %. While NSVT is common, the number of episodes is low in most (1–3 runs in 24 h), bursts are usually short (3–5 beats) and episodes are typically asymptomatic [9, 23–27].

There is conflicting data concerning the role of NSVT in the prognostication of sudden death. Early studies of referral based populations showed a significant association between NSVT and sudden death risk [25]. However, more recent studies done in non-referral based or community populations have failed to confirm this, showing a low positive predictive value (9 %) and high negative predictive value (95 %) [9, 24, 26, 28]. NSVT in patients <30 years of age has been shown to

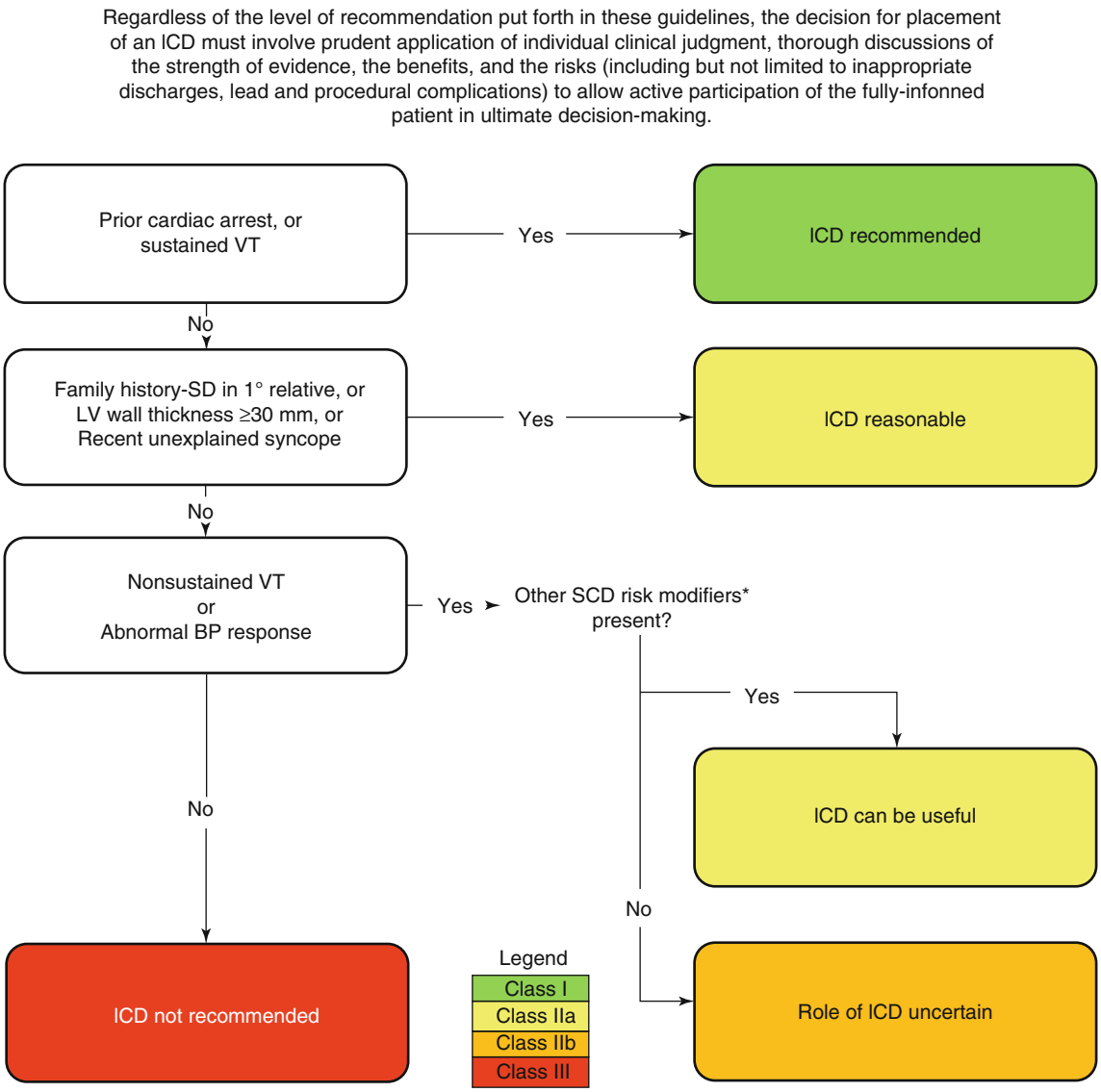


Fig. 10.1 Flow chart of the evaluation and treatment of patients with hypertrophic cardiomyopathy with regards to implantation of an implantable cardioverter defibrillator (*ICD*). Reprinted from *JACC* [12]. *Other potential risk factors include LVOT obstruction, late gadolinium enhancement on CMR, LV apical aneurysm, high risk genetic mutations. *BP* indicates blood pressure, *ICD* implantable cardioverter-defibrillator, *LV* left ventricle, *SCD* sudden cardiac death, *SD* sudden death, and *VT* ventricular tachycardia

be a strong independent predictor of SCD, while this is not necessarily true in those >30 years of age [23]. Although there is no supportive data, longer and more rapid runs of NSVT likely portend higher risk than short bursts at lower rates.

Abnormal Exercise Blood Pressure Response

Abnormal blood pressure response during exercise is seen in ~20–35 % of HCM patients and is thought to be a marker of hemodynamic instability caused by either left ventricular outflow tract obstruction, abnormal autonomic function, or some combination of the two phenomena [29, 30]. This measure is a stronger predictor in young patients, but has consistently shown low positive predictive value and high negative predictive value [8, 13, 29, 31].

Emerging Risk Factors for SCD

SCD occurs even in those patients with no conventional risk factors [13, 32]. Further, advanced imaging, genetic testing, as well as evaluation of long-term observational databases, have allowed other risk factors to emerge. The degree to which these novel risk factors impact management is a matter of debate, but they will likely interact with more traditional risk factors to elevate or mitigate global risk assessment in any given patient.

Late Gadolinium Enhancement on Cardiovascular Magnetic Resonance Imaging

Emerging evidence suggests that contrast-enhanced magnetic resonance (CMR) imaging may be a useful risk stratification tool for SCD in HCM [33]. Late gadolinium enhancement (LGE) on CMR represents areas of increased collagen deposition and myocardial fibrosis [34]. Late gadolinium enhancement by CE-MRI in HCM is common, seen in ~40–80 % of patients [5, 33, 35–37], occupies ~10 % of the myocardium and is not seen in perfusion territories of the epicardial coronary arteries, thus distinct from findings in ischemic disease [35–37]. Late enhancement is associated with other risk factors for sudden death, particularly in patients younger than 40 years of age [33]. Asymptomatic or mildly symptomatic patients with late enhancement had a seven-fold higher risk of NSVT [35]. Though an earlier study found increased event rates of SCD/ICD discharge in late gadolinium enhancement patients which did not reach statistical significance [36], a more recent study with a larger cohort of HCM patients and longer follow up found late enhancement to be significantly associated with sudden cardiac death and appropriate ICD discharges, even after controlling for traditional risk factors [5]. The optimal threshold percent of myocardium with LGE that elevates risk remains unknown.

Left Ventricular Apical Aneurysms

In a large cohort of HCM patents, LV apical aneurysms had a prevalence of ~2 % [32]. These patients experienced adverse disease consequences at 10.5 %/year, including sudden death, aborted cardiac arrest, and appropriate ICD interventions for SCD [32]. Apical aneurysms are typically ringed with scar and associated with further transmural myocardial scarring and fibrosis, which likely serves as the arrhythmogenic substrate [32, 38]. Interestingly, in one study >40 % of patients with LV aneurysm who experienced cardiac arrest, SCD or appropriate ICD interventions had no conventional risk markers present, suggesting the possible role for the presence of LV aneurysm as another, possibly independent, marker of SCD risk [32].

End-Stage Phase

The end-stage phase of HCM, with LV systolic function less than 50 %, is characterized by poor outcomes and increased risk for sudden death [39]. In a large multicenter cohort of HCM patients, end-stage disease had a SCD prevalence of 3.5 %, with an overall annual mortality rate of 11 %/year and appropriate ICD interventions in 10 % of patients annually [39]. This observational data suggests that end-stage disease may be regarded as another risk marker for SCD [39]. Importantly, patients with HCM with end-stage disease may not fulfill traditional criteria for ICD implantation in the non-ischemic population, where ejection fractions below 35 % are typically required. An ejection fraction below 50 % in a patient with HCM, where the function is usually hyperdynamic, indicates significant systolic dysfunction and elevated risk.

Left Ventricular Outflow Tract Obstruction

About 20–30 % of HCM patients have left ventricular outflow tract obstruction at rest, and up to two-thirds have provocable obstruction [40–42]. LVOT basal gradient ≥30 mmHg is an independent predictor of sudden death or appropriate ICD discharge, with obstructive patients at significantly higher risk of SCD than those without obstruction [8, 40, 41]. Severity of outflow tract obstruction was associated with a higher occurrence of sudden death and appropriate ICD discharges in one large cohort study [41]. Like other known risk factors, considered alone outflow tract obstruction has high negative predictive value (95–95.9 %) but low positive predictive value (7–9.7 %) due to its high prevalence in patients with HCM [40, 41].

High Risk Genetic Mutations

Early studies reported that patients with troponin T mutations had substantial rates of sudden cardiac death at a young age [15–18]. However, with over 1,000 different mutations currently known in HCM, including many on troponin T, and significant phenotypical heterogeneity, clinical risk stratification based on genetic testing has been limited [43, 44]. Yet, there is likely an increased risk of SCD for those patients with double or compound sarcomere mutations [45]. Further prospective observations of large genetic databases with clinical correlations will be required to further elucidate whether individual mutations or gene defects correlate with elevated risk, and to what degree.

Myocardial Ischemia

Patients with HCM and concomitant atherosclerotic coronary artery disease (CAD) have reduced survival free of SCD compared with HCM patients with no CAD [46]. Rates of SCD in these patients exceed historical rates seen in CAD with normal left ventricular function, with SCD at 2 %/year and overall mortality at 6.6 %/year.

In addition, patients with HCM have been found to have poor coronary flow reserve, with the perturbations in flow reserve resulting in ischemia and severity correlating with long-term outcome [47]. This microvascular dysfunction also may cause abnormal stress findings, and in some studies was an independent predictor of death from cardiovascular causes [48, 49].

Prevention of SCD

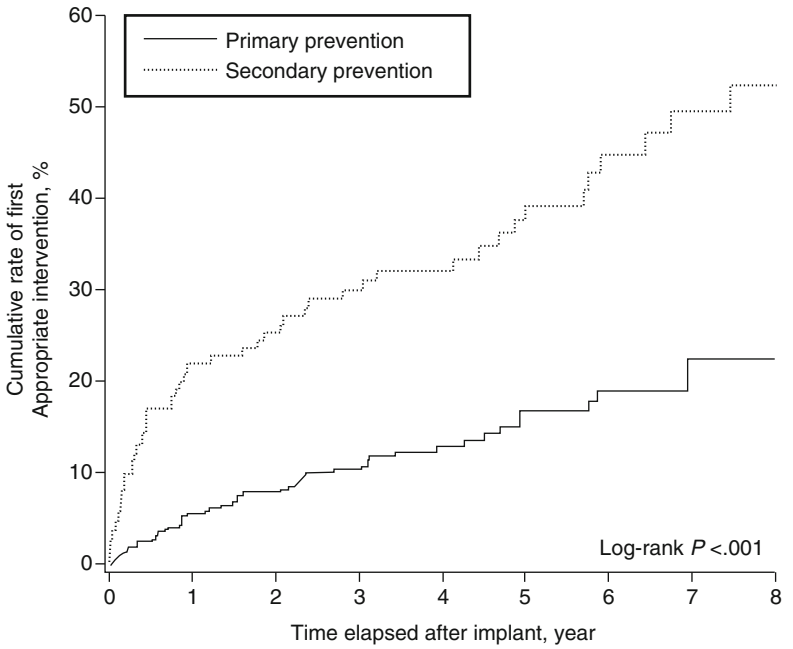
Medical Management

Pharmaceutical management of HCM patients at risk for SCD has not been supported in the literature. Before the introduction of ICDs, pharmaceutical agents including amiodarone, β-blockers, calcium antagonists and type I-A antiarrhythmic agents were used prophylactically [9]. While early reports suggested amiodarone as potentially protective [9, 28, 50, 51], it is clear that amiodarone does not provide absolute protection from sudden death in HCM patients [2, 20, 52]. Moreover, amiodarone is associated with significant cumulative toxicity, making it a poor candidate for treatment in young patients needing long-term treatment [9]. None of the other pharmaceutical agents has shown a reduction of SCD and therefore routine prophylactic administration of these agents is not recommended.

Although not sufficient as a sole therapy for primary or secondary prevention, pharmaceutical agents may have a role in patients with prior ICD implantation who continue to present with symptomatic ventricular arrhythmias. The most experience to prevent recurrent arrhythmias is with amiodarone; however, dofetilide and sotalol may also occasionally be beneficial.

Implantable Cardioverter Defibrillators

Despite the increased cardiac mass and thickened substrate in HCM, ICDs still have excellent efficacy in terminating lethal arrhythmias [2]. High risk patients with ICDs placed for primary or secondary prevention experience annual appropriate discharge rates for ventricular arrhythmias of 4–7 %/year (Fig. 10.2), with appropriate treatment occurring more frequently when placed for secondary prevention (7–11 %/year) compared to primary prevention (3–5 %/year) [2, 53–55]. There is often a delay of many years to first therapy [2, 53]. Unfortunately, inappropriate discharges are also common in HCM patients, with up to 25 % receiving inappropriate shocks [2, 53, 56]. Younger age and a history of atrial fibrillation have been associated with inappropriate ICD shocks [53, 54]. Inappropriate discharge due to sinus tachycardia, atrial fibrillation or lead malfunction are the most common ICD complications in



No. at risk

Primary prevention	383	332	256	205	148	95	70	43	28
Secondary prevention	123	95	85	70	51	39	28	18	16

Fig. 10.2 Cumulative rates to first appropriate ICD intervention in HCM patients who received an ICD for primary (n = 383) or secondary prevention (n = 123) (From Maron et al. *JAMA*, with permission [53]).

HCM, followed by infection, hemorrhage/thrombosis, lead fracture, dislodgement and oversensing, which are found at rates similar to the general population of patients with pacemakers and ICDs [56]. Complications of ICD therapy appear more common in patients with HCM due to the young age at which they are typically implanted, necessitating numerous modifications during the course of a lifetime, active lifestyle of younger individuals which may produce more physical wear, and the higher mechanical wear and tear produced by the hypertrophied myocardium, which may result in a higher incidence of lead fracture in these patients [55].

Recommendations for ICD Implantation

The most recent AHA, ACC, HRS guidelines for the implantation of ICDs in patients with HCM was published in 2011 (Fig. 10.1) [12]. Recommendations for management are graded in this as well as the AHA/ACC/ESC guidelines into Class 1: recommended; class IIA: reasonable; class IIB: may be considered; and class III: not advisable or harmful. In addition the strength of evidence supporting the recommendations is graded into levels of evidence (LOE). In general, LOE A is supported by several randomized trials; LOE B is supported by prospective or retrospective data, and LOE C is supported by expert opinion. Patients with resuscitated SCD or sustained VT should have an ICD implanted (class I, LOE B). Also, in this document, three major risk factors for SCD were recognized, including massive hypertrophy, personal unexplained syncope, and SCD due to HCM in a first degree relative (Fig. 10.1). With any of these risk factors, it is reasonable to implant an ICD (IIA, LOE C). For individuals with solely a minor, but known, risk factor of NSVT or hypotensive response to exercise, ICD implantation may be reasonable if one or more of the emerging risk factors is present (class IIA, LOE C). If there are no additional risk modifiers in patients with NSVT or hypotensive response to exercise then the recommendation falls to IIB (LOE C). An additional IIB recommendation (LOE C) is for those individuals with class III or IV heart failure with an LVEF less than or equal to 50 %. ICD implantation is not recommended (class III, LOE C) solely to permit athletic participation, or solely on the basis of prior alcohol septal ablation or need for permanent pacemaker.

In addition this document offers guidance on the type of ICD to be implanted. Single chamber ICDs (class IIA) are recommended for all except those who will need atrial pacing (LOE C), who have a history of AFib (LOE C), or those with an LV outflow gradient >50 mmHg and clinical heart failure who may potentially benefit from RV pacing (LOE B). Insertion of dual chamber ICDs is associated with a greater risk of lead complications, both in short term and long term follow-up. Thus, in clinical practice, one should carefully weigh the risks and benefits of dual chamber vs. single chamber devices, taking into consideration the age of the patient.

The older AHA/ACC/European Society of Cardiology guidelines, published in 2006, give a class 1 recommendation (LOE B) for ICD implantation in patients with resuscitated SCD or sustained VT [11]. There is a class IIA recommendation (LOE B) for patients with any of the five traditional major risk factors. These guidelines also give a IIA recommendation (LOE C) for amiodarone in patients with prior resuscitated SCD or sustained VT in whom an ICD is not feasible. IIB recommendations (both LOE C) include amiodarone for those patients with risk factors for SCD in whom an ICD is not feasible and EP testing for risk assessment of SCD. However, the guidelines do not state if an abnormal EP test would itself be a major or even a minor risk factor. And, in contrast, the ACCF/AHA 2011 guidelines give EP testing a Class III recommendation.

A newer guide to appropriateness of medical intervention is the Appropriate Use Criteria [3]. These criteria are primarily designed for a wide range of conditions, often in which randomized control data or even registry data are lacking. Scoring in this system is from 1 to 9; 7–9 (A) are designated appropriate with benefits outweighing risks; 4–6 (M): may be appropriate, and 1–3 (R); rarely appropriate. These criteria for implantation of ICDs were developed by a panel of cardiologists including specialists in electrophysiology, general cardiology, and heart failure. Patients with HCM and resuscitated SCD or sustained VT received an A (score of 9) for implantation of an ICD, as well as those with unexplained syncope (score of 8). Patients with HCM and one or more risk factors received a score of 7 for implantation of an ICD.

Conclusion

SCD is a major cause of mortality in patients with HCM, especially in the young, but can occur at any age. In patients with HCM, SCD is the predominant concern in young patients, while progressive heart failure and associated symptoms dominate in the later years. SCD is due to ventricular fibrillation and tachycardia. Major risk factors for SCD include resuscitated SCD or sustained ventricular tachycardia, Family history of SCD due to HCM, recent unexplained syncope, and marked cardiac hypertrophy over 3.0 cm. Medications do not prevent SCD, but may be palliative; the only effective treatment is with an ICD. Risk assessment schemes, performed at initial presentation and repeated annually or when new risk factors arise, are vital in the primary and secondary prevention of these patients.

Clinical Pearls

- HCM patients who have survived a cardiac arrest or sustained VT should receive an ICD.
- HCM patients with a single major risk factor of unexplained syncope, family history of SCD or massively thick myocardium (>3.0 cm) should be offered an ICD.
- Unexplained syncope requires a workup to eliminate outflow tract obstruction or autonomic dysfunction, and to monitor for underlying arrhythmia, prior to insertion of an ICD.
- HCM patients with a risk factor of NSVT or hypotensive blood pressure response should be considered for an ICD. NSVT in the young patient is likely of higher risk than in the older patient, especially when rapid and long in duration or associated with symptoms.
- Patients with intermediate levels of hypertrophy, in the 2.5–3.0 cm range, may benefit from cardiac MRI evaluation to determine if areas of the heart unseen by echo evidence >3.0 cm, and therefore qualify for ICD implantation as Class IIa.
- In patients with NSVT, a search for emerging risk factors may be undertaken, including performance of cardiac MRI for evidence of late gadolinium enhancement, or stress echocardiogram for evidence of outflow tract obstruction. When found, ICD is recommended as Class IIa.

References

1. Elliott PM, Gimeno JR, Thaman R, Shah J, Ward D, Dickie S, Tome Esteban MT, McKenna WJ. Historical trends in reported survival rates in patients with hypertrophic cardiomyopathy. Heart. 2006;92:785–91.
2. Maron BJ, Shen WK, Link MS, Epstein AE, Almquist AK, Daubert JP, Bardy GH, Favale S, Rea RF, Boriani G, Estes 3rd NA, Spirito P. Efficacy of implantable cardioverter-defibrillators for the prevention of sudden death in patients with hypertrophic cardiomyopathy. N Engl J Med. 2000;342:365–73.
3. Russo AM, Stainback RF, Bailey SR, Epstein AE, Heidenreich PA, Jessup M, Kapa S, Kremers MS, Lindsay BD, Stevenson LW. Accf/hrs/aha/ase/hfsa/scai/scct/scmr 2013 appropriate use criteria for implantable cardioverter-defibrillators and cardiac resynchronization therapy: a report of the American College of Cardiology Foundation appropriate use criteria task force, Heart Rhythm Society, American Heart Association, American Society of Echocardiography, Heart Failure Society of America, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. J Am Coll Cardiol. 2013;61:1318–68.
4. Kofflard MJ, Ten Cate FJ, van der Lee C, van Domburg RT. Hypertrophic cardiomyopathy in a large community-based population: clinical outcome and identification of risk factors for sudden cardiac death and clinical deterioration. J Am Coll Cardiol. 2003;41:987–93.
5. Rubinshtein R, Glockner JF, Ommen SR, Araoz PA, Ackerman MJ, Sorajja P, Bos JM, Tajik AJ, Valeti US, Nishimura RA, Gersh BJ. Characteristics and clinical significance of late gadolinium enhancement by contrast-enhanced magnetic resonance imaging in patients with hypertrophic cardiomyopathy. Circ Heart Fail. 2010;3:51–8.
6. Maron BJ, Olivotto I, Spirito P, Casey SA, Bellone P, Gohman TE, Graham KJ, Burton DA, Cecchi F. Epidemiology of hypertrophic cardiomyopathy-related death: revisited in a large non-referral-based patient population. Circulation. 2000;102:858–64.
7. Maron BJ, Casey SA, Poliac LC, Gohman TE, Almquist AK, Aeppli DM. Clinical course of hypertrophic cardiomyopathy in a regional united states cohort. JAMA. 1999;281:650–5.
8. Maki S, Ikeda H, Muro A, Yoshida N, Shibata A, Koga Y, Imaizumi T. Predictors of sudden cardiac death in hypertrophic cardiomyopathy. Am J Cardiol. 1998;82:774–8.
9. Maron BJ, Estes 3rd NA, Maron MS, Almquist AK, Link MS, Udelson JE. Primary prevention of sudden death as a novel treatment strategy in hypertrophic cardiomyopathy. Circulation. 2003;107:2872–5.
10. Epstein AE, DiMarco JP, Ellenbogen KA, Estes 3rd NA, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO, Smith Jr SC, Jacobs AK, Adams CD, Anderson JL, Buller CE, Creager MA, Ettinger SM, Faxon DP, Halperin JL, Hiratzka LF, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura RA, Ornato JP, Page RL, Riegel B, Tarkington LG, Yancy CW. Acc/aha/hrs 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the acc/aha/naspe 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) Developed in Collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008;51:e1–62.
11. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, Gregoratos G, Klein G, Moss AJ, Myerburg RJ, Priori SG, Quinones MA, Roden DM, Silka MJ, Tracy C, Smith Jr SC, Jacobs AK, Adams CD, Antman EM, Anderson JL, Hunt SA, Halperin JL, Nishimura R, Ornato JP, Page RL, Riegel B, Blanc JJ, Budaj A, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL. Acc/aha/esc 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death): Developed in Collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation. 2006;114:e385–484.
12. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naidu SS, Nishimura RA, Ommen SR, Rakowski H, Seidman CE, Towbin JA, Udelson JE, Yancy CW. 2011 accf/aha guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in Collaboration with the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2011;58:e212–60.
13. Elliott PM, Poloniecki J, Dickie S, Sharma S, Monserrat L, Varnava A, Mahon NG, McKenna WJ. Sudden death in hypertrophic cardio-

myopathy: identification of high risk patients. J Am Coll Cardiol. 2000;36:2212–8.
14. Maron BJ. Hypertrophic cardiomyopathy; a systemic review. JAMA. 2002;287:1308–20.
15. Fiset C, Giles WR. Cardiac troponin t mutations promote life-threatening arrhythmias. J Clin Invest. 2008;118:3845–7.
16. Baudenbacher F, Schober T, Pinto JR, Sidorov VY, Hilliard F, Solaro RJ, Potter JD, Knollmann BC. Myofilament ca2+ sensitization causes susceptibility to cardiac arrhythmia in mice. J Clin Invest. 2008;118:3893–903.
17. Watkins H, McKenna WJ, Thierfelder L, Suk HJ, Anan R, O'Donoghue A, Spirito P, Matsumori A, Moravec CS, Seidman JG, et al. Mutations in the genes for cardiac troponin t and alpha-tropomyosin in hypertrophic cardiomyopathy. N Engl J Med. 1995;332:1058–64.
18. Tsoutsman T, Lam L, Semsarian C. Genes, calcium and modifying factors in hypertrophic cardiomyopathy. Clin Exp Pharmacol Physiol. 2006;33:139–45.
19. Spirito P, Autore C, Rapezzi C, Bernabo P, Badagliacca R, Maron MS, Bongioanni S, Coccolo F, Estes NA, Barilla CS, Biagini E, Quarta G, Conte MR, Bruzzi P, Maron BJ. Syncope and risk of sudden death in hypertrophic cardiomyopathy. Circulation. 2009;119:1703–10.
20. Spirito P, Bellone P, Harris KM, Bernabo P, Bruzzi P, Maron BJ. Magnitude of left ventricular hypertrophy and risk of sudden death in hypertrophic cardiomyopathy. N Engl J Med. 2000;342:1778–85.
21. Elliott PM, Gimeno Blanes JR, Mahon NG, Poloniecki JD, McKenna WJ. Relation between severity of left-ventricular hypertrophy and prognosis in patients with hypertrophic cardiomyopathy. Lancet. 2001;357:420–4.
22. Olivotto I, Gistri R, Petrone P, Pedemonte E, Vargiu D, Cecchi F. Maximum left ventricular thickness and risk of sudden death in patients with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2003;41:315–21.
23. Monserrat L, Elliott PM, Gimeno JR, Sharma S, Penas-Lado M, McKenna WJ. Non-sustained ventricular tachycardia in hypertrophic cardiomyopathy: an independent marker of sudden death risk in young patients. J Am Coll Cardiol. 2003;42:873–9.
24. Spirito P, Rapezzi C, Autore C, Bruzzi P, Bellone P, Ortolani P, Fragola PV, Chiarella F, Zoni-Berisso M, Branzi A, et al. Prognosis of asymptomatic patients with hypertrophic cardiomyopathy and nonsustained ventricular tachycardia. Circulation. 1994;90:2743–7.
25. Maron BJ, Savage DD, Wolfson JK, Epstein SE. Prognostic significance of 24 hour ambulatory electrocardiographic monitoring in patients with hypertrophic cardiomyopathy: a prospective study. Am J Cardiol. 1981;48:252–7.
26. Adabag AS, Casey SA, Kuskowski MA, Zenovich AG, Maron BJ. Spectrum and prognostic significance of arrhythmias on ambulatory holter electrocardiogram in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2005;45:697–704.
27. Adabag AS, Maron BJ. Implications of arrhythmias and prevention of sudden death in hypertrophic cardiomyopathy. Ann Noninvasive Electrocardiol. 2007;12:171–80.
28. Cecchi F, Olivotto I, Montereggi A, Squillatini G, Dolara A, Maron BJ. Prognostic value of non-sustained ventricular tachycardia and the potential role of amiodarone treatment in hypertrophic cardiomyopathy: assessment in an unselected non-referral based patient population. Heart. 1998;79:331–6.
29. Olivotto I, Maron BJ, Montereggi A, Mazzuoli F, Dolara A, Cecchi F. Prognostic value of systemic blood pressure response during exercise in a community-based patient population with hypertrophic cardiomyopathy. J Am Coll Cardiol. 1999;33:2044–51.
30. Frenneaux MP, Counihan PJ, Caforio AL, Chikamori T, McKenna WJ. Abnormal blood pressure response during exercise in hypertrophic cardiomyopathy. Circulation. 1990;82:1995–2002.
31. Sadoul N, Prasad K, Elliott PM, Bannerjee S, Frenneaux MP, McKenna WJ. Prospective prognostic assessment of blood pressure response during exercise in patients with hypertrophic cardiomyopathy. Circulation. 1997;96:2987–91.
32. Maron MS, Finley JJ, Bos JM, Hauser TH, Manning WJ, Haas TS, Lesser JR, Udelson JE, Ackerman MJ, Maron BJ. Prevalence, clinical significance, and natural history of left ventricular apical aneurysms in hypertrophic cardiomyopathy. Circulation. 2008;118:1541–9.
33. Moon JC, McKenna WJ, McCrohon JA, Elliott PM, Smith GC, Pennell DJ. Toward clinical risk assessment in hypertrophic cardiomyopathy with gadolinium cardiovascular magnetic resonance. J Am Coll Cardiol. 2003;41:1561–7.
34. Moon JC, Reed E, Sheppard MN, Elkington AG, Ho SY, Burke M, Petrou M, Pennell DJ. The histologic basis of late gadolinium enhancement cardiovascular magnetic resonance in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2004;43:2260–4.
35. Adabag AS, Maron BJ, Appelbaum E, Harrigan CJ, Buros JL, Gibson CM, Lesser JR, Hanna CA, Udelson JE, Manning WJ, Maron MS. Occurrence and frequency of arrhythmias in hypertrophic cardiomyopathy in relation to delayed enhancement on cardiovascular magnetic resonance. J Am Coll Cardiol. 2008;51:1369–74.
36. Maron MS, Appelbaum E, Harrigan CJ, Buros J, Gibson CM, Hanna C, Lesser JR, Udelson JE, Manning WJ, Maron BJ. Clinical profile and significance of delayed enhancement in hypertrophic cardiomyopathy. Circ Heart Fail. 2008;1:184–91.
37. Choudhury L, Mahrholdt H, Wagner A, Choi KM, Elliott MD, Klocke FJ, Bonow RO, Judd RM, Kim RJ. Myocardial scarring in asymptomatic or mildly symptomatic patients with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2002;40:2156–64.
38. Paul M, Schafers M, Grude M, Reinke F, Juergens KU, Fischbach R, Schober O, Breithardt G, Wichter T. Idiopathic left ventricular aneurysm and sudden cardiac death in young adults. Europace. 2006;8:607–12.
39. Harris KM, Spirito P, Maron MS, Zenovich AG, Formisano F, Lesser JR, Mackey-Bojack S, Manning WJ, Udelson JE, Maron BJ. Prevalence, clinical profile, and significance of left ventricular remodeling in the end-stage phase of hypertrophic cardiomyopathy. Circulation. 2006;114:216–25.
40. Maron MS, Olivotto I, Betocchi S, Casey SA, Lesser JR, Losi MA, Cecchi F, Maron BJ. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. N Engl J Med. 2003;348:295–303.
41. Elliott PM, Gimeno JR, Tome MT, Shah J, Ward D, Thaman R, Mogensen J, McKenna WJ. Left ventricular outflow tract obstruction and sudden death risk in patients with hypertrophic cardiomyopathy. Eur Heart J. 2006;27:1933–41.
42. Autore C, Bernabo P, Barilla CS, Bruzzi P, Spirito P. The prognostic importance of left ventricular outflow obstruction in hypertrophic cardiomyopathy varies in relation to the severity of symptoms. J Am Coll Cardiol. 2005;45:1076–80.
43. Alcalai R, Seidman JG, Seidman CE. Genetic basis of hypertrophic cardiomyopathy: from bench to the clinics. J Cardiovasc Electrophysiol. 2008;19:104–10.
44. Maron BJ. Contemporary insights and strategies for risk stratification and prevention of sudden death in hypertrophic cardiomyopathy. Circulation. 2010;121:445–56.
45. Maron BJ, Maron MS, Semsarian C. Double or compound sarcomere mutations in hypertrophic cardiomyopathy: a potential link to sudden death in the absence of conventional risk factors. Heart Rhythm. 2012;9:57–63.

46. Sorajja P, Ommen SR, Nishimura RA, Gersh BJ, Berger PB, Tajik AJ. Adverse prognosis of patients with hypertrophic cardiomyopathy who have epicardial coronary artery disease. Circulation. 2003;108:2342–8.
47. Maron MS, Olivotto I, Maron BJ, Prasad SK, Cecchi F, Udelson JE, Camici PG. The case for myocardial ischemia in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2009;54:866–75.
48. Cecchi F, Olivotto I, Gistri R, Lorenzoni R, Chiriatti G, Camici PG. Coronary microvascular dysfunction and prognosis in hypertrophic cardiomyopathy. N Engl J Med. 2003;349:1027–35.
49. Petersen SE, Jerosch-Herold M, Hudsmith LE, Robson MD, Francis JM, Doll HA, Selvanayagam JB, Neubauer S, Watkins H. Evidence for microvascular dysfunction in hypertrophic cardiomyopathy: new insights from multiparametric magnetic resonance imaging. Circulation. 2007;115:2418–25.
50. McKenna WJ, Oakley CM, Krikler DM, Goodwin JF. Improved survival with amiodarone in patients with hypertrophic cardiomyopathy and ventricular tachycardia. Br Heart J. 1985;53:412–6.
51. McKenna WJ, Harris L, Rowland E, Kleinebenne A, Krikler DM, Oakley CM, Goodwin JF. Amiodarone for long-term management of patients with hypertrophic cardiomyopathy. Am J Cardiol. 1984;54:802–10.
52. Melacini P, Maron BJ, Bobbo F, Basso C, Tokajuk B, Zucchetto M, Thiene G, Iliceto S. Evidence that pharmacological strategies lack efficacy for the prevention of sudden death in hypertrophic cardiomyopathy. Heart. 2007;93:708–10.
53. Maron BJ, Spirito P, Shen WK, Haas TS, Formisano F, Link MS, Epstein AE, Almquist AK, Daubert JP, Lawrenz T, Boriani G, Estes 3rd NA, Favale S, Piccininno M, Winters SL, Santini M, Betocchi S, Arribas F, Sherrid MV, Buja G, Semsarian C, Bruzzi P. Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy. JAMA. 2007;298:405–12.
54. Woo A, Monakier D, Harris L, Hill A, Shah P, Wigle ED, Rakowski H, Rozenblyum E, Cameron DA. Determinants of implantable defibrillator discharges in high-risk patients with hypertrophic cardiomyopathy. Heart. 2007;93:1044–5.
55. Maron BJ, Spirito P, Ackerman MJ, Casey SA, Semsarian C, Estes 3rd NA, Shannon KM, Ashley EA, Day SM, Pacileo G, Formisano F, Devoto E, Anastasakis A, Bos JM, Woo A, Autore C, Pass RH, Boriani G, Garberich RF, Almquist AK, Russell MW, Boni L, Berger S, Maron MS, Link MS. Prevention of sudden cardiac death with implantable cardioverter-defibrillators in children and adolescents with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2013;61:1527–35.
56. Lin G, Nishimura RA, Gersh BJ, Phil D, Ommen SR, Ackerman MJ, Brady PA. Device complications and inappropriate implantable cardioverter defibrillator shocks in patients with hypertrophic cardiomyopathy. Heart. 2009;95:709–14.

Youth and Athletic Screening: Rationale, Methods and Outcome

11

David S. Owens and Sanjay Sharma

Abstract

Sudden cardiac death is a tragic event under any circumstance, but is especially devastating when it occurs in youth and athletes. In the 'paradox of sports', exercise both promotes health and acutely increases the risk of SCD among those with underlying heart disorders such as HCM, arrhythmogenic right ventricular cardiomyopathy, or coronary artery anomalies. Developed societies agree that pre-participation screening is valuable and warranted to improve the safety of sports competition, but there remain significant differences in opinion regarding the best methods to employ. ECG screening in particular remains controversial, with European societies generally in favor of ECG and US guidelines against ECG inclusion. New, athlete-specific ECG criteria may decrease the false positive rate, but the sensitivity and specificity of these criteria have not yet been established.

Keywords

Sudden cardiac death • Screening • Athlete • Exercise • Cardiac remodeling • Hypertrophic cardiomyopathy • Electrocardiography • Cost-effectiveness

Key Points

- Sudden cardiac death (SCD) in youth and athletes is an uncommon but tragic event that profoundly affects both families and communities.
- In athletes with susceptible heart conditions, exercise (particularly burst activities) can increase the risk of SCD acutely.
- SCD in youth and athletes (≤35 years of age) is most commonly due to inherited heart conditions or congenital abnormalities such as hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, or coronary artery anomalies.
- The conditions that cause SCD in youth and athletes often have long latent periods, and would often be identifiable pre-mortem using routine testing methods.
- Athletes undergo cardiac adaptation to exercise that can result in morphologic and electrical changes mimicking disease, and these "gray zones" pose challenges for diagnosis.
- Although there is consensus among developed societies that it is appropriate to screen athletes for inherited heart conditions, there is considerable controversy as to the best screening methods.

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- ECG screening for youth and athletes is endorsed by the European Society of Cardiology and many international sports organizations but not by US professional societies, largely due to concerns about false positive rates, cost effectiveness and logistics of health care delivery.
- Despite the US professional society recommendations against ECG screening, many universities and local foundations offer voluntary screening programs for youth and athletes due to the high impact of SCD in athletes and public interest in screening.
- Newly proposed criteria for interpreting ECG in athletes offer the potential to reduce the false positive rate and costs of screening, and are currently being tested in prospective studies.

Introduction

Sudden death, occurring without preceding symptoms and seemingly striking at random, is a shocking occurrence under any circumstance. When it occurs in youth and adolescents, or in athletes who are otherwise the epitome of health, these events are especially devastating. Frequently, the cause of death is an undiagnosed genetic or congenital disorder that may have been identifiable pre-mortem. There is consensus across developed societies that athletes and youth should undergo screening for potentially life-threatening disorders, but the rigorousness and resources devoted to screening efforts varies widely based on health system resources and society valuations. At present, there remains considerable controversy over what screening methods should be employed, the acceptable financial and practical costs of screening, and whether more intensive screening leads to reduced morbidity or mortality.

The present chapter will review current knowledge about the etiologies and incidence of sudden cardiac death in youth and athletes, discuss the rationale for screening programs and their potential benefits and limitations, and review data from real-world screening experiences and outcomes. In particular, this chapter will focus on hypertrophic cardiomyopathy (HCM) as a cause of sudden death, and the benefits and limitations of screening for HCM on a population basis.

SCA in Youth and Athletes

Sudden death is defined as an abrupt loss of life in the absence of prior symptoms (or with symptoms of short duration) and is most often due to cardiovascular causes such as myocardial infarction, ventricular arrhythmias, cerebrovascular accidents or ruptured aortic aneurysms. The incidence of sudden cardiac death in the general population increases with age and the presence of underlying heart disorders, but is a significant contributor to all-cause mortality. Estimates of the annual incidence of SCD vary widely, with an estimated 180,000–450,000 deaths in the US annually [1, 2]. Because of this, there have been considerable public health efforts to raise awareness of SCD, and to increase the availability and utilization of cardiopulmonary resuscitation and automated electrical defibrillators.

Table 11.1 Causes of sudden cardiac death in athletes

Cardiomyopathies
Hypertrophic cardiomyopathy
Arrhythmogenic right ventricular cardiomyopathy
Dilated cardiomyopathy
Left ventricular non-compaction
Aortopathies
Marfan syndrome
Loewy Deitz syndrome
Ehler-Danlos disorder
Thoracic aortic aneurysm and dissection
Channelopathies
Long QT syndrome
Short QT syndrome
Catecholaminergic polymorphic ventricular tachycardia
Brugada syndrome
Wolff-Parkinson white syndrome
Congenital abnormalities
Coronary artery anomalies
Bicuspid aortic valve with aortopathy
Acquired disorders
Myocarditis
Coronary artery disease
Commotio cordis

The epidemiology of SCD appears to be largely age-dependent. SCD in individuals over 35 years of age is most often caused by acquired forms of heart disease and coronary heart disease in particular, whereas SCD among youth and athletes is more often due to inherited or congenital heart disorders and primary arrhythmia syndromes. A list of disorders capable of causing SCD in youth and athletes is shown in Table 11.1.

The incidence rate of SCD among younger individuals (≤35 year of age) is estimated to be approximately 0.7–3.0 cases per 100,000 person-years. The exact incidence has been challenging to determine, largely due to differences in populations being studied and incomplete case identification when relying on media reports or insurance claims. Among active military personnel <35 years of age, the rate of SCD was observed to be 13.0 per 100,000 person-years (1:9,000) among military recruits during initial training [3], but only 1.2 per 100,000 person-years over a 10-year period of observation [4].

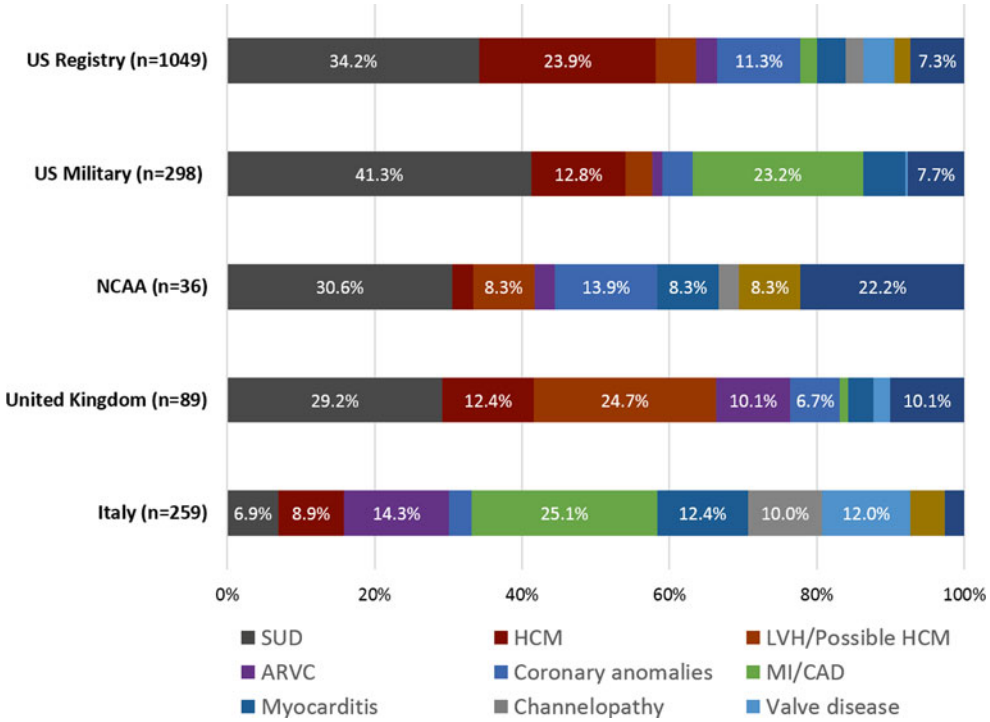

Fig. 11.1 Comparison of Etiologies of Sudden Cardiac Death among Youth and Athletes from (a) U.S. Registry [11] (age ≤39 years); (b) U.S. military [4] (age ≤35 years); (c) NCAA athletes [8] (ages 17–26 years); (d) United Kingdom [12] (age <35 years); and (e) Italy [6] (age 12–35 years)

Observational studies have consistently demonstrated that rate of SCD is higher among males compared to females, both in the general population and among youth [5] and athletes [6–8]. Whereas men have an estimated 1.3-fold relative risk in the general population [1, 2] this may be as high 5.6-fold relative risk for athletes. The reason for the higher relative risk among athletes is unclear, but may be related to the historic underrepresentation of women in athletic competition. Individuals of African descent appear to have an increased risk of SCD compared to Caucasians, both in the general population [9] and among athletes [8], but are less likely to experience SCD due to coronary heart disease [10].

Additionally, there are regional variations in the reported distributions of underlying causes of SCD in youth and athletes. Whereas definite or possible hypertrophic cardiomyopathy (HCM) appears to be the most common cause of SCD in the US and UK [11, 12], arrhythmogenic right ventricular cardiomyopathy (ARVC) is the most common cause of SCD in Italy (Fig. 11.1) [6]. This may be due to population differences in the frequency of gene mutations for these disorders, societal differences in healthcare and screening, or differences in the medical examiners' approach to postmortem diagnosis. Importantly, sudden unexplained death (SUD), in which the autopsy reveals a structurally normal heart and in which primary arrhythmia syndromes are suspected, may be present in 15–40 % of cases [4, 12, 13].

Although exercise has myriad benefits on health and overall well-being, exercise has clearly been shown to increase the risk of SCD. Data from the Physicians Health Study estimated a 16.9 (95 % CI: 10.5–27.0)-fold increased risk of SCD during or within 30 min of exercise [14]. This risk was highest among sedentary individuals who exercised intermittently [14]. A prospective study of Italian youth (age 12–35 years) comprising 29 million person-years of observation suggested that the relative risk of SCD was 2.8 (95 % CI: 1.9–3.7) times higher among athletes compared to non-athletes, with 89 % of athlete deaths and 9 % of non-athletes deaths occurring in the setting of acute exercise [6].

In both young and old alike, SCD is thought to arise from an acute trigger superimposed on an underlying susceptible substrate, and there are a number of mechanisms by which exercise may serve as an arrhythmogenic trigger. Exercise increases catecholamine levels, may cause dehydration and electrolyte imbalances, increases blood pressure and shear stress on the aorta, and may induce myocardial ischemia in susceptible individuals [15]. It has been observed that sports involving burst activities (e.g., basketball, soccer, football) have a higher rate of SCD than other sporting disciplines [15, 16]. The exact reasons for this are unclear, but may be related to abrupt changes in heart rate and/or greater periods of anaerobic exercise. Alternatively, patients with underlying heart disorders may be underrepresented in sporting disciplines that require high aerobic conditioning due to inability to compete at high aerobic levels [17].

A study by Harmon et al examined the incidence of SCD among NCAA athletes (2004–2008, aged 17–23 years) and showed differences based on gender, ethnicity and sporting discipline [8]. The overall risk of SCD was 1:43,770 person-years, but was observed to be higher in males (1:33,134 person-years) and in African-Americans (1:17,696 person-years). Male basketball players had the highest rate of SCD

(1:3,100 person-years). In this series, SUD and coronary anomalies were the most common causes of death in these athletes, and HCM was less common than in other US registries [13]. This confers with data from Basavarajaiah et al suggesting that the prevalence of HCM in elite athletes may be rare [17].

Rationale for Screening

Pre-participation cardiovascular screening is the systematic evaluation of athletes and adolescents prior to the participation in sport activities for the purpose of both identifying underlying cardiovascular abnormalities that can lead to SCD and enhancing the safety of sports participation. There is consensus across developed societies that athletes and youth should undergo pre-participation cardiovascular screening, albeit considerable disagreement surrounding the proper methods to employ. The American Heart Association views pre-participation screening as an important public health issue that is "*justifiable*, *necessary*, and *compelling* on the basis of ethical, legal, and medical grounds" [18].

In 1968, the World Health Organization established criteria for evaluating the appropriateness of health screening programs (Table 11.2) [19], and these criteria remain applicable today. Pre-participation cardiovascular screening fulfills many if not all of these criteria. Important features of pre-participation screening for underlying heart disorders in adolescents and athletes include the following:

- SCD in athletes has been deemed by many professional organizations to be an important health problem, and many community-based non-profit organizations have arisen to meet the societal demands for more intensive youth and adolescent screening.
- Whereas adolescents and athletes are often asymptomatic prior to SCD, most of the inherited heart conditions and congenital abnormalities that confer increased risk have a years-long latent period during which disease may be detectable.
- The natural histories of these disorders are well understood, and guidelines for treatment and SCD risk reduction are generally available. Recommendation may include implantable cardioverter-defibrillator (ICD) placement and lifestyle changes including avoidance of vigorous or competitive exercise.
- The underlying conditions that place youth and athletes at increased risk are identifiable using widely accepted cardiac testing, including medical examination (history and cardiac auscultation), electrocardiography, and echocardiography.

Thus, many of the WHO criteria for effective screening are fulfilled and in several important respects, inherited and congenital heart conditions are ideally suited for screening programs. However, there are practical challenges to implementing these screening programs that have rendered many of the details regarding pre-participation screening controversial.

Screening tests are generally imperfect and false-positive results that require evaluation with more expensive testing are expected. Both the sensitivity (ability to detect true disease) and the specificity (ability to not detect normals) of the screening test are factors that must be considered when evaluating the effectiveness of a screening program. The costs of screening include both the financial costs of the screening tests as well as the financial costs of any downstream testing of suspected cases. In the case of cardiovascular screening, this additional diagnostic testing can be extensive. And finally, both personal and psychological costs of screening must be considered. Athletes identified as potentially having cardiovascular disease may experience anxiety, and temporary or permanent sports disqualification may have important personal ramifications.

Table 11.2 World Health Organization criteria for effective screening programs [19]

1. The condition should be an important health problem.
2. There should be a treatment for the condition.
3. Facilities for diagnosis and treatment should be available.
4. There should be a latent stage of the disease.
5. There should be a test or examination for the condition.
6. The test should be acceptable to the population.
7. The natural history of the disease should be adequately understood.
8. There should be an agreed policy on whom to treat.
9. The total cost of finding a case should be economically balanced in relation to medical expenditure as a whole.
10. Case-finding should be a continuous process, not just a "once and for all" project.

Cardiac Adaptation to Exercise

A major challenge to pre-participation cardiovascular screening is the fact that cardiac structure and function adapt to and remodel in response to repetitive exercise. This physiologic adaptation may lead to abnormalities (classically defined) on electrocardiography or echocardiography. In some instances, it becomes challenging to differentiate the "athletic heart" from an underlying cardiomyopathy capable of causing sudden death, such as HCM or ARVC [20, 21]. Indeed, these "gray zones" can be the source of considerable consternation for medical professionals, which can lead to unnecessary and expensive diagnostic testing or to excluding an athlete from sporting competition unnecessarily. It is therefore essential for clinicians who care for or evaluate athletes to have a fundamental understanding of the ways in which athletic training can affect the cardiovascular system.

The 'Morganroth Hypothesis' postulates that the manner of cardiac remodeling is in large part determined by the type of exercise performed [22, 23]. Athletes who participate in high dynamic sports (e.g., running, cycling, rowing) experience a repetitive increase in cardiac output with high flow states and lesser increases in afterload. In response, cardiac chambers are believed to undergo balanced eccentric dilation and hypertrophy resulting in enlargement of all four cardiac chambers. In contrast, athletes who participate in high resistance sports (e.g., weight lifting), experience a repetitive increase in afterload with less increase in cardiac output, and are thought to develop concentric left ventricular hypertrophy.

Recent studies have cast doubt on this hypothesis, particularly in regard to resistance training [24, 25]. Studies of sedentary individuals who begin endurance training clearly show an increase in chamber size and volumes in response to training, findings which comport with the large LV cavity volumes seen in elite athletes. While the idea that resistance training results in LV hypertrophy makes theoretic sense, LV hypertrophy is not consistently seen in strength-trained individuals, and co-existent hypertension may be confounding some of this association. Additionally, the increases in afterload may be short in duration or offset by increases in intrathoracic pressure during Valsalva maneuver.

In addition to cardiac structural remodeling, exercise also induces changes in cardiac autonomic tone. Endurance training generally results in an increase in vagal parasympathetic innervation. As a result, bradycardia, junctional escape rhythms, and Mobitz I second degree AV block (i.e., Wenckebach) are not uncommonly seen on ECG or rhythm monitoring and should not be confused with disease.

Black athletes in particular may have greater degrees of cardiac remodeling in response to exercise. Black hypertensive patients have greater degrees of LV hypertrophy compared to white patients with similar age, gender and blood pressures [26]. Similarly, black athletes have greater LV wall thickness and LV mass index compared to white athletes (Fig. 11.2) [28–30], and are more likely to demonstrate ECG abnormalities [31]. In a study of 300 normotensive male black athletes in the U.K., 18 % demonstrated LV wall thickness ≥13 mm and 3 % were ≥15 mm [27]. Because of this, black athletes in particular may fall into the 'gray zone' between athletic remodeling and HCM, and careful diagnostic evaluation is needed so as to ensure proper diagnosis and to not inappropriately disqualify athletes with physiologic LV hypertrophy.

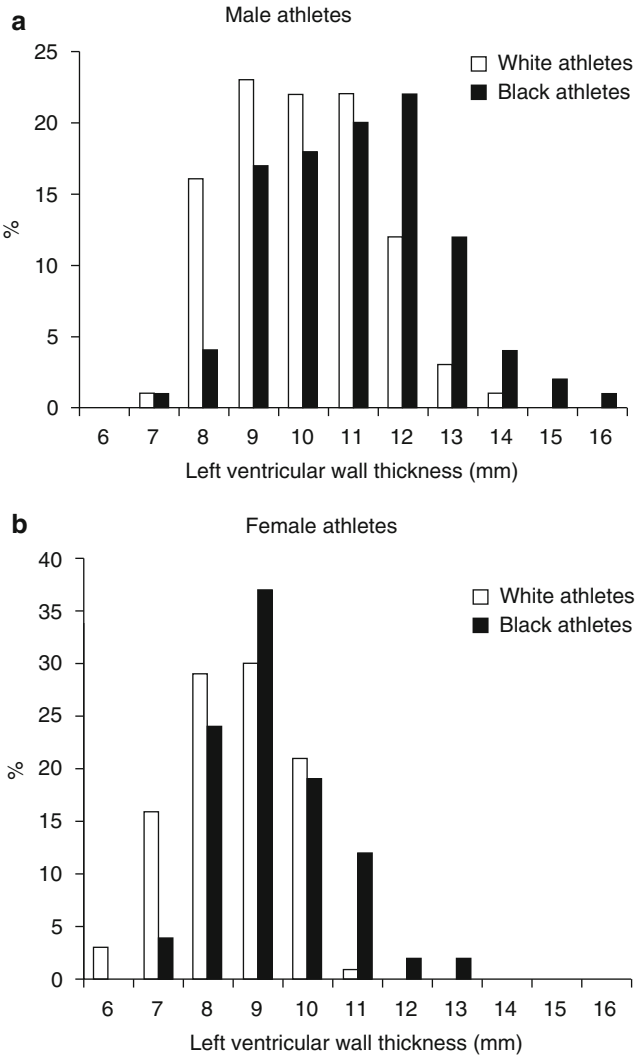

Fig. 11.2 Distribution of LV wall thickness among (**a**) white and black male athletes [27] and (**b**) white and black female athletes [28] (Reproduced from Chandra et al. [29], copyright 2012 with permission from BMJ Publishing Group Ltd.)

Basic Pre-participation Screening

Pre-participation cardiovascular screening can take many forms. Basic screening programs, such as those advocated by the American Heart Association [18] and the joint professional guidelines Preparticipation Physical Evaluation Monograph (4th Edition) [32], consists of a history and physical examination with additional evaluations as indicated based on physician judgment. The AHA recommends a 12-point preparticipation cardiovascular screening for competitive athletes (Table 11.3). Of note, these AHA preparticipation recommendations are chiefly based on standard of care and expert opinion.

In the US, most PPE examinations are performed by local pediatricians and/or family medicine physicians in the context of a healthy-child visit, and these providers may have only a modicum of training in evaluating athletes. Real world data suggests that the AHA recommended pre-participation screening is rarely performed in full [33], and because screening is performed by local physicians, there may be barriers to pursuing additional cardiovascular evaluation as ECG and echocardiography testing may not be available on site.

Table 11.3 The 12-element AHA recommendations for preparticipation cardiovascular screening of competitive athletes [18]

Medical history[a]
Personal history
1. Exertional chest pain/discomfort
2. Unexplained syncope / near-syncope[b]
3. Excessive exertional and unexplained dyspnea / fatigue associated with exercise
4. Prior recognition of a heart murmur
5. Elevated systemic blood pressure
Family history
6. Premature death (sudden, unexpected or otherwise) before age 50 years due to heart disease in ≥1 relative
7. Disability from heart disease in a close relative <50 years of age
8. Specific knowledge of certain cardiac conditions in family members: hypertrophic or dilated cardiomyopathy, long-QT syndrome or other ion channelopathies, Marfan syndrome, or clinically important arrhythmia.
Physical examination
9. Heart murmur[c]
10. Femoral pulses to exclude aortic coarctation
11. Physical stigmata of Marfan syndrome
12. Brachial artery blood pressure (sitting position)[d]

[a]Parental verification is recommended for high school and middle school athletes
[b]Judged not to be neurocardiogenic (vasovagal); of particular concern when related to exertion
[c]Auscultation should be performed in both supine and standing positions (or with Valsalva maneuver), specifically to identify murmurs of dynamic left ventricular outflow tract obstruction
[d]Preferably taken in both arms

Whether cardiovascular screening should be performed in all youth and adolescents or only in those participating is sports is an important ethical issue. At present, US screening programs have focused on athletes because of the observed increased risk compared to non-athletes., but this raises issues of equality and fairness. Several European countries perform cardiovascular screening routinely for all youth and adolescents.

Electrocardiography

The use of the electrocardiogram (ECG) for cardiovascular screening is controversial [34–36]. Some practitioners advocate for including ECG in a standard pre-participation screening program, and this is the standard of care in the United Kingdom and many countries in Europe, and for international sporting competitions including the Olympic Games and FIFA World Cup. Up to 90–95 % of athletes are asymptomatic or minimally symptomatic prior to experiencing SCD [11], and ECG provides a potential means to diagnose the asymptomatic cardiomyopathies and electrical heart disorders (e.g., ion channelopathies, WPW). It has been estimated that 90 % of asymptomatic HCM patients have an abnormal ECG, and conversely, HCM patients with a normal ECG have a more favorable prognosis [37].

In Europe, pre-participation screening is often performed in more centralized practice and the providers who perform the screening often have expertise in evaluating athletes. This serves to limit the number of unnecessary follow up or diagnostic tests performed.

Opponents of mandatory ECG screening as a component of pre-participation evaluations point to a number of challenges [38]. There is a rate of false-positive ECGs (up to 10–20 % or more using standard criteria), which can lead to expensive, unnecessary evaluations and/or inappropriate exclusion of individuals from sport competition. Given that SCD in athletes is a rare event, these expenses – financial, personal and psychological – may not be justifiable. Moreover, widespread ECG screening may not easily translate from Europe to the US given its expansive geography and decentralized evaluations that would take place.

Recognizing that exercise-induced cardiac remodeling is an important factor in the high false-positive rate, there have been several recent attempts to redefine the criteria used for interpreting ECGs in athletic populations. In 2011, the European Society of Cardiology enumerated the ECG changes considered to be due to training, and differentiated these from ECG changes potentially related to disease [39]. In 2013, an international group of sports medicine physicians and cardiologists revised these criteria further in what has become known as the "Seattle Criteria" (Table 11.4) [40–43]. While there criteria chiefly represent expert opinion, there is ongoing research to provide evidence base for the recommendations. Modifications of these athlete-specific ECG criteria were recently shown to dramatically decrease the false positive rate (to as low as 5 %) without significantly compromising specificity (94 %) [31]. Although these criteria require expertise and training in athlete ECG interpretation, the development of software interpretation algorithms tailored to these criteria may facilitate broad adoption.

Several important features of these athlete-specific ECG criteria merit discussion. First, voltage criteria for LV hypertrophy are commonly seen in athletes due to cardiac remodeling and thin body habitus, and are generally not applied to adolescent and young adult populations. Additionally, it is now recognized that individuals of Afro-Caribbean descent may demonstrate a pattern of early repolarization involving ST segment elevation and T wave inversion in the anterior leads (Fig. 11.3). The recognition of this pattern as a normal variant will decrease the need for unnecessary testing.

Echocardiography

There are no professional medical organizations that currently advocate for the inclusion of echocardiography as a component of cardiovascular screening. However, echocardiography

Table 11.4 Recommended criteria for ECG interpretation in athletes (2013 Seattle Summit Criteria)

Normal ECG findings	
Sinus bradycardia	
Sinus arrhythmia	
Ectopic atrial rhythm	
Junctional escape rhythm	
First-degree AV block	
Mobitz type I (Wenckebach) second degree AV block	
Incomplete RBBB	
Isolated QRS voltage for LVH	
Early repolarization	
Convex ('domed') ST segment elevation combined with T wave inversion in leads V1-V4 in black/African athletes.	
Abnormal ECG findings	**Definition**
T wave inversions	>1 mm in 2 or more leads V2-V6, II and aVF, or I and aVL (excludes III, aVR and V1)
ST depression	≥0.5 mm in depth in 2 or more leads
Q waves	>3 mm in depth or >40 ms in duration in 2 or more leads (except III and aVR)
Complete left bundle branch block	QRS ≥120 ms, predominantly negative QRS complex in lead V1 (QS or rS) and upright monophasic R wave in leads I and V6
Intraventricular conduction delay	Any QRS duration ≥140 ms
Left axis deviation	−30 to −90°
Left atrial enlargement	P wave duration of ≥120 ms in leads I or II with negative portion of P wave ≥1 mm in depth and ≥40 ms in duration in lead V1
Right ventricular hypertrophy	R-V1 + S-V5 > 10.5 mm AND right axis deviation >120°
Long QT interval[a]	QTc ≥470 ms (males) QTc ≥480 ms (females) QTc >500 ms (definitive long QT syndrome)
Short QT interval[a]	QTc ≤320 ms
Brugada-like pattern	High takeoff and downsloping ST segment elevation followed by a negative T wave in ≥2 leads V1-V3
Profound sinus bradycardia	HR <30 BPM or sinus pauses ≥3 s
Premature ventricular contractions	>2 PVCs per 10 s tracing
Ventricular arrhythmias	Couplets, triplets, and non-sustained ventricular tachycardia.

These ECG findings are unrelated to regular training or expected physiological adaptation to exercise, may suggest the presence of pathological cardiovascular disease and require further diagnostic evaluation
Top normal ECG findings, *Bottom* abnormal ECG findings [40]
[a]The QT interval corrected for heart rate is ideally measured with heart rates of 60–90 bpm. Consider repeating the ECG after mild aerobic activity for borderline or abnormal QTc values with a heart rate <50 bpm

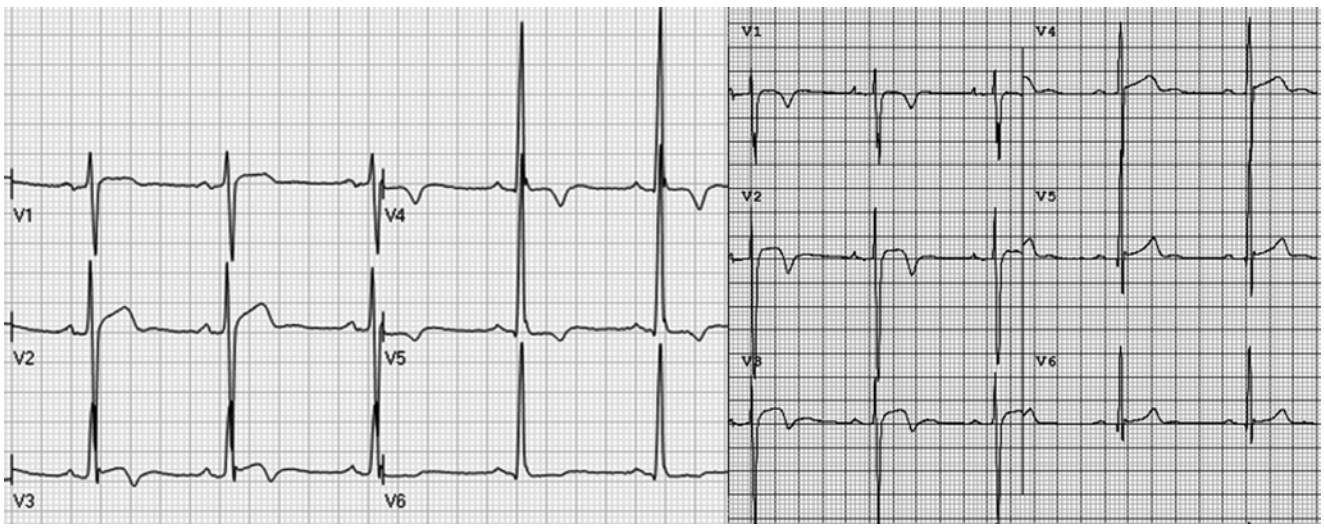

Fig. 11.3 Precordial ECGs from a patient with hypertrophic cardiomyopathy (*left*) and a normal variant repolarization pattern in an athlete of Afro-Caribbean decent (*right*), with domed (convex) ST segment elevation and T wave inversion in leads V1-V3

may be able to detect asymptomatic and electrically silent cardiovascular abnormalities such as aortic aneurysms, coronary artery anomalies, and the subset of cardiomyopathies with normal ECGs. After several high-profile sudden cardiac deaths in athletes, many amateur and professional organizations and institutions are including echocardiography as part of their standard screening. For example, both the National Basketball Association and National Football League now include routine echocardiographic screening, and many NCAA institutions have chosen to do the same.

Point of care echocardiography is being increasingly utilized and may decrease the costs associated with echocardiographic screening. However, routine use of echocardiography may identify more individuals who fall into the "grey zones" between health and disease, increasing the costs through downstream diagnostic testing. One particularly troublesome area is the differentiation of benign LV hypertrabeculation from LV non-compaction, which can be seen in the setting of normal ejection fraction and normal ECG. LV hypertrabeculation is more common in blacks and athletes and current diagnostic criteria for LV non-compaction may be overly sensitive [44, 45]. Until this 'grey zone' is better clarified, screening echocardiography should be handled cautiously.

ECG Screening: Cost Effectiveness and Outcomes

Whether ECG screening reduces the rate of SCD within the population remains uncertain. In the absence of randomized control trials, temporal and observational studies provide the best guidance. Beginning in 1982, Italian law began requiring pre-participation screening of young athletes (age 12–35) including ECG analysis. The rate of SCD was observed to be 3.6 per 100,000 person-years in the years prior to the law's enactment and 0.4 per 100,000 person-years during the late follow up period [46]. This represented an 89 % reduction in the rate of SCD among athletes over 20 years, while unscreened non-athletes showed no significant change in the rate of SCD over this same time period. This study suggests that preparticipation screening may save lives, but because this was an observation study, the cause of this improvement cannot be conclusively assigned and other temporal factors could be playing a role.

A comparable analysis in Israel challenged these results. Investigators used media reports to capture SCD events for the 10-year period before and after implementation of a mandatory screening law in 1998 [47]. The rate of SCD was estimated to be 2.54 per 100,000 person-years in the period before the law, and 2.66 per 100,000 person years afterwards ($p=0.88$). This study could not control for other temporal factors, such as changes in media coverage of SCD events, and the different results have to be placed in context of each society. For example, it is unclear if Israel's mandatory conscription (and subsequent health evaluations) influences the efficacy of preparticipation screening. At the least, these results add uncertainty to the debate.

Several studies have evaluated the cost-effectiveness of ECG screening for athletes, but lead to disparate conclusions based on differences in assumptions. Wheeler and colleagues examined the costs of screening high school and college aged athletes and estimated that the addition of ECG would save 2.06 life-years for every 1,000 athletes screened at an incremental cost of $89 per athlete or $42,900 per life-year saved [48]. On the other hand, Halkin et al estimated that a mandatory ECG screening program in the US would cost between $2.55 and $3.45 billion annually, and would be expected to save approximately 240 lives, yielding a cost per life saved between $10.6 and $14.4 million [49]. The marked discrepancy in the estimates is reflective of many of the uncertainties related to false positive rates, costs of diagnostic testing, and usefulness of ECG screening for preventing SCD events.

Summary

Exercise and athletic competition is associated with an increased risk of SCD for individuals with susceptible heart conditions, and when it strikes, SCD is devastating to families and communities alike. Because of this, there is significant public health interest in preparticipation screening of youth and athletes. A major challenge to preparticipation screening is that athletes undergo cardiac adaptation to exercise, with structural and functional changes that can resemble cardiac pathology capable of causing sudden death. Substantial expertise is needed to reliably differentiate health from disease and avoid unnecessary sports disqualification. Although there is widespread agreement that preparticipation screening is useful, there is disagreement as to the best methods to employ, particularly in regard to whether ECG should be a standard component of screening. Athlete-specific ECG criteria have been developed to reduce the false-positive ECG rate in athletes, and ongoing research will help provide an evidence-base for many of the current recommendations.

Clinical Pearls

- When performing pre-participation screening for athletes it is important to perform cardiac auscultation both at rest (supine) and with a maneuver to decrease preload such as having the athlete perform a Valsalva or having the athlete stand from a squatting position. These maneuvers will help to elicit a murmur in the 1/3 of HCM patients with only provocable LVOT obstruction.

- Athletes may demonstrate a number of 'abnormal' ECG and rhythm findings due to high vagal tone, including extreme bradycardia, ectopic atrial or junctional escape rhythms, or first or second degree (Mobitz 1, Wenckebach) heart block. These are seldom the source of symptoms and are usually benign findings.
- A subset of black athletes demonstrate a variant of early repolarization characterized by domed ST segment elevations followed by negative T waves in leads V1-V4. This pattern is training-related, will often resolve with deconditioning, and does not require additional evaluation.
- Endurance athletes generally manifest balanced chamber enlargement. Right ventricular enlargement without left ventricular chamber enlargement is concerning for ARVC or left to right shunts (e.g., atrial septal defect or anomalous pulmonary venous return) and should be evaluated further.
- Athletes (particularly black athletes) may exhibit left ventricular hypertrophy, but most commonly this hypertrophy is 15 mm or less and the upper limits of physiologic remodeling is generally considered 17 mm. Evaluation of athletes in the 'grey zone' between athlete's heart and HCM can be extensive and relies on assessment of family history, diastolic function, cardiopulmonary functional capacity, Holter monitoring and cardiac MRI.

References

1. Kong MH, Fonarow GC, Peterson ED, et al. Systematic review of the incidence of sudden cardiac death in the United States. J Am Coll Cardiol. 2011;57(7):794–801.
2. Stecker EC, Reinier K, Marijon E, et al. Public health burden of sudden cardiac death in the United States. Circ Arrhythm Electrophysiol. 2014;7(2):212–7.
3. Eckart RE, Scoville SL, Campbell CL, et al. Sudden death in young adults: a 25-year review of autopsies in military recruits. Ann Intern Med. 2004;141(11):829–34.
4. Eckart RE, Shry EA, Burke AP, et al. Sudden death in young adults: an autopsy-based series of a population undergoing active surveillance. J Am Coll Cardiol. 2011;58(12):1254–61.
5. Drezner JA, Chun JS, Harmon KG, Derminer L. Survival trends in the United States following exercise-related sudden cardiac arrest in the youth: 2000–2006. Heart Rhythm. 2008;5(6):794–9.
6. Corrado D, Basso C, Rizzoli G, Schiavon M, Thiene G. Does sports activity enhance the risk of sudden death in adolescents and young adults? J Am Coll Cardiol. 2003;42(11):1959–63.
7. Van Camp SP, Bloor CM, Mueller FO, Cantu RC, Olson HG. Nontraumatic sports death in high school and college athletes. Med Sci Sports Exerc. 1995;27(5):641–7.
8. Harmon KG, Asif IM, Klossner D, Drezner JA. Incidence of sudden cardiac death in National Collegiate Athletic Association athletes. Circulation. 2011;123(15):1594–600.
9. Galea S, Blaney S, Nandi A, et al. Explaining racial disparities in incidence of and survival from out-of-hospital cardiac arrest. Am J Epidemiol. 2007;166(5):534–43.
10. Burke AP, Farb A, Pestaner J, et al. Traditional risk factors and the incidence of sudden coronary death with and without coronary thrombosis in blacks. Circulation. 2002;105(4):419–24.
11. Maron BJ, Doerer JJ, Haas TS, Tierney DM, Mueller FO. Sudden deaths in young competitive athletes: analysis of 1866 deaths in the United States, 1980–2006. Circulation. 2009;119(8):1085–92.
12. de Noronha SV, Sharma S, Papadakis M, Desai S, Whyte G, Sheppard MN. Aetiology of sudden cardiac death in athletes in the United Kingdom: a pathological study. Heart. 2009;95(17):1409–14.
13. Harmon KG, Drezner JA, Maleszewski JJ, et al. Pathogenesis of sudden cardiac death in national collegiate athletic association athletes. Circ Arrhythm Electrophysiol. 2014;7(2):198–204.
14. Siscovick DS, Weiss NS, Fletcher RH, Lasky T. The incidence of primary cardiac arrest during vigorous exercise. N Engl J Med. 1984;311(14):874–7.
15. Maron BJ, Chaitman BR, Ackerman MJ, et al. Recommendations for physical activity and recreational sports participation for young patients with genetic cardiovascular diseases. Circulation. 2004; 109(22):2807–16.
16. Maron BJ, Shirani J, Poliac LC, Mathenge R, Roberts WC, Mueller FO. Sudden death in young competitive athletes. Clinical, demographic, and pathological profiles. JAMA. 1996;276(3):199–204.
17. Basavarajaiah S, Wilson M, Whyte G, Shah A, McKenna W, Sharma S. Prevalence of hypertrophic cardiomyopathy in highly trained athletes: relevance to pre-participation screening. J Am Coll Cardiol. 2008;51(10):1033–9.
18. Maron BJ, Thompson PD, Ackerman MJ, et al. Recommendations and considerations related to preparticipation screening for cardiovascular abnormalities in competitive athletes: 2007 update: a scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism: endorsed by the American College of Cardiology Foundation. Circulation. 2007; 115(12):1643–55.
19. Wilson JMG, Jungner G. Principles and practice of screening for disease. WHO Chronicle. Geneva: World Health Organization; 1968:22(11):473. Public Health Papers #434.
20. Chandra N, Bastiaenen R, Papadakis M, Sharma S. Sudden cardiac death in young athletes: practical challenges and diagnostic dilemmas. J Am Coll Cardiol. 2013;61(10):1027–40.
21. Maron BJ. Distinguishing hypertrophic cardiomyopathy from athlete's heart physiological remodelling: clinical significance, diagnostic strategies and implications for preparticipation screening. Br J Sports Med. 2009;43(9):649–56.
22. Morganroth J, Maron BJ, Henry WL, Epstein SE. Comparative left ventricular dimensions in trained athletes. Ann Intern Med. 1975; 82(4):521–4.
23. Naylor LH, George K, O'Driscoll G, Green DJ. The athlete's heart: a contemporary appraisal of the 'Morganroth hypothesis'. Sports Med. 2008;38(1):69–90.
24. Spence AL, Naylor LH, Carter HH, et al. A prospective randomised longitudinal MRI study of left ventricular adaptation to endurance and resistance exercise training in humans. J Physiol. 2011;589(Pt 22):5443–52.
25. Utomi V, Oxborough D, Whyte GP, et al. Systematic review and meta-analysis of training mode, imaging modality and body size influences on the morphology and function of the male athlete's heart. Heart. 2013;99(23):1727–33.
26. Mayet J, Shahi M, Foale RA, Poulter NR, Sever PS, Mc GTSA. Racial differences in cardiac structure and function in essential hypertension. BMJ. 1994;308(6935):1011–4.
27. Basavarajaiah S, Boraita A, Whyte G, et al. Ethnic differences in left ventricular remodeling in highly-trained athletes relevance to differentiating physiologic left ventricular hypertrophy from

hypertrophic cardiomyopathy. J Am Coll Cardiol. 2008;51(23): 2256–62.
28. Rawlins J, Carre F, Kervio G, et al. Ethnic differences in physiological cardiac adaptation to intense physical exercise in highly trained female athletes. Circulation. 2010;121(9):1078–85.
29. Chandra N, Papadakis M, Sharma S. Cardiac adaptation in athletes of black ethnicity: differentiating pathology from physiology. Heart. 2012;98(16):1194–200.
30. Sheikh N, Papadakis M, Carre F, et al. Cardiac adaptation to exercise in adolescent athletes of African ethnicity: an emergent elite athletic population. Br J Sports Med. 2013;47(9):585–92.
31. Sheikh N, Papadakis M, Ghani S, et al. Comparison of electrocardiographic criteria for the detection of cardiac abnormalities in elite black and white athletes. Circulation. 2014;129(16):1637–49.
32. Bernhardt DT, Roberts WO. Preparticipation physical evaluation. Elk Grove Village: American Academy of Pediatrics; 2010.
33. Madsen NL, Drezner JA, Salerno JC. Sudden cardiac death screening in adolescent athletes: an evaluation of compliance with national guidelines. Br J Sports Med. 2013;47(3):172–7.
34. Thiene G, Corrado D, Schiavon M, Basso C. Screening of competitive athletes to prevent sudden death: implement programmes now. Heart. 2013;99(5):304–6.
35. Sharma S, Estes 3rd NA, Vetter VL, Corrado D. Clinical decisions. Cardiac screening before participation in sports. N Engl J Med. 2013;369(21):2049–53.
36. Mackie A. Screening of competitive athletes to prevent sudden death: think twice. Heart. 2013;99(5):306–7.
37. McLeod CJ, Ackerman MJ, Nishimura RA, Tajik AJ, Gersh BJ, Ommen SR. Outcome of patients with hypertrophic cardiomyopathy and a normal electrocardiogram. J Am Coll Cardiol. 2009;54(3): 229–33.
38. Maron BJ. National electrocardiography screening for competitive athletes: feasible in the United States? Ann Intern Med. 2010;152(5): 324–6.
39. Uberoi A, Stein R, Perez MV, et al. Interpretation of the electrocardiogram of young athletes. Circulation. 2011;124(6):746–57.
40. Drezner JA, Ackerman MJ, Anderson J, et al. Electrocardiographic interpretation in athletes: the 'Seattle criteria'. Br J Sports Med. 2013;47(3):122–4.
41. Drezner JA, Fischbach P, Froelicher V, et al. Normal electrocardiographic findings: recognising physiological adaptations in athletes. Br J Sports Med. 2013;47(3):125–36.
42. Drezner JA, Ashley E, Baggish AL, et al. Abnormal electrocardiographic findings in athletes: recognising changes suggestive of cardiomyopathy. Br J Sports Med. 2013;47(3):137–52.
43. Drezner JA, Ackerman MJ, Cannon BC, et al. Abnormal electrocardiographic findings in athletes: recognising changes suggestive of primary electrical disease. Br J Sports Med. 2013;47(3): 153–67.
44. Gati S, Chandra N, Bennett RL, et al. Increased left ventricular trabeculation in highly trained athletes: do we need more stringent criteria for the diagnosis of left ventricular non-compaction in athletes? Heart. 2013;99(6):401–8.
45. Kawel N, Nacif M, Arai AE, et al. Trabeculated (noncompacted) and compact myocardium in adults: the multi-ethnic study of atherosclerosis. Circ Cardiovasc Imaging. 2012;5(3):357–66.
46. Corrado D, Basso C, Pavei A, Michieli P, Schiavon M, Thiene G. Trends in sudden cardiovascular death in young competitive athletes after implementation of a preparticipation screening program. JAMA. 2006;296(13):1593–601.
47. Steinvil A, Chundadze T, Zeltser D, et al. Mandatory electrocardiographic screening of athletes to reduce their risk for sudden death proven fact or wishful thinking? J Am Coll Cardiol. 2011;57(11): 1291–6.
48. Wheeler MT, Heidenreich PA, Froelicher VF, Hlatky MA, Ashley EA. Cost-effectiveness of preparticipation screening for prevention of sudden cardiac death in young athletes. Ann Intern Med. 2010; 152(5):276–86.
49. Halkin A, Steinvil A, Rosso R, Adler A, Rozovski U, Viskin S. Preventing sudden death of athletes with electrocardiographic screening: what is the absolute benefit and how much will it cost? J Am Coll Cardiol. 2012;60(22):2271–6.

Lifestyle Modification: Diet, Exercise, Sports and Other Issues

12

David S. Owens

Abstract

Patients with hypertrophic cardiomyopathy face a lifetime of living with a heart condition that is at once heterogeneous, often unpredictable, and poorly understood. Lifestyle adjustments are essential to controlling symptoms, and factors such as diet, fluid intake, caffeine, alcohol and exercise can all have profound effects on patient well-being. However, because HCM physiology can vary widely from patient to patient, physician recommendations must be personalized to each individual patient's physiology. Hydration should be encouraged for patients with dynamic LVOT obstruction, but diuretics and strict regulation of fluid balance may be needed when congestion is present. Moreover, although exercise has myriad health benefits, it carries acute risks in HCM patients. Professional guidelines prohibit competitive sports and vigorous recreational activities, and this may have implications on a patient's employment. However, strict exercise proscriptions are not warranted, and in most cases exercise should be encouraged as a component of a healthy lifestyle. As with nearly all aspects of HCM patient care, recommendations about lifestyle are not simple but require ongoing conversations tailored to individual patients. These conversations need to be placed in the context of each patient's physiology, their risks, and informed by the patient's overall life goals. Discussion with the patient and family, often repeated over multiple visits, will be necessary in order to develop the trust and partnership that leads to effective management.

Keywords

Hypertrophic cardiomyopathy • Diet • Caffeine • Alcohol • Medications • Supplements • Sports • Exercise • Employment • Insurance

Key Points

- Diet and hydration factors can have a large impact on HCM patient symptoms due to the dynamic nature of the LVOT obstruction.
- Patients without evidence of volume overload should drink plenty of fluids and avoid eating large meals.
- Caffeine and alcohol can potentially worsen LVOT obstruction and should be avoided in symptomatic patients. At the very least, patients should drink in moderation and avoid "binge-drinking".
- Exercise increases the risks of sudden cardiac death acutely, but this risk needs to be balanced against the known chronic health benefits.

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- HCM patients should be restricted from competitive sports, with the possible exception of low dynamic, low static sports (e.g., bowling, archery).
- Recommendations for recreational activities should be individualized. High intensity and burst activities should be avoided, but brisk walking, swimming and/or jogging may be permitted as components of a healthy lifestyle.
- Patients with ICDs can usually live everyday life without major adjustments, though adjustments may be needed if large sources of electromagnetic interference are encountered occupationally. The presence of an ICD, however, does not modify the recommendations on allowable levels of exertion or sports participation.
- HCM patients may be unable to work in specific professions (e.g., airline pilots or active duty military) due to public safety concerns if transient loss of consciousness were to occur.
- Several recent patient rights legislation offer protection against discrimination on the basis of genetic information or pre-existing conditions, but these protections do not generally apply to life or long-term care insurance.

Introduction

As a lifelong condition and one that carries risk of sudden death, an HCM diagnosis can have profound impact on patients' health behaviors, lifestyle and psychological outlook. Patients may have a number of questions about how HCM affects their everyday life, and this is especially true for patients with ICDs. Patients with LVOT obstruction or congestion often find that their symptoms are dependent on their dietary choices and hydration status. Moreover, patients are confronted with restrictions on exercise, employment and insurability. This chapter will focus on lifestyle issues for patients with varied clinical manifestations of HCM, including issues related to diet and hydration, obesity and weight loss, and recommendations for physical activity. It will also address some of the lifestyle considerations for patients with ICDs.

Dietary and Fluid Intake

A common question patients have when they are first diagnosed with HCM is whether dietary or lifestyle factors caused or contributed to the condition. HCM is now defined as a genetic disorder of the cardiac sarcomere and related proteins, and currently there are no known lifestyle factors that contribute to disease manifestation [1]. Systemic hypertension may contribute to LV hypertrophy, but hypertensive heart disease is considered a separate entity with unique natural history.

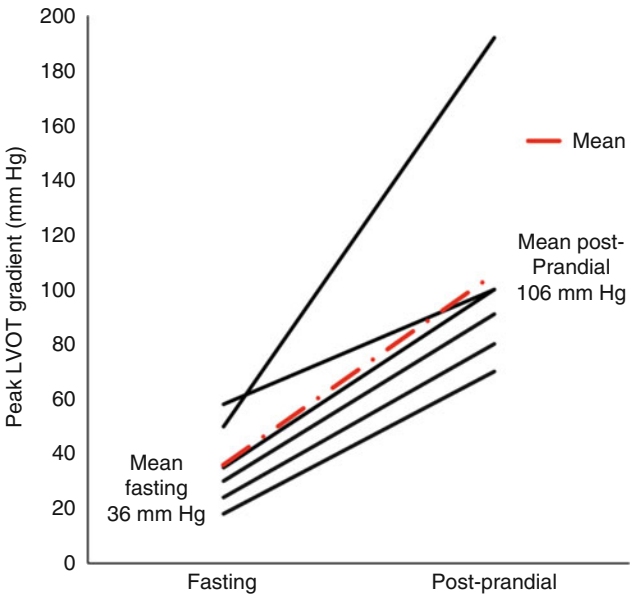

Fig. 12.1 Fasting and post-prandial peak LVOT gradients among six patients with symptomatic, obstructive HCM and post-prandial increase in symptoms (Reprinted from Kansal et al. [5]. Copyright (2010), with permission from Elsevier)

However, lifestyle factors can profoundly affect symptomatology. Approximately 2/3 of HCM patients have resting or provocable outflow tract obstruction [2]. This obstruction is most often "dynamic", and factors such as preload, afterload and contractility greatly influence its severity. Factors that decrease preload (e.g., dehydration, some medications, or Valsalva maneuver) can decrease LV cavity volumes, bring the mitral leaflets closer to the LV outflow septum, and thereby worsen the systolic anterior motion of the mitral leaflets that causes the LV obstruction. LVOT gradients may vary widely from day to day or even throughout the course of a single day depending on when patients last ate, drank, or took their medications.

A post-prandial increase in symptoms of dyspnea, angina or exercise limitation is a common complaint for patients with obstructive HCM [3–5]. As splanchnic blood flow increases, there is a resultant decrease in circulating plasma volume which can decrease LV preload and increase LVOT gradients (Fig. 12.1). For these patients, it may be prudent to avoid large meals and overeating in lieu of smaller, more frequent meals or snacks.

It is important for all patients with HCM to avoid dehydration, which can increase LVOT obstruction by reducing preload and increasing contractility; patients with non-obstructive HCM are also susceptible to the consequences of

low preload. Although there have been no scientific studies in HCM patients, the general rule of drinking eight 8-oz glasses of water (or other low calorie beverage) per day seems reasonable for patients who do not have signs or symptoms of congestion.

A subset of patients with HCM develops congestive heart failure, either due to progression to "end-stage" phenotype with low ejection fraction or due to severe diastolic dysfunction with restrictive physiology [6]. Indeed, any impairment of cardiac output in HCM, including both obstructive and non-obstructive forms, may result in volume overload over time. For these patients, salt and fluid restriction along with judicious use of diuretics may be needed. Standard heart failure management strategies, including daily weights with a triggered diuretic titration protocol, may be beneficial. In those with obstructive physiology, however, care must be taken to avoid overdiuresis and inadvertently increasing obstructive symptoms. Gradually increasing diuretics, starting with less potent agents such as hydrochlorothiazide, and moving to dyazide, maxzide, loop diuretics or zaroxolyn as needed may be a prudent strategy, with careful attention to electrolyte balance.

Caffeine

A common question from patients is whether it is safe to drink coffee. Coffee, caffeinated teas and energy drinks with caffeine supplements are widely consumed, and daily intake is common due to caffeine dependence. Caffeine is a xanthine alkaloid that stimulates the central nervous system and is often used to reduce fatigue and increase mental alertness. While a standard 8-oz cup of coffee may contain 50–200 mg of caffeine, energy drinks are growing in popularity and may contain up to 500 mg. The rate of caffeine metabolism varies widely between individuals due to variability in the hepatic CYP1A2 enzyme, which accounts for much of the marked variability in the response to caffeine seen clinically.

Caffeine has acute effects on the cardiovascular system, including mild positive inotropic effects from phosphodiesterase inhibition, increased norepinephrine release and increased intracellular calcium availability and sensitivity. Caffeine can also induce vasoconstriction, which can results in up to a 10 mmHg increase in systolic BP in caffeine-naïve individuals, and particularly in patients with resting hypertension. Caffeine in higher doses (250–300 mg) can also have diuretic effects, although little diuretic effect is seen with a standard cup of coffee. All of these effects appear to be attenuated in individuals with habitual caffeine intake.

There is no data on the effects of caffeine on HCM patients specifically, but the known physiologic effects of caffeine may be theoretically adverse. The increased contractility and mild diuretic effects of caffeine could combine to worsen LVOT obstruction, although this may be offset by an increase in afterload. Although there is concern about caffeine being pro-arrhythmic, caffeine does not appear to increase the risk of atrial fibrillation in the general population, nor does it appear to increase inducibility of ventricular tachycardia in patients with symptomatic VT. On the other hand, population studies have suggested that moderate caffeine consumption may have protective effects on cardiovascular health.

The 2011 HCM Guidelines do not make recommendations concerning coffee intake [1]. Given the above data, strict caffeine prohibition does not appear to be warranted for all HCM patients. However, caffeine intake should be limited – and preferably avoided – in patients with resting or labile LVOT obstruction, in patients who have intermittent dysrhythmias, or patients whose symptoms are temporally linked to caffeine consumption. For patients who choose to drink coffee, it should be consumed in moderation (1–2 cups of coffee per day), with avoidance of caffeine binge drinking.

Alcohol

Alcoholic beverages (including beer, wine and liquors) are also commonly consumed, and in one study up to 90 % of HCM patients reported drinking ≥12 alcoholic beverages within the past year [7]. Ethanol is the principle component in alcohol and the source of its psychoactive effects, due to its interactions with GABA receptors in the brain. Alcoholic beverages differ in their ethanol content, and for purposes of standardization, 1 alcoholic drink contains 10–14 g of ethanol, which is approximately the equivalent of 12-oz of beer (~5 % alcohol), 5-oz of wine (~12 % alcohol), or 1.5 oz of hard liquor (~40 % alcohol).

In addition to its acute psychoactive effects, alcohol has both acute and chronic effects on cardiac function. Acute ethanol ingestion is associated with reduced myocardial contractility, and a decrease in vascular tone, and a reflexive tachycardia. Alcohol also has diuretic effect that can promote dehydration. Thus alcohol can induce both reductions in preload and afterload that may worsen LVOT gradients, although this may be offset somewhat by reduction in contractility.

One study examined the effects of ethanol on patients with HCM and systolic anterior motion (SAM) of the mitral valve (but not necessarily resting obstruction) [8]. After ingesting the equivalent of about 1 alcoholic drink, there was on average an 8 mmHg drop in systolic blood pressure, an increase in SAM severity, and an increase in peak LVOT gradients from 38.1 to 62.2 mmHg, while there were no such changes in a placebo group (Fig. 12.2). These subjects were asymptomatic with this change, but this represented only a small amount of alcohol compared to levels that may be consumed socially.

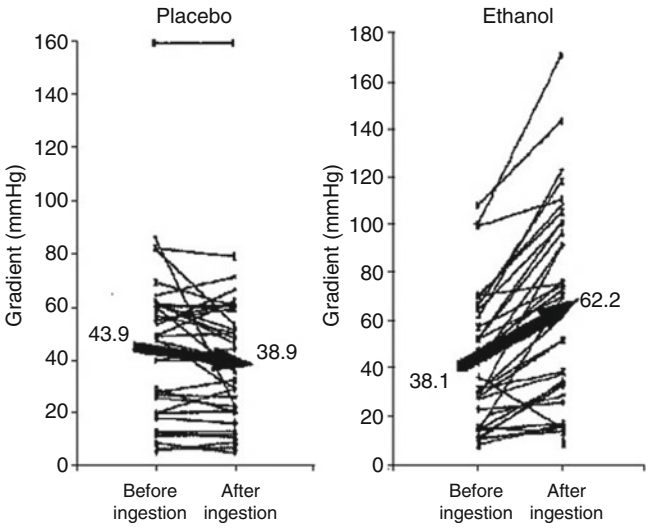

Fig. 12.2 Peak LVOT gradients before and after ingestion of placebo (*left*) or 50 mL of 40 % ethanol (*right*) in patients with HCM and systolic anterior motion of the mitral valve (From Paz et al. [8] Copyright ©1996 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society)

In the general population, there is evidence for a "J-curve" for the effect of alcohol on overall health, with benefit at low levels and harm at high levels of exposure. A number of large, prospective studies have demonstrated improvement in coronary heart disease outcomes and overall mortality with moderate alcohol consumption (1 drink per day for women, 1–2 drinks per day for men), with an estimated risk reduction of 30–50 % [9]. The mechanisms of this benefit are uncertain, but improvements in insulin sensitivity, HDL cholesterol, and endothelial function and reductions in inflammatory markers have been described. High levels of alcohol consumption are cardiotoxic and clearly adverse, with increased risk of hypertension, non-ischemic dilated cardiomyopathy, atrial fibrillation, and stroke in addition to liver cirrhosis and other organ damage.

In contrast to the "J-curve" effect on coronary heart disease outcomes, there appears to be a linear increase in risk of atrial fibrillation across the range of alcohol consumption. Heavy alcohol consumption has long been known to be a precipitant of atrial or ventricular arrhythmias (aka, "holiday heart"), but even at lower levels of consumption, each additional 1 drink per day appears to increase the risk of atrial fibrillation by about 10 % [10]. It is unknown if this linear association holds true for HCM patients, or if the risk is greater in this population because of their increased susceptibility to arrhythmias.

The 2011 HCM Guidelines did not make recommendations concerning alcohol consumption in patients with HCM. There are clear adverse consequences of heavy alcohol consumption both acutely and chronically, and "binge drinking" should be discouraged. Patients with resting or labile LVOT obstruction should limit or abstain from alcohol consumption, as should patients whose symptoms are temporally linked to alcohol consumption. Abstinence may reduce the occurrence or atrial fibrillation in patients experiencing or at risk for atrial dysrhythmias. However, it is unclear if strict prohibition from alcohol is appropriate for all HCM patients given evidence that it may improve outcomes at low to moderate levels of consumption. Recommendations regarding alcohol consumption must therefore involve a discussion about the risks and benefits for individual patients.

There is evidence that an HCM diagnosis may modify patients' health behaviors in a positive manner. After adjusting for age, gender and body mass index (BMI), HCM patients were found to consume 0.9 fewer alcoholic drinks per day on average over the 1-year prior to the survey, and were 41 % less likely to have engaged in binge-drinking (≥5 drinks in 1 day) over the course of their lifetime.

Other Drugs

In addition to increasing risks of lung, throat and other cancers, tobacco use is associated with increased cardiovascular morbidity and mortality. Since there are no known health benefits of tobacco use, a clear and strong recommendation for tobacco cessation should be given to all patients who smoke. The coexistence of coronary artery disease and HCM has been linked to adverse outcomes. Although 20 % of HCM patients are current smokers (representing room for improvement) they compare favorably to the general population. HCM patients are 25 % less likely to be past or current smokers and 74 % less likely to be current smokers comparatively [7].

There are recent trends in the US toward legalization of marijuana and cannabinoids for either medical or recreational purposes. Although there are over 125–200 million marijuana users worldwide, the effects of marijuana on the cardiovascular system are not well studied [11, 12]. Moreover, it is often difficult to separate the effects of marijuana from other drugs, as tobacco or other recreational drugs are often used concurrently. Acutely, marijuana appears to increase heart rate and catecholamine levels, with a reduction in peripheral vascular resistance [13]. Marijuana consumption may be associated with worsened cardiovascular outcomes in patients with known CAD, including increasing risks of myocardial infarction and overall mortality [14–16].

There are several reports of patients experiencing myocardial infarctions, arrhythmias and/or sudden death after marijuana use [17], including an autopsy series of six

young individuals (all age <45 years) with likely cardiac deaths in which marijuana was the only drug found on toxicology [18]. However, none of these individuals appeared to have HCM and it is unclear if marijuana was a causal factor. Several case reports and series have suggested a link between acute marijuana use and onset of atrial fibrillation in otherwise low-risk individuals [19, 20]. This raises some concerns that marijuana may have heightened effects in individuals at risk for atrial fibrillation, but this has not been studied.

As there is little data on the safety of cannabis use in HCM patients, it seems prudent to recommend against its use on a recreational basis (where legal). If cannabis is being prescribed for medical reasons (e.g., chronic oncologic pain), the benefits should be weighed against its unknown risks.

Medications and Supplements

The mostly commonly prescribed medications for the treatment of HCM are beta-adrenergic blocking agents (e.g., metoprolol, atenolol) and calcium channel blockers (e.g., verapamil). Beta blockers are the first-line agent for the treatment of obstruction and are also commonly prescribed for patients with non-obstructive HCM. Beta blockers have both negative chronotropic and negative inotropic effects, decreasing resting and exertional heart rates, improving LV filling, decreasing exertional gradients and possibly reducing arrhythmias. However, these medications can have numerous side effects, especially in young people. Fatigue, general malaise, depression, and erectile dysfunction are common, often dose-limiting complaints. Some providers have suggested that Toprol XL, the name brand formulation of metoprolol succinate, is better tolerated and that using divided doses for more consistent blood levels may reduce severity of side effects.

For patients that do not tolerate beta blockers or remain symptomatic, calcium channel blockers such as Verapamil are used. Verapamil comes in both short and extended release (both once and twice daily) formulations. Verapamil improves diastolic filling and, can reduce resting LVOT gradients to a greater degree than beta blockers. Additionally, some providers prefer Verapamil over beta blockers for the treatment of microvascular angina. Common side effects include constipation, fatigue, and lower extremity edema. Calcium channel blockers should be used with caution when added on to beta blocker therapy, as the combination may induce AV block. In addition, high doses of verapamil may reduce afterload and provoke obstruction, and are therefore best avoided. Diltiazem is less well studied and generally not considered a first line agent.

Disopyramide is a class Ia antiarrhythmic that was originally designed to treat ventricular tachycardia. It is also a potent negative inotropic agent and the combined effects can be especially beneficial for patients with LVOT obstruction and refractory symptoms. This agent can prolong the QT interval and speed up AV nodal conduction, and the ACC/AHA guidelines recommend inpatient monitoring during drug initiation and simultaneous use of an AV nodal blocking agent [1]. Several experts have recently advocated for outpatient initiation, however, with outpatient ECG monitoring. It is important to remember that disopyramide can only be prescribed in addition to AV nodal blocking agents, and should never be given in isolation. Disopyramide comes in both short acting (TID or QID) or long-acting (BID) formulations. Because of the potent effects but short half-life of the drug, patients are often reminded to take their next dose because of worsening of their symptoms. In general, however, disopyramide ER is preferred but may require non-formulary insurance approval.

The side effects of disopyramide are chiefly anticholinergic in nature and mostly dose-dependent. At starting doses, dry mouth, constipation and urinary retention may begin. At higher doses, blurred vision becomes a common complaint. Pyridostigmine is a cholinesterase inhibitor that can counteract the anticholinergic side effects of disopyramide. Pyridostigmine is best prescribed as a long-acting agent (name brand Mestinon Timespan), with doses of 180–360 mg daily to match the severity of the side effect symptoms. It is generally not necessary to monitor blood levels of disopyramide, though periodic symptom and QTc assessment is warranted.

Over-the-counter medications may contain hidden stimulants, and it is important for HCM patients to be aware of ingredients of all OTC remedies. For instance, pseudoephedrine is commonly found in "non-drowsy" cold therapies and decongestion/anti-histamine combinations. It functions primarily as a vasoconstrictor due to its α-adrenergic effects, but can have both direct and indirect cardiac effects including a rise in heart rate and blood pressure. As with all stimulants, there is concern about arrhythmias and these should be avoided if possible.

In addition, many patients take vitamin, herbal or health supplements, either to promote general health or for perceived benefits on HCM. To date there is little data on the safety or efficacy of most of these supplements. One supplement commonly taken by HCM patients is Coenzyme Q-10, which is commonly found in dietary sources (e.g., meats, poultry, and oils) purported to have antioxidant properties and improve mitochondrial energetics. While Coenzyme Q-10 supplementation has been tested in several medical disorders and in low doses it appears safe [21], there is no data proving its efficacy in HCM patients.

Obesity, Sleep Apnea and Coronary Artery Disease Risk Factors

Recent survey data has shed light on how HCM patient compare to the general population in some of their health behaviors and physical activity levels [7]. Using the National Health and Nutrition Examination Survey (NHANES) data and propensity matching for age and gender, HCM patients were found to have higher body mass index (BMI) and are more likely to be obese (BMI >30 kg/cm [2]). However, there were no clear differences in eating habits between HCM patients and controls. HCM patients reported eating fewer fast food meals, but were more likely to eat ready-to-eat meals in the 30-days prior to the survey.

The relationship between obesity and HCM is complex. It is unclear to what extent obesity is a result of physical inactivity caused by disease-related exercise limitations or by physician imposed exercise restrictions, and to what extent HCM phenotype and/or symptoms are due to obesity. Obese HCM patients have higher blood pressure, greater LV mass, and worse NYHA functional status and exercise tolerance compared to non-obese HCM patients [22, 23]. They may also have greater likelihood of provocable LVOT obstruction [23]. There are some potential and interesting biological pathways that may mediate this association (e.g., leptin induced hypertrophy) but the direction of causality here remains uncertain [24].

Obesity is often (but not always) accompanied by coronary artery disease risk factors of hypertension, dysglycemia (insulin resistance, metabolic syndrome or diabetes), and hypercholesterolemia. It is unknown if these risk factors are more common in HCM patients compared to the general population, but the coexistence of coronary artery disease and HCM has been linked to increased mortality [25], and coronary disease prevention is an essential component of the care of HCM patients. Coronary artery disease risk factors should be treated according to standard primary and secondary prevention guidelines [1], although the treatment of hypertension can be particularly challenging [26].

Obstructive sleep apnea is also common in HCM patients, with up to 40 % of HCM patients having an apnea-hypopnea index >15 events/h [27] and up to 71 % having repetitive nocturnal desaturations [28]. Moreover, OSA has been independently linked to atrial fibrillation in HCM patients [27], and a low index of suspicion should be used for diagnosis and treatment.

Weight loss is primarily determined by the balance of caloric intake and expenditures. Patients with HCM may find it challenging to achieve and maintain weight loss due to exercise limitations or restrictions. Symptomatic HCM patients tend to gain weight because of inactivity, and obesity taxes cardiac reserves and increases symptoms. Obesity can also increases the peri-procedural risks of either surgical myectomy or alcohol septal ablation. Patients may benefit from a referral to a dietician, and in some instances a referral for bariatric surgery can be considered.

Competitive Sports and Recreational Exercise

Several professional guidelines detail recommendations for the types and intensity of exercise activities appropriate for patients with HCM [29, 30]. These guidelines make the important distinction been competitive sports and recreational exercise. In competitive sports, there are usually external motivators in the form of a coach, monetary reward, or the thrill of victory. Athletes train intensively with the goal of pushing their limits and achieving personal bests, and may disregard their short-term physical health to reach these goals. In contrast, recreational activities are less vigorous and usually self-regulated, with a primary goal of maintaining fitness.

The 36th Bethesda Conference Task Force 4 recommendations address HCM patient participation in competitive sports [29]. These guidelines state that patients with a "probable or unequivocal" diagnosis of HCM should be excluded from all competitive sports with the possible exception of low intensity sports. These recommendations are universal, and apply to all HCM patients regardless of age, sex, or race, the presence of outflow obstruction, the number of sudden death risk factors present, and the use of medications or ICDs.

A list of sporting disciplines categorized by intensity of static and dynamic components is shown in Fig. 12.3 [29, 31]. The 36th Bethesda Guidelines recommend that HCM patients only participate in Class IA competitive sports that have both low static and low dynamic components, such as billiards, bowling, cricket, curling or golf (bottom left panel in Fig. 12.3).

The European Society of Cardiology consensus statement on competitive sports participation is largely in agreement with these recommendations (Table 12.1) [30]. However, they differ from the 36th Bethesda Conference recommendations in regard to patients with pre-clinical HCM (i.e., individuals who carry an HCM-causing gene mutation but who do not express LV hypertrophy) [32]. The ESC recommends disqualification from competitive sports due to the uncertainty in the natural history of the disease, though recreational exercise is permitted. In contrast, the Bethesda Conference recommendations do not place any restrictions on competitive or recreational activities.

There are myriad benefits of exercise on cardiovascular health and overall well-being, and complete exclusion from exercise could have negative consequences on overall health [33]. Regular, moderate levels of exercise promote weight

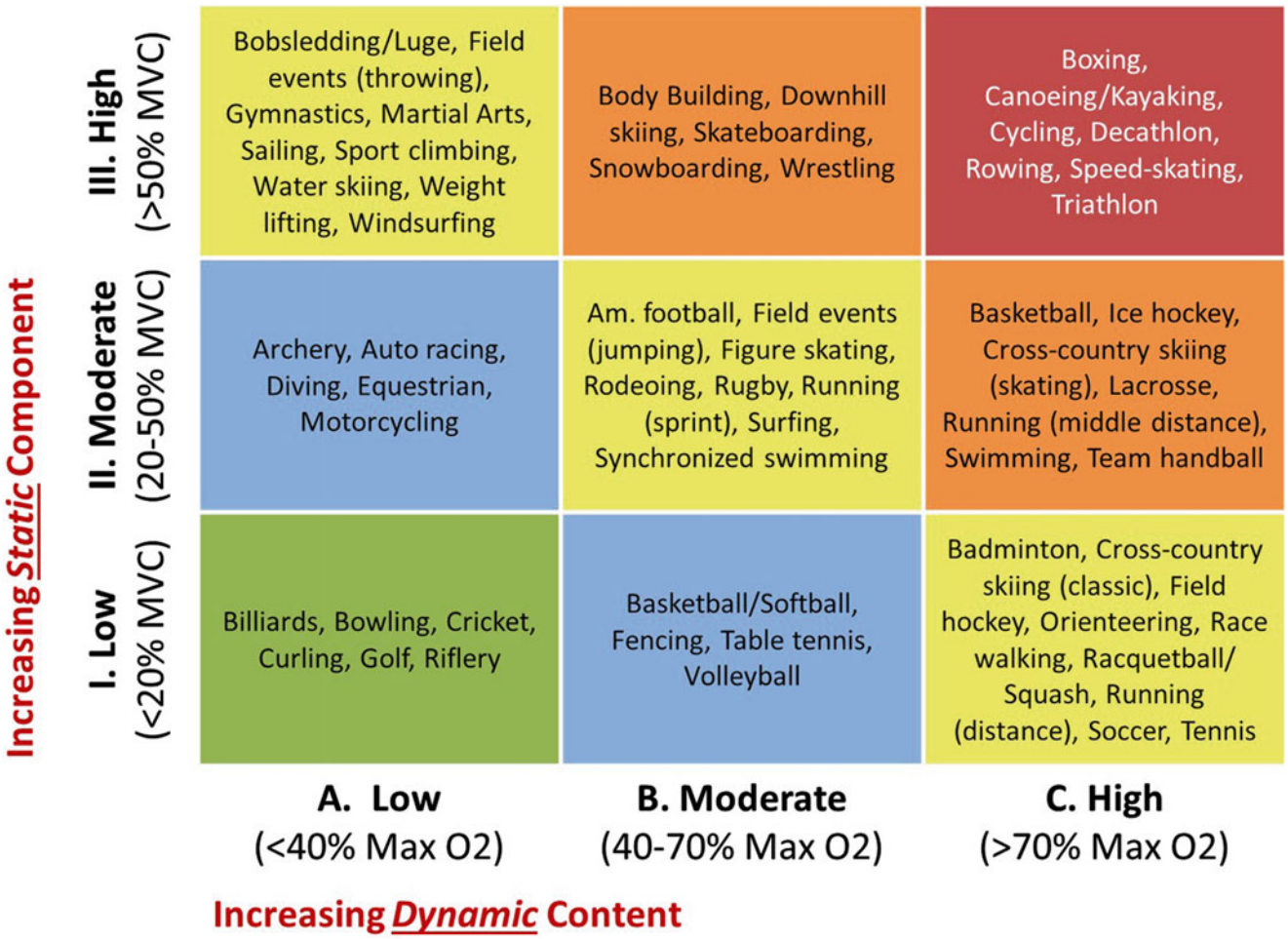

Fig. 12.3 Classification of sports based on peak static and dynamic components achieved during competition

Table 12.1 Comparison of US and European guideline recommendations for participation is competitive sports and recreational exercise

	US	Europe
Overt HCM		
Competitive sports	Class 1A sports only	Class IA sports if low-risk profile, otherwise no competitive sports.
Recreational activities	Some restrictions	Some restrictions
Pre-clinical HCM[a]		
Competitive sports	No restrictions	No competitive sports
Recreational activities	No restrictions	No restrictions

[a]Gene carrier without HCM phenotype

loss, combat hypertension, hypercholesterolemia and dysglycemia, maintain bone density, and improve sleep, self-esteem and mental outlook. Thus excluding patients from regular exercise can negatively impact cardiovascular risk, overall health and quality of life.

There has been a misconception by some medical providers that patients with HCM should not engage in any forms of exercise other than those outlined for competitive sports. Not only are such stringent restrictions potentially detrimental to overall health, they can also have a profound psychological impact on patients. In a survey of HCM patients, 60 % felt that exercise restrictions had a negative impact on their emotional health, and 71 % expressed anxiety towards exercise although this was generally mild and did not correlate with physical activity.

Both US and European expert panels have provided recommendations for the intensity and types of recreational activities that might be appropriate for patients with HCM [1, 30, 34]. Acknowledging the health benefits of regular, low to moderate-intensity exercise, these recreational activity guidelines are less restrictive than those for competitive sports. European consensus recommendations divide activities into categories of "not recommended", "allowed on an individual basis", or "permitted" (Table 12.2) [30]. In general, vigorous activities, burst activities (e.g., basketball) and activities where a transient loss of consciousness would have profound impact (e.g., scuba diving) are to be avoided.

Table 12.2 European Society of Cardiology recommendation for amateur and leisure-time sport activities in patient with HCM

Sports not recommended	Sports allowed on individual basis	Sports permitted
Baseball	Moderate-intensity weights	Stationary bicycle
Basketball	Cross-country skiing (flat)	Bowling
Road cycling	Horseback riding[a]	Brisk walking
Ice hockey[a]	Jogging	Golfing
Rowing/canoeing	Running	Moderate hiking
Rock climbing	Motorcycling[a]	Skating
Scuba diving	Sailing[b]	Tennis (doubles)
Sprinting	Stationary rowing	Treadmill
Soccer	Swimming[b]	Low-intensity weights
Squash[a]		
Tennis (singles)		
Track events		
High-intensity weights		
Windsurfing[b]		

Based on recommendations provided in Pelliccia et al. [30]
[a]These sports involve the potential for traumatic injury, which should be taken into consideration for individuals with a risk for impaired consciousness
[b]The possibility of impaired consciousness occurring during water-related activities should be taken into account with respect to the clinical profile of the individual patient

The U.S. guidelines are very similar in their scope and purpose, but grade activities on a 0–5 point scale of 'permissibility': activities with scores of 0–1 are "not advisable", 2–3 are "intermediate" and 4–5 are "probably permitted" [34]. The U.S. guidelines are more lenient towards biking/cycling and baseball (intermediate sports) and swimming (probably permitted), but are more strict towards running (not advisable), although both categorize jogging as a medium risk activity. Additionally, the U.S. guidelines do not comment on rowing sports and track events, and divide weight lifting into machine weights (probably permitted) and free weights (not advisable).

Ultimately, the proper balance between the risks and benefits of exercise is not a one-size-fits-all recommendation but involves a conversation with individual patients. Several general observations and common-sense strategies can inform this conversation:

- The goal of exercise should be for health maintenance, not a competition against the clock, yourself or others.
- The activities that appear to carry the highest risk are the high-intensity activities and those that involve intermittent bursts (e.g., basketball, soccer).
- The risks associated with exercise are highest for patients who exercise intermittently (zero to one times per week). Exercise should be incorporated into a daily routine.
- If patients are too dyspneic to hold a conversation, they are exercising too vigorously.
- Patients should exercise with a partner or a group whenever possible, and ideally with someone who knows about their heart condition. If there is an event, someone is around to initiate emergency response; many gyms now have AEDs on site.
- Patients need to listen to their body and stop exercising if things don't feel right.

Because of the guideline recommendations against competitive or vigorous exercise, as well as the underlying cardiac limitations to exercise that come with HCM, it is surprising that a higher percentage of HCM patients engaged in moderate or vigorous recreational activities compared to the NHANES control population, although the time spent doing those activities was lower [7]. Moreover, approximately 10 % of HCM patients were engaging in >1 competitive sport. This may in part be due to inadequate patient education, as only 29 % of HCM patients were aware of the professional guideline recommendations on exercise, and among this subset only 59 % reported being adherent. Only 46 % of HCM patients reported having conversations about exercise with their doctor. HCM patients with ICDs were less likely to engage in vigorous exercise but equally likely to engage in moderate exercise activities compared to HCM patients without ICDs. ICD presence, however, is not an indication that more aggressive sports are now allowable, and restrictions are not modified.

Sexual Activity

Patients often inquire about another type of recreational activity, namely sexual intercourse. This is a topic that was not addressed in either the 2004 guidelines on recreational activity or in the 2011 HCM guidelines [1, 34]. The 2012 AHA Scientific Statement on Sexual Activity and Cardiovascular Disease states that sexual activity is reasonable (class IIa recommendation) for most patients with HCM, but should be deferred in severely symptomatic patients [35]. It should be noted that the treatment of erectile dysfunction with phosphodiesterase inhibitors (e.g., sildenafil) is contraindicated in patients with resting or provocable LVOT obstruction due to concerns that decreased preload will worsen obstruction and cause hemodynamic compromise or arrhythmias. Worsening LVOT obstruction [36] and atrial fibrillation [37] have been reported after use of sildenafil, although the guideline committee was unaware of any deaths in patients with HCM or outflow stenosis [35]. The safety of phosphodiesterase inhibitors in patients with clearly documented *non-obstructive* HCM has not been proven, and should be considered only after careful discussion about the risks and benefits, and perhaps echo assessment of LVOT gradients following drug administration.

For patients of childbearing age, a proactive conversation regarding contraception is warranted. Although pregnancy is

usually well tolerated hemodynamically in women with HCM and maternal mortality remains very low, pregnancy may be discouraged in some patients with severe symptoms, congestion or active arrhythmias [38, 39]. Most forms of contraception carry acceptable risks for HCM patients, including barrier methods, combined hormonal agents (e.g., estrogen/progestin formulations), progestin only regimens, intrauterine devices, or sterilization [40, 41]. Patients with atrial fibrillation or prior strokes or those on anticoagulation should avoid estrogen combinations that could increase the risk of thrombus formation. In all cases, pre-conception counselling should include a discussion about contraception options, an evaluation of the risk of pregnancy, a review of medications and their safety during pregnancy, and prenatal genetic counselling to inform the prospective parents about the risks of transmitting the gene mutation and other options available.

Patients with ICDs

Although the guidelines for both competitive sports and recreational activities apply to all HCM patients, there are special considerations for patients with ICDs. These patients have been identified as being higher-risk, either because of a prior event or because of the presence of SCD risk factors. There are additional concerns about electromagnetic interference, inappropriate shocks or damage to the device. And finally, there is concern about the effectiveness of appropriate ICD shocks in an exercise milieu that may involve increased adrenergic tone, electrolyte imbalances, and/or myocardial ischemia.

Following ICD placement, some lifestyle modifications may be prudent. In the modern world, there are a number of potential sources of electromagnetic interference (EMI) including microwaves, cellular telephones, portable media players, slot machines and metal detectors [42]. While there are occasional reports of ICDs being impacted by these devices, they are generally considered safe in the context of typical daily exposures. It is recommended that patients do not carry cellular phones and other electronic equipment within 6 in. of the ICD generator, and to avoid their use during device interrogation [43, 44]. It is considered safe for patients with an ICD to walk through metal detectors, such as those at an airport, at a normal pace although the device may trigger the alarm. [42] However, patients should avoid lingering near the detectors for prolonged periods. Wand-screening or manual "pat-down" searches are safe alternatives [45]. Occupational or recreational exposures to EMI in the form of welding, chain saws, electric motors and magnetic coils may present greater sources of EMI and need to be considered on a case-by-case basis [42, 46]. Occasionally, the implantation of an ICD will have ramifications on type or place of employment.

Following ICD placement, several precautions are generally recommended, including restrictions on ipsilateral arm motion and heavy lifting/pulling. Although regulations differ from state-to-state, patients should generally avoid driving for 1 week after ICD placement, and for 6 months after an appropriate ICD shock or VT/VF event [47, 48]. Long term recommendations regarding competitive sports and recreational activities are similar to those for all patients with HCM, but some additional precautions might be recommended due to concerns for lead fracture or device damage. Inappropriate shocks are common in patients with HCM [49], who are often younger and more active than other patients with ICDs.

The SPORT-ICD study evaluated the safety of sports participation in individuals with an ICD who voluntarily chose to exercise at greater than recommended levels [50]. There were 372 registry participants, of whom 13 and 11 % had at least 1 appropriate and inappropriate ICD shock, respectively. More shocks occurred during exercise than at rest (16 % vs. 6 %, $p<0.0001$), but these shocks were just as likely to occur during recreational activities as compared to competition or training. There were 2 deaths over a median 31 month follow up period, and neither death occurred during or after exercise. Lead malfunctions were present in 13–14 participants, which was higher than would be predicted by temporal trends. Among the 65 registry participants who carried an HCM diagnosis, 13 participated in competitive sports. The numbers of shocks that occurred in the HCM subgroup was not reported, but 1 had an ICD shock that required multiple shocks before return to spontaneous circulation. In this registry setting, sports participation with an ICD appeared safe, but more data and longer follow up periods are needed before this data can be confidently extrapolated to HCM patients broadly.

Employment and Insurability

Because HCM is a lifelong disorder potentially associated with periods of incapacitation (e.g., syncope, collapse, dizziness) or SCD, and because of the recommendations for restricting exercise, an HCM diagnosis can have important implications on employment and insurability.

Some occupations that involve public health risk require medical clearance as a component of employability, and in many instances, HCM patients will be excluded from these positions regardless of prior events, number of SCD risk factors or presence of ICD. The Federal Aviation Administration is cautious about issuing medical certificates for commercial pilot's license to patients with HCM, and most individuals will be excluded [51, 52]. The Federal Motor Carrier Safety Administration has similar regulations for commercial motor vehicle licenses [53]. In general, because HCM carries an unpredictable risk of periods of incapacitation, these vocations should be avoided both for personal and public health reasons.

The US military has medical standards for enlistment and appointment (Department of Defense Directive 6130.3), and current or prior HCM are considered disqualifying, as is LV hypertrophy with a wall thickness ≥15 mm [54]. However, some military members become newly diagnosed with HCM after enlistment. These individuals will go before a Medical Evaluation Board (MEB) and their cases will be assessed on a case-by-case basis taking into consideration their ability to perform their assigned duties. Some individuals may undergo an administrative discharge form the military based on medical grounds.

Other physically demanding occupations, such as law enforcement, fire-fighting, construction and other activities may not have specific medical criteria for employment. In these cases, either the physician or the employer may have concerns about their ability to perform work without endangering public safety or the safety of coworkers.

HCM patients may also face unique challenges when applying for insurance, but fortunately there have been some recent regulations protecting patient's rights. Under the Affordable Care Act and beginning in 2014, it became illegal for health insurance companies to deny coverage, deny treatment or charge higher premiums based on pre-existing conditions such as HCM. Uninsured patients with a new diagnosis of HCM are therefore protected against discrimination when they go to apply for medical coverage. However, these policies do not apply to life insurance or long-term care insurance, and it is therefore legal for companies to deny these types of insurance to HCM patients or to charge them higher premiums.

The Genetic Information Non-discrimination Act (GINA), enacted in 2008, is another patient's rights legislation that has positively impacted the care of HCM patients [55]. GINA prohibits the use of genetic information in health insurance and employment, thereby barring insurance companies from using the results of genetic testing to deny health insurance or increase premiums, or to make employment decisions (e.g., hiring, firing, promoting workers). Once again, however, this legislation does not apply to life insurance or long-term care insurance, and these insurance companies are free to use genetic information in making coverage decisions. It is recommended that all patients undergoing genetic testing speak with a genetic counselor in advance to ensure that they understand these ramifications. Some patients may choose to delay testing until after they obtain life insurance. This is an important consideration when testing children of affected individuals.

Conclusions

HCM is a lifelong, chronic condition and patients have many questions about how this diagnosis impacts everyday life, including health behaviors, lifestyle factors and exercise restrictions. Some patients may be required to stop playing competitive sports or to change careers, while others may not have major changes in everyday life. However, given the multiple lifestyle aspects that must be discussed, a dedicated and frank discussion with the patient and family, often repeated over multiple visits, will be necessary in order to develop trust and partnership in their effective management.

Clinical Pearls

- Patients with resting or provocable LVOT obstruction may have post-prandial exacerbation of symptoms. When present, patients should be encouraged to drink plenty of fluids and eat smaller meals spread throughout the day.
- Recommendations on fluid intake may vary based on stage of HCM. Patients with robust contractility and LVOT gradients should be encouraged to hydrate; patients with end-stage phenotype and congestion may require strict fluid management akin to standard heart failure protocols.
- Although competitive sports and vigorous exercise should be avoided (particularly burst activities), the SCD event rate for the average HCM patients is low and moderate levels of exercise should be encouraged as a part of a healthy lifestyle. Exercising in groups or at a gym improves the chances that there is someone available to seek assistance if an event occurs.
- Most patients with ICDs (transvenous or subcutaneous) will not encounter significant electromagnetic interference in the course of daily living, but the presence of an ICD may have important implications on location or type of employment.
- Recent legislation has improved patient protections for health insurance based on pre-existing conditions or the results of genetic testing, but patients with HCM may legally be denied life or long-term care insurance. Family members should be informed of these issues prior to ECG/echo screening and genetic testing.

References

1. Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011;124(24):e783–831.
2. Maron MS, Olivotto I, Zenovich AG, et al. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. Circulation. 2006;114(21):2232–9.

3. Adams JC, Ommen SR, Klarich KW, Tajik AJ, Nishimura RA. Significance of postprandial symptom exacerbation in hypertrophic cardiomyopathy. Am J Cardiol. 2010;105(7):990–2.
4. Feiner E, Arabadjian M, Winson G, Kim B, Chaudhry F, Sherrid MV. Post-prandial upright exercise echocardiography in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2013;61(24):2487–8.
5. Kansal MM, Mookadam F, Tajik AJ. Drink more, and eat less: advice in obstructive hypertrophic cardiomyopathy. Am J Cardiol. 2010;106(9):1313–6.
6. Harris KM, Spirito P, Maron MS, et al. Prevalence, clinical profile, and significance of left ventricular remodeling in the end-stage phase of hypertrophic cardiomyopathy. Circulation. 2006;114(3): 216–25.
7. Reineck E, Rolston B, Bragg-Gresham JL, et al. Physical activity and other health behaviors in adults with hypertrophic cardiomyopathy. Am J Cardiol. 2013;111(7):1034–9.
8. Paz R, Jortner R, Tunick PA, et al. The effect of the ingestion of ethanol on obstruction of the left ventricular outflow tract in hypertrophic cardiomyopathy. N Engl J Med. 1996;335(13):938–41.
9. O'Keefe JH, Bybee KA, Lavie CJ. Alcohol and cardiovascular health: the razor-sharp double-edged sword. J Am Coll Cardiol. 2007;50(11):1009–14.
10. Kodama S, Saito K, Tanaka S, et al. Alcohol consumption and risk of atrial fibrillation: a meta-analysis. J Am Coll Cardiol. 2011;57(4): 427–36.
11. Hall W, Degenhardt L. Adverse health effects of non-medical cannabis use. Lancet. 2009;374(9698):1383–91.
12. Thomas G, Kloner RA, Rezkalla S. Adverse cardiovascular, cerebrovascular, and peripheral vascular effects of marijuana inhalation: what cardiologists need to know. Am J Cardiol. 2014;113(1): 187–90.
13. Jones RT. Cardiovascular system effects of marijuana. J Clin Pharmacol. 2002;42(11 Suppl):58S–63.
14. Gottschalk LA, Aronow WS, Prakash R. Effect of marijuana and placebo-marijuana smoking on psychological state and on psychophysiological cardiovascular functioning in anginal patients. Biol Psychiatry. 1977;12(2):255–66.
15. Mukamal KJ, Maclure M, Muller JE, Mittleman MA. An exploratory prospective study of marijuana use and mortality following acute myocardial infarction. Am Heart J. 2008;155(3):465–70.
16. Mittleman MA, Lewis RA, Maclure M, Sherwood JB, Muller JE. Triggering myocardial infarction by marijuana. Circulation. 2001;103(23):2805–9.
17. Jouanjus E, Lapeyre-Mestre M, Micallef J, French Association of the Regional Abuse, Dependence Monitoring Centres Working Group on Cannabis Complications. Cannabis use: signal of increasing risk of serious cardiovascular disorders. J Am Heart Assoc. 2014;3(2):e000638.
18. Bachs L, Morland H. Acute cardiovascular fatalities following cannabis use. Forensic Sci Int. 2001;124(2–3):200–3.
19. Charbonney E, Sztajzel JM, Poletti PA, Rutschmann O. Paroxysmal atrial fibrillation after recreational marijuana smoking: another "holiday heart"? Swiss Med Wkly. 2005;135(27–28):412–4.
20. Korantzopoulos P, Liu T, Papaioannides D, Li G, Goudevenos JA. Atrial fibrillation and marijuana smoking. Int J Clin Pract. 2008;62(2):308–13.
21. Soukoulis V, Dihu JB, Sole M, et al. Micronutrient deficiencies an unmet need in heart failure. J Am Coll Cardiol. 2009;54(18): 1660–73.
22. Olivotto I, Maron BJ, Tomberli B, et al. Obesity and its association to phenotype and clinical course in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2013;62(5):449–57.
23. Canepa M, Sorensen LL, Pozios I, et al. Comparison of clinical presentation, left ventricular morphology, hemodynamics, and exercise tolerance in obese versus nonobese patients with hypertrophic cardiomyopathy. Am J Cardiol. 2013;112(8):1182–9.
24. Ommen SR, Lopez-Jimenez F. Obesity and hypertrophic cardiomyopathy: chickens, eggs, and causality: clinical skills remain the key to caring for patients. J Am Coll Cardiol. 2013; 62(5):458–9.
25. Sorajja P, Ommen SR, Nishimura RA, Gersh BJ, Berger PB, Tajik AJ. Adverse prognosis of patients with hypertrophic cardiomyopathy who have epicardial coronary artery disease. Circulation. 2003;108(19):2342–8.
26. Argulian E, Messerli FH, Aziz EF, et al. Antihypertensive therapy in hypertrophic cardiomyopathy. Am J Cardiol. 2013;111(7): 1040–5.
27. Pedrosa RP, Drager LF, Genta PR, et al. Obstructive sleep apnea is common and independently associated with atrial fibrillation in patients with hypertrophic cardiomyopathy. Chest. 2010;137(5): 1078–84.
28. Eleid MF, Konecny T, Orban M, et al. High prevalence of abnormal nocturnal oximetry in patients with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2009;54(19):1805–9.
29. Maron BJ, Zipes DP. 36th Bethesda Conference: eligibility recommendations for competitive athletes with cardiovascular abnormalities-general considerations. J Am Coll Cardiol. 2005;45(8):2–64.
30. Pelliccia A, Fagard R, Bjornstad HH, et al. Recommendations for competitive sports participation in athletes with cardiovascular disease: a consensus document from the Study Group of Sports Cardiology of the Working Group of Cardiac Rehabilitation and Exercise Physiology and the Working Group of Myocardial and Pericardial Diseases of the European Society of Cardiology. Eur Heart J. 2005;26(14):1422–45.
31. Mitchell JH, Haskell WL, Raven PB. Classification of sports. J Am Coll Cardiol. 1994;24(4):864–6.
32. Pelliccia A, Zipes DP, Maron BJ. Bethesda Conference #36 and the European Society of Cardiology Consensus Recommendations revisited a comparison of U.S. and European criteria for eligibility and disqualification of competitive athletes with cardiovascular abnormalities. J Am Coll Cardiol. 2008;52(24):1990–6.
33. Thompson PD, Franklin BA, Balady GJ, et al. Exercise and acute cardiovascular events placing the risks into perspective: a scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism and the Council on Clinical Cardiology. Circulation. 2007;115(17):2358–68.
34. Maron BJ, Chaitman BR, Ackerman MJ, et al. Recommendations for physical activity and recreational sports participation for young patients with genetic cardiovascular diseases. Circulation. 2004;109(22):2807–16.
35. Levine GN, Steinke EE, Bakaeen FG, et al. Sexual activity and cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2012;125(8):1058–72.
36. Stauffer JC, Ruiz V, Morard JD. Subaortic obstruction after sildenafil in a patient with hypertrophic cardiomyopathy. N Engl J Med. 1999;341(9):700–1.
37. Awan GM, Calderon E, Dawood G, Alpert MA. Acute, symptomatic atrial fibrillation after sildenafil citrate therapy in a patient with hypertrophic obstructive cardiomyopathy. Am J Med Sci. 2000; 320(1):69–71.
38. Krul SP, van der Smagt JJ, van den Berg MP, Sollie KM, Pieper PG, van Spaendonck-Zwarts KY. Systematic review of pregnancy in women with inherited cardiomyopathies. Eur J Heart Fail. 2011;13(6):584–94.
39. Stergiopoulos K, Shiang E, Bench T. Pregnancy in patients with preexisting cardiomyopathies. J Am Coll Cardiol. 2011;58(4):337–50.
40. Bulletins-Gynecology ACoP. ACOG practice bulletin. No. 73: use of hormonal contraception in women with coexisting medical conditions. Obstet Gynecol. 2006;107(6):1453–72.
41. Silversides CK, Sermer M, Siu SC. Choosing the best contraceptive method for the adult with congenital heart disease. Curr Cardiol Rep. 2009;11(4):298–305.

42. Pinski SL, Trohman RG. Interference in implanted cardiac devices, Part I. Pacing Clin Electrophysiol. 2002;25(9):1367–81.
43. Fetter JG, Ivans V, Benditt DG, Collins J. Digital cellular telephone interaction with implantable cardioverter-defibrillators. J Am Coll Cardiol. 1998;31(3):623–8.
44. Hayes DL, Carrillo RG, Findlay GK, Embrey M. State of the science: pacemaker and defibrillator interference from wireless communication devices. Pacing Clin Electrophysiol. 1996;19(10):1419–30.
45. Jilek C, Tzeis S, Vrazic H, et al. Safety of screening procedures with hand-held metal detectors among patients with implanted cardiac rhythm devices: a cross-sectional analysis. Ann Intern Med. 2011;155(9):587–92.
46. Fetter JG, Benditt DG, Stanton MS. Electromagnetic interference from welding and motors on implantable cardioverter-defibrillators as tested in the electrically hostile work site. J Am Coll Cardiol. 1996;28(2):423–7.
47. Epstein AE, Baessler CA, Curtis AB, et al. Addendum to "Personal and public safety issues related to arrhythmias that may affect consciousness: implications for regulation and physician recommendations: a medical/scientific statement from the American Heart Association and the North American Society of Pacing and Electrophysiology": public safety issues in patients with implantable defibrillators: a scientific statement from the American Heart Association and the Heart Rhythm Society. Circulation. 2007;115(9):1170–6.
48. Epstein AE, Miles WM, Benditt DG, et al. Personal and public safety issues related to arrhythmias that may affect consciousness: implications for regulation and physician recommendations. A medical/scientific statement from the American Heart Association and the North American Society of Pacing and Electrophysiology. Circulation. 1996;94(5):1147–66.
49. Maron BJ, Shen WK, Link MS, et al. Efficacy of implantable cardioverter-defibrillators for the prevention of sudden death in patients with hypertrophic cardiomyopathy. N Engl J Med. 2000;342(6):365–73.
50. Lampert R, Olshansky B, Heidbuchel H, et al. Safety of sports for athletes with implantable cardioverter-defibrillators: results of a prospective, multinational registry. Circulation. 2013;127(20):2021–30.
51. Administration FA, Guide for aviation medical examiners. 2014. http://www.faa.gov/about/office_org/headquarters_offices/avs/offices/aam/ame/guide.pdf
52. Maron BJ, Barry JA, Poole RS. Pilots, hypertrophic cardiomyopathy, and issues of aviation and public safety. Am J Cardiol. 2004;93(4):441–4.
53. U.S. Department of Transportation, Administration FMCS. Medical examiner handbook. 2014. http://nrcme.fmcsa.dot.gov/documents/FMCSAMedicalExaminerHandbook-2014MAR18.pdf
54. U.S. Department of Defense, Directive 6130.03: Medical standards for appointment, enlistment, or induction in the military services. 2011. http://www.dtic.mil/whs/directives/corres/pdf/613003p.pdf
55. Hudson KL, Holohan MK, Collins FS. Keeping pace with the times–the Genetic Information Nondiscrimination Act of 2008. N Engl J Med. 2008;358(25):2661–3.

Family Screening: Who, When and How

13

Michelle Michels and Folkert J. ten Cate

Abstract

Hypertrophic cardiomyopathy (HCM) is an autosomal dominant familial cardiac disease. The most devastating presentation of HCM is SCD in a presumed healthy person. The goals of family screening are to identify relatives with unrecognized HCM and to follow at-risk individuals for risk factors of SCD and disease development.

After confirmation of the HCM diagnosis, the patient is informed about the familial character of the disease, the high potential for familial transmission and the possibility to perform genetic testing. Currently the power of genetic testing in HCM lies in identifying family members carrying the genotype (G+) who are at risk for developing disease and excluding unaffected, genotype negative relatives for further cardiac evaluation.

In specialized cardio-genetic outpatient clinics familial and genetic counseling is performed in close collaboration between the cardiologist and the clinical geneticist. Family members at risk are identified and first-degree relatives are informed either via the patient or via direct communication. It is important that ramifications of genetic and/or cardiac testing, especially with regards to health and life insurance, are explained to the family members prior to analysis.

G+ family members and family members of HCM families in which no pathogenic mutation is found are offered longitudinal cardiac evaluation by electrocardiogram and echocardiogram with variable intervals.

Keywords

Hypertrophic cardiomyopathy • Familial screening • Genetic counseling • Genetic testing • Electrocardiogram • Echocardiogram

Key Points

- Hypertrophic cardiomyopathy (HCM) is an autosomal dominant disease.
- HCM has an age-related variable penetrance; cardiac analysis has to be repeated over time.
- Only truly pathogenic mutations can be used for predictive testing in family members.
- The clinical screenings algorithm consists of an ECG and TTE at regular intervals.
- Cardiac events are virtually absent in G+/LVH– subjects with normal ECG.

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Introduction

For over 50 years, hypertrophic cardiomyopathy (HCM) has been recognized as an autosomal dominant familial cardiac disease, with a risk for sudden cardiac death (SCD) and progression to end-stage disease [1]. With HCM being a familial disease, family screening is important to identify those with unrecognized disease. According to the most recent clinical guideline on HCM, clinical screening, with or without genetic testing is recommended in first-degree relatives of HCM patients (Class I, level of evidence B) [2]. In this chapter we will focus on the importance of family screening, the genetic – and clinical – aspects of family screening and provide practical tips for the organization of family screening in HCM.

The Importance of Family Screening

The most devastating presentation of HCM is SCD in a previously asymptomatic and presumed healthy person. HCM is accountable for a significant portion of SCD cases, especially in young persons [3]. Since it is an autosomal dominant disease first-degree family members of a HCM patient have a 50 % chance of inheritance of the disease. Once the diagnosis of HCM is made SCD risk can be modified by lifestyle adjustments (especially cessation of intensive physical activity), and by prescription of high doses of beta-blockers in children [4–6]. At adult age medication does not protect against SCD, but the implantation of an implantable cardioverter defibrillator can protect against SCD in high-risk patients [7].

The goals of family screening are therefore to identify relatives with unrecognized HCM and to follow at-risk individuals for risk factors of SCD and disease development. Family screening also helps build awareness of the various phenotypes within a given family, and the likelihood that multiple family members may be affected despite the lack of overt symptoms.

General Aspects of Family Screening

Proband

Family screening in HCM always starts with the correct clinical diagnosis of HCM (phenotype) in the proband (the first person of a family presenting with HCM); other causes of left ventricular hypertrophy (LVH), like aortic valve stenosis, hypertension or storage diseases should be excluded. After confirmation of the diagnosis, the HCM patient should be informed about the familial character of the disease, the high potential for familial transmission and the possibility to perform genetic testing. During genetic counseling attention should be given to the risks and possible benefits of genetic testing [2, 8].

In specialized cardio-genetic outpatient clinics this familial and genetic counseling is performed in close collaboration between the cardiologist and the clinical geneticist. The flow chart used at the cardio-genetic outpatient clinic of the Erasmus MC, Rotterdam, the Netherlands is provided in Fig. 13.1.

The Role of the Clinical Geneticist/Genetic Counselor

The cardiac genetic counselor gives information about inheritance risk, provides pre-and post test counseling, investigates and confirms family history by retrieving medical information of family members with possible HCM (i.e. family members with SCD or heart failure) from general practitioners, cardiologists and/or pathologists, and discusses worries and fears about the HCM diagnosis. During genetic counseling family members at risk are identified and first-degree relatives, those sharing 50 % of genetic material with the proband, are selected for further analysis. In most cases these first-degree family members are provided with information on HCM through a letter provided to them via the proband (indirect cascade screening) or via direct communication. In the UK and the Netherlands direct medical contact, with consent of the proband, has been used for screening of familial hypercholesterolemia. Although family members accept this approach, a more recent study shows that family members prefer indirect cascade screening [9, 10]. Genetic counselors assist in determining the best method of contacting family members, who also may be at some distance or reluctant to learn more.

Genetic Testing of the Proband

After counseling and consent, blood is drawn for DNA analysis. For the proband the potential medical, physiological, financial and familial implications of genetic testing are minimal, as all these consequences are determined by the phenotype which is already documented. Since the costs of genetic testing are only covered by general health insurance in some countries (i.e. the Netherlands), in other countries reimbursement of costs may be a problem and may lead to a limited access to genetic testing.

Currently not all genes causing HCM have been identified and the likelihood of obtaining a positive genetic test in a proband is about 50–60 %. The chance of finding a pathogenic mutation significantly increases in HCM patients with a family history of HCM [11]. The relatively low percentage

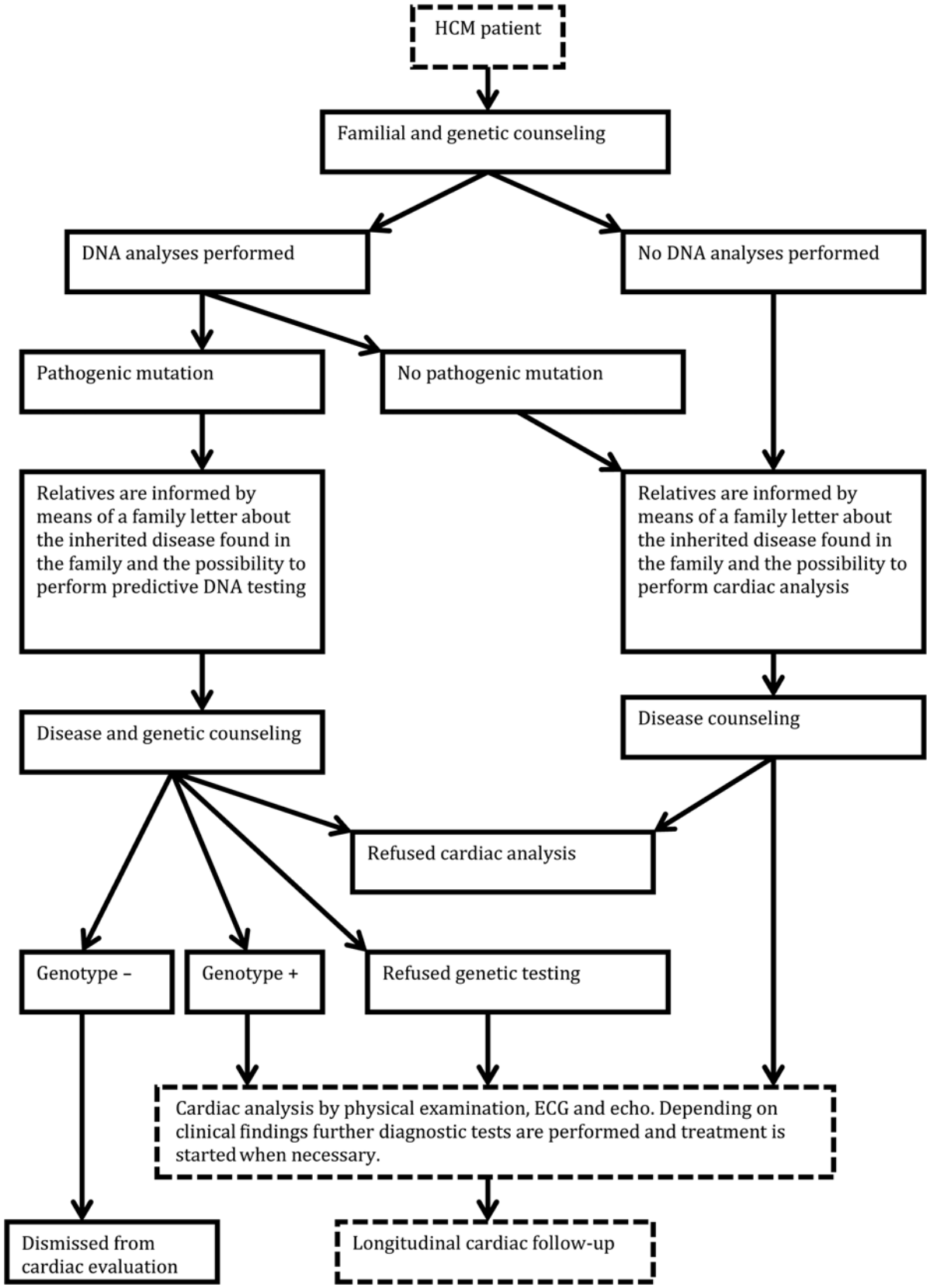

Fig. 13.1 Flowchart used at cardio-genetic outpatient clinic at the Erasmus MC, Rotterdam, the Netherlands. *Dashed boxes* are taking care of by the cardiologist; solid line boxes are taking care of by the clinical geneticist or genetic counselor (*HCM* hypertrophic cardiomyopathy, *ECG* electrocardiogram, *echo* echocardiogram)

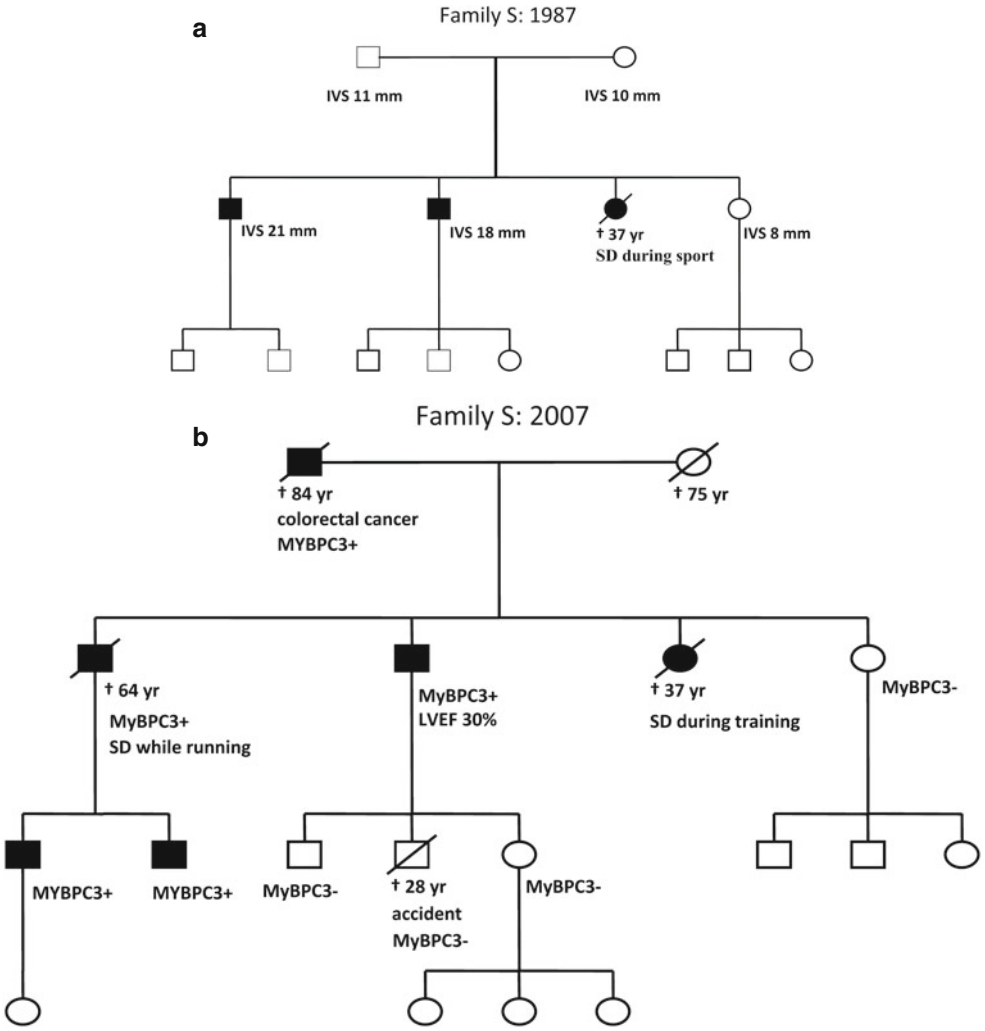

Fig. 13.2 (**a**) Pedigree of a hypertrophic cardiomyopathy (HCM) family at presentation in 1987. The proband presented after resuscitation for ventricular fibrillation, she died of severe neurological damage. Her first-degree relatives underwent cardiac evaluation by electrocardiogram and echocardiogram. Her two elderly brothers had HCM; her parents and younger sister had no signs of HCM. (**b**) Same HCM pedigree drawn in 2007. Genetic testing revealed a pathogenic mutation in myosin binding protein C, after which predictive genetic testing was offered to family members. The father was G+/LVH− and died of colorectal cancer. The eldest brother experienced SCD during running; both his sons are G+/LVH−. The other brother developed end-stage HCM; his three children are genotype negative and dismissed from follow-up. The youngest sister is also reassured, since she is genotype negative

of HCM families in which a mutation is found, and the fact that only truly pathogenic mutations can be used for predictive testing in family members, excludes a reasonable portion of the HCM families to be screened with genetic testing [8, 12]. Recent data from population-based exome data are questioning the pathogenicity of previously HCM-associated genetic variants. This reclassification of mutations in HCM patients might lead to misdiagnosis of family members and this could have potentially devastating clinical consequences. It is therefore crucial that variants being reported as causative of HCM are truly disease causing [13]. The complexity of interpreting genetic test results further warrants close collaboration with clinical geneticists.

Predictive Genetic Testing in Family Members at Risk for HCM

Currently, the power of HCM mutational analysis lies most prominently in identifying family members carrying the genotype (G+) who are at risk for developing disease and excluding unaffected, genotype negative (G-) relatives of further cardiac evaluation; this is information not achievable otherwise. In Fig. 13.2a, b, a 20-year follow-up of an HCM family is described, in which the advantages of genetic testing are made clear. Predictive genetic testing provides a cost-effective and definitive means of family screening as longitudinal evaluation can be focused on G+ family members because only they are at risk for disease development [14]. Therefore, and according to the ACCF/AHA guidelines, genetic testing, preceded by genetic counseling, is reasonable (class IIa) to facilitate the identification of at-risk family members [2]. G+ family members should subsequently undergo cardiac testing to determine if the HCM phenotype (presence of LVH) is present. In HCM the prognosis, risk of SCD and treatment are currently determined by the phenotype, not the genotype.

Predictive genetic testing can only be offered in HCM families in which a truly pathogenic mutation is identified. In other families, family screening should be offered by cardiac testing of first-degree relatives [2, 8]. It is essential that family members be counseled about the potential med-

ical, physiological, financial and familial implications of genetic and cardiac test results to enable informed decision-making about potential risks and benefits before blood is drawn. If a pathogenic mutation is identified in a family member, this may lead to consequences for employment and insurances, especially life-and long term care insurances. As much of this testing is performed on a young, asymptomatic population, these concerns are indeed real and must be discussed at length prior to proceeding. The legal implications of genetic testing are dependent on the country of residence; in the United States the Genetic Information Non-Discrimination Act (GINA), a federal law, prohibits denying or terminating of health insurance, employment or promotion solely on the presence of a mutation or a family history of genetic disease. However, GINA does not protect against discrimination for disability, life, or long-term care insurance, or when there is a documented medical condition [15]. In most European countries the presence of a pathogenic mutation may lead to problems in getting disability and life insurances.

Identifying a G+ family member will also lead to extension of the family screening, as the first degree relatives of the newly diagnosed genotype positive (G+) subject will be offered genetic testing (so-called cascade screening). This has far-reaching implications to the family as a whole, and may allow screening to cross borders including distant countries.

Predictive Genetic Testing in Children

Whether or not to offer predictive genetic testing to children is subject to debate; there may be good reason to defer testing, including to enhance the opportunity of the child to participate in the discussion. However, it is likely that young children are not fully able to comprehend the implications of genetic testing. With the current lack of prognostic value of a pathogenic mutation on disease development and risk, and the possible negative consequences of predictive testing, we are reticent to perform predictive genetic testing routinely in children. An argument in favor of genetic testing of children lies in the fact that knowing that the young child is at risk can be beneficial for advocating and encouraging alternative pastimes [16]. This however can also lead to unnecessary stigmatization and unfounded withdrawal from competitive sports, since cardiovascular events in G+/LVH− subjects are virtually absent. A recent study focusing on follow-up of G+/LVH− children found a very low conversion rate to G+/LVH+ of 6 % in a follow-up period of 12 years; children were in their twenties when HCM was diagnosed and there were no cardiovascular events in G+/LVH− children [17]. Currently, our HCM program makes decisions on a case-by-case basis after extensive counseling of the family and the child, including psychological support and taking all the above considerations into account.

Family Planning in HCM Families

Special attention should be paid to HCM patients and G+/LVH− family members with questions about family planning regarding the risk of transmission of the disease to their offspring. These aspects should be part of the genetic counseling in subjects in the reproductive age, both male and female. When the underlying mutation is known, prenatal screening or pre-implantation genetic testing is theoretical possible. These are not routinely performed due to the variable disease expression, the fact that disease manifestation usually occurs later in life, the fact that there are treatment options available, and the fact that longevity is maintained in these patients when viewed as a group [18].

In both children and adults who have been counseled before they underwent genetic or cardiac testing in screening for HCM, no psychological harm or negative effect on quality of life has been observed [19, 20]. Long-term impact on quality of life however requires further research.

Cardiac Evaluation in Family Screening for HCM

Cardiac evaluation should be offered to family members of HCM families in which no pathogenic mutation is found, G+ family members identified during predictive genetic testing and in family members refusing predictive genetic testing. In addition, in cases where the proband has died, and no gene testing was performed, cardiac evaluation is oftentimes the only remaining screening modality prior to the identification of a new proband within the family. It is important that counseling is provided to family members before they undergo cardiac evaluation, since the possible consequences as described before for genetic testing remain for clinical testing.

Because the expression of LVH is highly age dependent, overt cardiac hypertrophy often does not emerge until late adolescence or beyond; guidelines therefore recommend longitudinal screening with variable intervals according to age (Table 13.1). G+/LVH− subjects and family members with unknown genetic status should be evaluated clinically and by electrocardiogram (ECG) and transthoracic echocardiogram (TTE) at period intervals of 12–18 months in asymptomatic children and adolescents and about every 5 years in asymptomatic adults (Table 13.1).

Although the current guidelines advise to start with cardiac evaluation at the age of 12 years, recent data has shown that sarcomere protein gene mutation account for over 50 % of HCM cases in children once other causes are excluded and

Table 13.1 Proposed clinical screening strategies in family members of HCM patients

Age (years)	History, clinical examination, ECG and echo
<8–12	Optional unless: Malignant family history Competitive athlete Symptoms or signs of possible LVH
12 to 18–21	Every 12–18 months
>18–21	At least every 5 years

Based on current guideline by Gersh et al. [2]
ECG electrocardiogram, *echo* echocardiogram, *LVH* left ventricular hypertrophy

that the SCD risk increases after the age of 8 years. If you take these data into account it is reasonable to start cardiac screening earlier, roughly at the time when the child shows signs of puberty. This is especially the case if there is a malignant family history, if the child is a competitive athlete or when there are other signs or symptoms of early HCM [2, 16, 21].

Electrocardiogram

The ECG is abnormal in the vast majority (75–95 %) of HCM patients [22, 23]. Abnormalities mainly consist of Q waves, repolarization abnormalities and isolated voltage criteria for LVH or LAE and can be present before there is hypertrophy on echocardiography [24]. The severity of ECG abnormalities is directly related to both the degree of hypertrophy and the prevalence of fibrosis expressed as late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (CMR) [22]. The ECG is therefore recommended as a screening tool to raise the suspicion of HCM in family members of HCM patients [2].

In a recent study the presence of Q-waves and/or repolarization abnormalities were highly specific (98 %) for the presence of a sarcomeric mutation in family members without LVH; unfortunately ECG abnormalities had a low sensitivity (25 %) and therefore a normal ECG is non-informative and does not reliably indicate the absence of a sarcomeric mutation [25]. A normal ECG however excludes severe phenotypic expression of HCM [22].

Echocardiogram

The diagnosis of HCM is conventionally made by cardiac imaging, with at present transthoracic echocardiography (TTE) most often used. A combination of ECG and TTE are recommended as a clinical screening algorithm in family members of HCM patients [2].

The diagnosis of HCM is typically made when the LV thickness is ≥15 mm; in affected family members with HCM the degree of hypertrophy may be below this diagnostic threshold and different criteria combining ECG and echo data have been proposed to diagnose HCM in 50 % risk carriers. Although HCM is predominantly characterized by the presence of hypertrophy other features, like mitral valve or papillary muscle abnormalities or diastolic dysfunction have been described. Presence of these features in 50 % risk carriers should raise the suspicion of an early manifestation of HCM [26].

Especially in patients with suboptimal echo windows TTE can fail to identify focal areas of myocardial hypertrophy, mainly at the inferoseptum, apex, or free wall of the left – or right – ventricle. In these patients other imaging techniques like CMR should be performed [27].

In animal models of HCM it has been shown that diastolic dysfunction can precede the development of HCM [28]. Tissue Doppler Imaging studies in humans revealed differences in different mitral annular velocities; decreased Sm and Em velocities have been described and one study found increased Am velocities [29–31]. Because of the discrepancies seen in the tissue Doppler Imaging and speckle tracking echocardiography in G+/LVH− subjects, the identification of G+/LVH− family members with echocardiography remains challenging. However, as alluded to above, the presence of diastolic dysfunction in the absence of overt LVH that meets anatomic criteria for HCM may be a sign of preclinical disease.

Cardiac Magnetic Resonance

Although the current clinical guidelines do not mention CMR in the screening algorithm for family members of HCM patients, it can be a useful adjunct in HCM family screening in selected patients. With CMR the wall thickness of any segment of the ventricle can be accurately assessed and the use of gadolinium contrast allows tissue characterization, including scar burden. In a recent paper by Valente et al. the diagnostic agreement between echo and CMR was 90 %; however CMR detected mild hypertrophy in 10 % of patients, which was missed by echocardiography [32].

CMR studies in G+/LVH− subjects revealed the presence of myocardial crypts, mitral valve abnormalities and diastolic abnormalities [33, 34]. Myocardial crypts occur particularly in the septum and inferior (posterior) right ventricular insertion point [35]. These crypts are present in a subset of the G+/LVH− subjects and their presence may be a prephenotypic marker of HCM; however their prognostic value needs to be determined [36].

The presence of LGE is extremely rare in G+/LVH− subjects. However, G+/LVH− subjects with LGE on CMR have been described; unfortunately no data on ECG were given in these patients [37]. The presence of an abnormal ECG may

raise the suspicion of missed areas of focal hypertrophy or the presence of LGE. The latter is especially important, since sporadic cases of SCD have been described in G+/LVH− patients [38]. In the described patients the ECG was abnormal, suggesting myocardial abnormalities. LGE is associated with increased risk of heart failure and recently special attention has been given to the extent of LGE as a possible risk factor for SCD and end-stage disease (systolic dysfunction) [39, 40].

Accordingly, CMR may especially be useful if echocardiographic images are suboptimal or suggest borderline LVH; if there are unexplained ECG abnormalities or in the case of high risk situations i.e. high familial prevalence of SCD or G+/LVH− subjects engaging in competitive sports. Subtle findings on CMR may indicate a likely diagnosis of HCM, and prompt more frequent monitoring, lifestyle modification or even solidify a diagnosis through the confluence of evidence, with resultant clinical implications.

Genotype-Positive/Phenotype-Negative Subjects

The penetration of genetic testing in clinical practice has revealed a new subset within the HCM spectrum; the G+/LVH− family members. Although this subset is very important for improving our understanding of how mutations cause disease, the identification of these individuals also leads to clinical decision-making dilemmas. The reported risk of adverse cardiac events in G+/LVH− is very low, and in the largest study thus fare no SCD occurred in mutation carriers without hypertrophy [41].

The precise proportion of the G+/LVH− subjects that will develop overt disease, and when, is still uncertain; this is due to the relatively short period of time that genetic testing has been available in clinical practice, with consequent limited follow-up duration. Disease progression is increasing with age, but seems to be slow, both in children and adults [17, 31]. The family described in Fig. 13.2 shows that HCM can be absent until very advanced age.

The current guidelines recommend the intervals for cardiac evaluation as described above [2, 42]. In G+/LVH− subjects with a family history indicating a high SCD risk periodic assessment of arrhythmias, by exercise testing and/or Holter monitoring may be appropriate. Until accurate penetrance data are available it is prudent to extend standard HCM surveillance with cardiac imaging at least through midlife, but perhaps even for the entirety of life.

Diastolic dysfunction, increased collagen synthesis, impaired energetics, expanded myocardial extracellular volume, myocardial crypts and mitral valve abnormalities have been described in G+/LVH− subjects. These features are very interesting for further unraveling pathophysiology, however their clinical relevance is still unclear [29–34, 43].

Whether or not G+/LVH− subjects should be excluded from sports is subject to debate. While the Bethesda Conference #36 consensus recommendations do not exclude G+/LVH− subjects from sports, the European recommendations do advice to exclude these subjects [44, 45]. Based on the current literature describing the virtual absence of any cardiovascular events in G+/LVH- subjects and the absence of robust disease penetrance data, our HCM program usually allows G+/LVH− subjects to enroll in competitive sport activities but keeps them under close clinical surveillance with cardiac evaluations every year.

Future Perspectives

The introduction of next generation genetic testing with the possibility to test a large number of genes at one time and the possibility of whole exome sequencing, will most likely lead to an increased number of pathogenic mutations identified. This will enable predictive testing in a larger portion of the families. It will however also lead to even more complex genetic information to interpret.

Current guidelines suggest a “one size fits all” approach to longitudinal cardiac follow up for all unaffected family members, both G+ and those with unknown genetic status, regardless of family history. Further studies should aim at developing a more “tailor-made” approach, with intervals possibly based on the presence of pre-phenotypic markers of HCM, confirmed genetic status and family history. The diagnostic algorithm, now consisting of ECG and echo in all family members, most likely can also be adjusted to specific situations. Questions of whether or not it is safe to screen family members with ECG alone, as well as if and when to perform CMR, exercise testing and Holter monitoring should be answered; i.e. the recent study by Jensen et al. does not support the current guidelines regarding the short interval of performing serial cardiac evaluation in children [18].

Longitudinal follow-up studies of G+/LVH− subjects are necessary to get robust data on disease penetration, the prognostic value of pre-phenotypic signs and the risks in these subjects. By studying this subset we will hopefully be able to unravel the pathophysiology of disease development to the level that drugs to prevent disease development can be developed.

Conclusions

Family screening in HCM is important since HCM is an autosomal dominant disease and SCD can be the first presentation. In both children and adults who have been counseled before they underwent genetic or cardiac testing in screening for HCM, no psychological harm or negative effect on quality of life has been observed [19, 20]. It is important to realize that only truly pathogenic

mutations can be used for predictive testing. Challenges of interpretation of genetic results are real and require careful review, best done in the setting of a multidisciplinary approach to care. When gene testing is not available, or refused, serial cardiac evaluations of family members is the next best approach, and likely should continue for the lifetime of all family members. G+/LVH− subjects are very interesting for research to unravel the pathophysiology of disease development, but the prognostic relevance of so-called signs of pre-phenotypic HCM, especially those found by CMR, remain unclear.

Clinical Pearls

- Disease development in G+/LVH− subjects is slow, and may reflect the phenotypic variability of this disease even within a given family.
- G+/LVH− subjects should not routinely be denied to enroll in competitive sports, but a CMR to fully exclude the phenotype may be reasonable.
- Ramifications of gene testing, especially with regards to health and life insurance, must be explained to the patient prior to drawing blood for analysis.
- Clinical presentation and treatment in HCM are based on the phenotype, not on the genotype.
- Enabling affected family members to reach the remainder of their family, for example by use of standardized letters describing the disease, inheritance pattern, and benefits of screening, is oftentimes helpful in raising awareness of HCM and identifying at-risk individuals.

References

1. Hollman A, Goodwin JF, Teare D, Renwick JW. A family with obstructive cardiomyopathy (asymmetrical hypertrophy). Br Heart J. 1960;22:449–56.
2. Gersh BJ, Maron BJ, Bonow RO, Dearini JA, Fifer MA, Link MS, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hyperthrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2011;25:e212–60.
3. Maron BJ. Sudden death in young athletes. N Engl J Med. 2003; 349:1064–75.
4. Corrado D, Basso C, Schiavon M, Thiene G. Screening for hypertrophic cardiomyopathy in young athletes. N Engl J Med. 1998; 339:364–9.
5. Corrada D, Pelliccia A, Bjornstad HH, Vanhees L, Biffi A, Borjesson M, et al. Cradiovascular pre-participation screening of young competitive athletes for prevention of sudden cardiac death: proposal for a common European protocol. Eur Heart J. 2005;26:516–24.
6. Bjornstad H, Corrado D, Pelliccia A. Prevention of sudden death in young athletes: a milestone in the history of sports cardiology. Eur J Cardiovasc Prev Rehabil. 2006;13:857–8.
7. Schinkel AF, Vriesendorp PA, Sijbrands EJ, Jordaens LJ, ten Cate FJ, Michels M. Outcome and complications after implantable cardioverter defibrillator therapy in hypertrophic cardiomyopathy: systematic review and meta-analysis. Circ Heart Fail. 2012;5:552–9.
8. Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. Heart Rhythm. 2011;8:1308–39.
9. Andreasen C, Nielsen JB, Refsgaard L, Holst AG, Christensen AH, Andreasen L, et al. New population-based exome data are questioning the pathogenicity of previously cardiomyopathy-associated genetic variants. Eur J Hum Genet. 2013;21:918–28.
10. Van Maarle MC, Stouthard ME, Marang-van de Meen PJ, Klazinga NS, Bonsel GJ. How disturbing it is to be approached for a genetic cascade screening programme for familial hypercholesteremia? Community Genet. 2001;4:244–52.
11. Ingles J, Sarina T, Yeates L, Hunt L, Macciocca I, McCormack L, et al. Clinical predictors of genetic testing outcomes in hypertrophic cardiomyopathy. Genet Med. 2013;15:972–7.
12. Maron BJ, Maron MS, Semsarian C. Genetics of hypertrophic cardiomyopathy after 20 years. J Am Coll Cardiol. 2012;60:705–15.
13. Hallowell N, Jenkins N, Douglas M, Walker S, Porteous M, et al. Patients' experiences and views of cascade screening for familial hypercholesterolemia (FH): a qualitative study. J Community Genet. 2011;2:249–57.
14. Wordsworth S, Leal J, Blair E, Legood R, Thomson K, Seller A. DNA testing for hypertrophic cardiomyopathy: a cost-effectiveness model. Eur Heart J. 2010;31:926–35.
15. Abiola S. Recent developments in health law. The Genetic Information Nondiscrimination Act of 2008. J Law Med Ethics. 2008;36:856–60.
16. Jensen MK, Havndrup O, Christiaensen M, Andersen PS, Diness B, Axelsson A, et al. Penetrance of hypertrophic cardiomyopathy in children and adolescents. Circulation. 2013;127:48–54.
17. Ormondroyd E, Oates S, Parker M, Blair E, Watkins H. Presymptomatic genetic testing for inherited cardiac conditions: a qualitative exploration of psychological and ethical implications. Eur J Hum Genet. 2014;22:88–93.
18. Krul SPJ, van der Smagt JJ, van de Berg MP, Sollie KM, Pieper PG, van Spaendonck-Zwarts KY. Systematic review of pregnancy in women with inherited cardiomyopathies. Eur J Heart Fail. 2011;13: 584–94.
19. Bratt EL, Ostman-Smith I, Axelsson A, Berntsson L. Quality of life in asymptomatic children and adolescents before and after diagnosis of hypertrophic cardiomyopathy through family screening. J Clin Nurs. 2012;22:211–2.
20. Christiaans I, van Langen IM, Birnie E, Bonsel GJ, Wilde AA, Smets EM. Quality of life and psychological distress in hypertrophic cardiomyopathy. Am J Med Genet. 2009;149A:602–12.
21. Moak JP, Kaski JP. Hypertrophic cardiomyopathy in children. Heart. 2012;98:1044–54.
22. Delcrè SDL, DiDonna P, Leuzzi S, Miceli S, Bisi M, Scaglione M, et al. Relationship of ECG findings to phenotypic expression in patients with hypertrophic cardiomyopathy: a cardiac magnetic resonance study. Int J Cardiol. 2013;167:1038–45.
23. Maron BJ. The electrocardiogram as a diagnostic tool for hypertrophic cardiomyopathy: revisited. Ann Noninvasive Electrocardiol. 2001;6:277–9.
24. Ryan MP, Cleland JG, French JA, Joshi J, Choudhury L, Chojnowska L. The standard electrocardiogram as a screening test for hypertrophic cardiomyopathy. Am J Cardiol. 1995;76:689–94.
25. Lakdawala NK, Thune JJ, Maron BJ, Cirino AL, Havndrup O, Bundgaard H, et al. Electrocardiographic features of sarcomere mutation carriers with and without clinically overt hypertrophic cardiomyopathy. Am J Cardiol. 2011;108:1606–13.
26. McKenna WJ, Spirito P, Desnos M, Dubourg O, Komajda M. Experience form clinical genetics in hypertrophic cardiomyopathy:

proposal for new diagnostic criteria in adult members of affected families. Heart. 1997;77:130–2.
27. Eriksson MJ, Sonnenberg B, Woo A, Rakowski P, Parker TG, Wigle D, et al. Long-term outcome in patients with apical hypertrophic cardiomyopathy. J Am Coll Cardiol. 2002;39:638–45.
28. Spindler M, Saupe KW, Christe ME, Sweeney HL, Seidman CE, Seidman JG, et al. Diastolic dysfunction and altered energetics in the alphaMHC403/+mouse model of familial hypertrophic cardiomyopathy. J Clin Invest. 1998;101:1775–83.
29. Nagueh SF, Bachinski LL, Meyer D, Hill R, Zoghbi WA, Tam JW, et al. Tissue Doppler imaging consistently detects myocardial abnormalities in patients with hypertrophic cardiomyopathy and provides novel means for an early diagnosis before and independently of hypertrophy. Circulation. 2001;104:128–30.
30. Ho CY, Sweitzer NK, McDonough B, Maron BJ, Casey SA, Seidman JG, et al. Assessment of diastolic function with Doppler tissue imaging to predict genotype in preclinical hypertrophic cardiomyopathy. Circulation. 2002;105:2992–7.
31. Michels M, Soliman OI, Kofflard MJ, Hoedemaekers YM, Dooijes D, Majoor-Krakauer D, et al. Diastolic abnormalities as the first feature of hypertrophic cardiomyopathy in Dutch myosin-binding protein C founder mutations. JACC Cardiovasc Imaging. 2009;2:58–64.
32. Valente AM, Lakdawala NK, Powell AJ, Evans SP, Cirino MS, Orav EJ, et al. Comparison of echocardiographic and cardiac magnetic resonance imaging in hypertrophic cardiomyopathy sarcomere mutation carriers without left ventricular hypertrophy. Circ Cardiovasc Genet. 2013;6:230–7.
33. Harrigan CJ, Appelbaum E, Maron BJ, Buros JL, Gibson CM, Lesser JR, et al. Significance of papillary muscle abnormalities identified by cardiovascular magnetic resonance in hypertrophic cardiomyopathy. Am J Cardiol. 2008;101:668–73.
34. Maron MS, Olivotto I, Harrigan C, Appelbaum E, Gibson CM, Lesser JR, et al. Mitral valve abnormalities identified by cardiovascular magnetic resonance represent a primary phenotypic expression of hypertrophic cardiomyopathy. Circulation. 2011;124:40–7.
35. Germans T, Wilde AA, Dijkmans PA, Chai W, Kamp O, Pinto YM, et al. Structural abnormalities of the inferoseptal left ventricular wall detected by cardiac magnetic resonance imaging in carriers of hypertrophic cardiomyopathies mutations. J Am Coll Cardiol. 2006;48:2518–23.
36. Maron MS, Rowin EJ, Lin D, Appelbaum E, Chan RH, Gibson M, et al. Prevalence and clinical profile of myocardial crypts in hypertrophic cardiomyopathy. Circ Cardiovasc Imaging. 2012;5:441–7.
37. Rowin EJ, Maron MS, Lesser JR, Maron BJ. CMR with late gadolinium enhancement in genotype positive-phenotype negative hypertrophic cardiomyopathy. JACC Cardiovasc Imaging. 2012;5:119–22.
38. Christiaans I, Lekanne dit Deprez RH, Van Langen I, Wilde AAM. Ventricular fibrillation in MYH7-related hypertrophic cardiomyopathy before the onset of ventricular hypertrophy. Heart Rhythm. 2009;6:1366–9.
39. O'Hanlon R, Grasso A, Rougthon M, Moon JC, Clark S, Wage R, et al. Prognostic significance of myocardial fibrosis in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2010;56:867–74.
40. Chan RH, Maron B, Olivotto I, Assenza G, Hong S, Lesser J, et al. Prognostic utility of contrast-enhanced cardiovascular magnetic resonance in hypertrophic cardiomyopathy: a multicenter study. JACC. 2012;59:E1570 (abstract).
41. Christiaans I, Birnie E, Bonsel GJ, Mannens MM, Michels M, Majoor-Krakauer D, et al. Manifest disease, risk factors for sudden cardiac death, and cardiac events in a large nationwide cohort of predictively tested hypertrophic cardiomyopathy mutation carriers: determining the best cardiological screening strategy. Eur Heart J. 2011;32:1161–70.
42. Michels M, Soliman OI, Phefferkorn J, Hoedemaekers YM, Kofflard MJ, Dooijes D, et al. Disease penetrance and risk stratification for sudden cardiac death in asymptomatic hypertrophic cardiomyopathy mutation carriers. Eur Heart J. 2009;30:2593–8.
43. Ho CY, Lopez B, Coelho-Filho OR, Lakdawala NK, Cirino AL, Jarolim P, et al. Myocardial fibrosis as an early manifestation of hypertrophic cardiomyopathy. N Engl J Med. 2010;363:552–63.
44. Maron BJ, Zipes DP. 36th Bethesda conference: eligibility recommendations for competitive athletes with cardiovascular abnormalities. J Am Coll Cardiol. 2005;45:1312–75.
45. Pelliccia A, Corrado D, Bjornstad HH, Panhuyzen-Goedkoop N, Urhausen A, Carre F, et al. Recommendations for participation in competitive sport and leisure-time activity in individuals with cardiomyopathies, myocarditis and pericarditis. Eur J Cardiovasc Prev Rehabil. 2006;13:876–85.

Medical Therapy: From Beta–Blockers to Disopyramide

14

Keith Mankowitz

Abstract

HCM is a heterogeneous disease with significant clinical variation requiring individualized treatment unique for each patient. Most patients can be managed conservatively with few or no medications.

The history, physical examination and baseline echocardiogram usually determine the need for, type of and titration of medications. Medications should be carefully titrated to manage each patient's unique pathophysiology. Septal reduction therapy should only be considered once a patient has failed maximal medical treatment. Atrial fibrillation is common in HCM and should be managed with rate control, attempts to maintain sinus rhythm and anticoagulation. This chapter also discusses the management of apical hypertrophic cardiomyopathy, hypertrophic cardiomyopathy associated with mid ventricular obstruction, End Stage Heart Failure, Tako-tsubo Cardiomyopathy in patients with Hypertrophic Cardiomyopathy and Tako-tsubo Cardiomyopathy with HCM features.

Keywords

Medical treatment • Beta-blockers • Disopyramide • Verapamil • Left ventricular outflow tract obstruction • Diastolic heart failure • Syncope • Atrial fibrillation • End stage heart failure • Apical hypertrophic cardiomyopathy • Mid ventricular obstruction

Introduction

Key Points

- HCM is a heterogeneous disease with significant clinical variation requiring individualized treatment unique for each patient.
- Most patients can be managed conservatively with few or no medications.
- The history, physical examination and baseline echocardiogram usually determine the need for, type of and titration of medications.
- Coronary risk factors and other medical conditions should be appropriately treated and coronary artery disease in particular should always be considered as a potential cause or contribution to the HCM patient's symptoms.
- Septal reduction therapy should only be considered once a patient has failed maximal medical treatment.

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Hypertrophic cardiomyopathy (HCM) is a heterogeneous heart disease with diverse clinical manifestations. Indeed, many patients can maintain an active, healthy lifestyle and have few or no symptoms [1–12]. Most patients with

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hypertrophic cardiomyopathy achieve a normal life expectancy without disability or the need for major therapeutic interventions [3, 4, 6–13].

Accordingly, patients with HCM should be counseled regarding the generally favorable natural history of HCM. Hypertrophic cardiomyopathy should be carefully explained to the patient especially the function of the heart (namely, impairment of filling (diastole) rather than systole (contraction)), the concept of wall thickness and normal ranges, and the concept of left ventricular outflow tract obstruction.

Comprehensive management aims are: improving quality of life, advising patients about acceptable forms of exercise, recommending screening of family members and first degree relatives for HCM by cardiologists experienced in diagnosing and managing HCM, recommending bacterial endocarditis prophylaxis where appropriate, anticoagulating patients with atrial fibrillation, identifying the patient at high risk for sudden cardiac death, and treating coronary risk factors including hypertension, obesity, diabetes mellitus and hyperlipidemia. Patients should be advised about appropriate physical activity, eating a healthy diet, weight management, maintaining adequate hydration and maintaining an ideal body weight. Smoking cessation should be encouraged, and a low-level aerobic exercise program should be recommended for all patients [14]. Patients should be assessed for coronary artery disease or other co-morbid conditions, such as chronic obstructive pulmonary disease, if clinically indicated. The risk of sudden death should be explained to the patient and their family as well as the need to perform periodic risk assessments to see if the patient needs an ICD. The prevention of sudden death is achieved by selecting the appropriate patients for implantation of a cardioverter-defibrillator (ICD) and advising patients to avoid sudden bursts of physical exertion [14].

Infective endocarditis is uncommon within the overall HCM population, but it can have devastating effects on valvular and cardiac function and can cause systemic embolization. Most reported cases of infective endocarditis have been associated with HCM patients with left ventricular outflow tract obstruction. Vegetations can develop on the anterior mitral leaflet or the adjacent proximal ventricular septum. Revisions to guidelines for endocarditis prophylaxis state that patients with HCM are among those who are no longer considered to require routine prophylaxis. HCM expert opinion continues to favor antimicrobial bacterial endocarditis prophylaxis before dental procedures particularly in patients with left ventricular outflow tract obstruction, as they appear to be susceptible to infective endocarditis [15, 16].

Patients with HCM should avoid dehydration, high doses of diuretics, pure vasodilators and inotropes. Caution should be used with decongestants such pseudoephedrine and beta-stimulants such as bronchodilators, as they can aggravate palpitations and arrhythmias. Non-steroidal anti-inflammatory drugs can cause fluid retention, increase blood pressure, interfere with renal function and should be minimized or avoided.

The pathophysiology of hypertrophic cardiomyopathy is complex with many different processes contributing to symptoms including diastolic dysfunction, myocardial ischemia, outflow tract obstruction, mitral regurgitation, arrhythmias and secondary pulmonary hypertension; a reduced cardiac output at rest or on exertion is almost universally present in symptomatic patients [1, 17, 18]. Left ventricular outflow tract obstruction which occurs in up to one third of patients at rest and another one third with physiological provocation causes an increase in left ventricular systolic pressure leading to a complex interplay of abnormalities including prolongation of ventricular relaxation, elevation of left ventricular diastolic pressure, mitral regurgitation, myocardial ischemia and a decrease in the cardiac output [1, 17, 18]. There is significant variability in a patient's symptoms from day to day, hence the classically "dynamic" nature of both the obstruction and the disease. There is often a large variation in the severity of the gradient in each patient during daily activities and in response to food and alcohol, both of which can aggravate symptoms [19–22].

The decision to begin medications should be based on the patient's symptoms. There are no data to support treating asymptomatic patients prophylactically with medications as medications do not protect patients from progression of their disease nor do medications prevent sudden death [17, 18, 23, 24]. The pediatric HCM population may be an exception to this rule. The need for and response to pharmacologic therapy is best assessed by symptoms and findings on the physical examination, aided by baseline echocardiogram. The physical examination is useful to assess the volume status and to auscultate for heart murmurs. The volume status is assessed by evaluating the jugular venous pressure and looking for signs of pulmonary and peripheral edema. Auscultation of the heart is useful to assess the presence of mitral regurgitation and assess the severity of the left ventricular outflow tract obstruction, which correlates with the loudness, and length of the ejection systolic murmur. There are no prospective randomized trials to guide medical therapy. An echocardiogram and stress echocardiogram are useful to assess the ventricular and valve function, to rule out myocardial ischemia and to assess for the presence, severity and mechanism of the left ventricular outflow tract gradient. Medical therapy needs to be tailored to each individual patient with the initiation and adjustment of medications based on the clinical response of the patient and not based on the echocardiogram or stress echocardiogram. In some cases an exercise treadmill test may help gauge symptoms and response to medical therapies.

Symptomatic patients should always be treated medically before considering septal reduction therapy such as myomectomy or alcohol septal ablation [25]. Septal reduction therapy should only be used for eligible patients with severe drug refractory symptoms that interfere with daily activity or quality of life despite optimal medical therapy [19]. One caveat to this, as alluded to above, is the childhood population, where symptoms may be difficult to gauge or the patient may present as a failure to thrive. In the adult population, invasive interventions to abolish the left ventricular outflow gradient should be considered only for the minority of patients (about 5 %) who have both significant left ventricular outflow tract obstruction and severe symptoms unresponsive to medical therapy [17, 18, 24, 26].

Clinical Pearls

- Reassure patients that most patients with HCM have a normal life expectancy. This will relieve a significant emotional burden.
- The history and examination (aided by a confirmatory echocardiogram) should be relied on to determine the appropriate use of medications.
- Cardiac auscultation is useful to assess the severity of the left ventricular outflow tract gradient. The loudness and length of the murmur correlates with the severity of the left ventricular outflow tract gradient.
- Utilizing a heart model is extremely beneficial to help patients understand HCM.
- A patient information sheet is very useful to explain exercise recommendations, screening for arrhythmias with holter monitoring, gene testing, family screening, coronary risk management, reporting symptoms, follow up and suggested web sites. Letting patients know that this is a long-term relationship, and that their understanding of the disease will grow over time, is oftentimes helpful.

Medications (Table 14.1)

Key Points

- Beta-blockers are the most useful drug to manage most complaints.
- Verapamil and diltiazem are useful if beta-blockers are ineffective or cause significant side effects. They may be particularly useful in non-obstructive HCM.
- Combining beta-blockers and calcium channel blockers are not more effective than either drug.
- Diuretics are useful to relieve pulmonary or systemic congestion. HCTZ or combinations with triamterene can usually be tried first in those with mild hypervolemia, in order to avoid dramatic shifts in filling pressure and provocation of outflow tract obstruction.
- Nitrates should be used cautiously due to the propensity to provoke outflow tract obstruction, but may be useful drugs to treat angina in select cases.
- Many patients, whose refractory symptoms are due to the effects of left ventricular out tract obstruction, will have significant clinical improvement with disopyramide. The benefits are seen early.
- There should be a low threshold for initiating anticoagulation for atrial fibrillation. Although warfarin is the gold standard, newer agents may be reasonable alternatives.

Beta-Blockers

Beta-blockers are usually the first line drugs to treat symptomatic obstructive hypertrophic cardiomyopathy [27, 28]. Beta-blockers result in an improvement in angina, exercise tolerance and syncope in 60–80 % of patients. Sustained symptomatic improvement occurs in about 40 % of patients [27, 28]. Beta-blockers reduce provocable obstruction, but have little effect on resting obstruction. They should be used with caution in patients with reactive airways disease and in this setting metoprolol is the beta-blocker of choice because of its cardio-selectivity. Beta-blockers should be used cautiously in patients with bradycardia and hypotension. The dose of beta-blockers should be titrated carefully to improve symptoms while minimizing side effects, especially those of fatigue, depression and impotence. In general, long-acting formulations given in twice daily format are utilized in the treatment of outflow tract obstruction. Propranolol and metoprolol are the best-studied beta-blockers for HCM patients. Although long-acting formulations are preferred, metoprolol tartrate used twice daily is a low cost beta-blocker that is usually well tolerated. Doses as low as 12.5 mg daily, and as high as 200–400 mg daily, can be used depending on the clinical response of the patient. Propranolol can be started at 10 mg twice a day and titrated as tolerated. Carvedilol and labetalol have alpha-blocking activity and are not preferred especially in patients with significant LVOT obstruction where they can theoretically aggravate the LVOT gradient. Carvedilol and labetalol have not been studied in HCM patients; however, they may prove beneficial in patients with

Table 14.1 Medical therapy in patients with hypertrophic cardiomyopathy

Drug					Side effects	
Beta-blocker						
	Reduces resting gradient	Reduces exercise gradient	Improves CP & SOB	Initial	Max	Bradycardia, hypotension, fatigue, depression, asthma
Metoprolol	+	+++	+++	25 mg bid	200 mg bid	
Propranolol	+	+++	+++	10 mg bid	320 mg	
Calcium channel blocker						
	Reduces resting gradient	Reduces exercise gradient	Improves CP & SOB	Initial	Max	Bradycardia, hypotension, constipation
Verapamil	+	+++	++	40 mg tid	480 mg	
Diltiazem	+	+++	++	30 mg tid	480 mg	
Disopyramide						
	Reduces resting gradient	Reduces exercise gradient	Improves CP & SOB	Initial	Max	Anticholinergic effect, increased QT interval
Disopyramide	+++	+++	+++	100 mg bid	600 mg	
Diuretics						
HCTZ			+	12.5 mg	25 mg	Hypotension, electrolyte abnormality
Furosemide			+++	20 mg	100 mg	
Torsemide			+++	50 mg	100 mg	
spironolactone			+/++	12.5 mg	100 mg	
HCTZ/Triamterene			++	25 mg/37.5 mg	25 mg/37.5 mg	
Nitrates						
			Improves CP	Initial	Max	Headaches, hypotension
Nitropaste			++	1 in. prn	2 in. prn	
Nitropatch			++	0.1 mg/h	0.4 mg/h	
Isosorbide dinitrate			++	10 mg tid	40 mg tid	

LVOT gradient and severe systemic hypertension, in which some alpha blocking effect (in combination with the beta-blocking effects) may be desirable. Nebivolol, a relatively new beta-blocker has not been studied in HCM patients.

Calcium Channel Blockers

If beta-blockers are ineffective or produce unsatisfactory side effects then verapamil or diltiazem can be used to control symptoms with certain precautions. In such cases, maintaining a low dose of a beta-blocker as combination therapy may aid in prevention of arrhythmias, particular atrial fibrillation. In addition, use of calcium channel blockers as first-line therapy for non-obstructive HCM may be reasonable. Dihidropyridine calcium channel blockers, such as nifedipine, are contraindicated in patients with obstructive HCM, due to their afterload-reducing properties. Similar to beta-blockers, calcium channel blockers primarily ameliorate provocable, as opposed to resting, gradients.

Non-dihydropyridine calcium channel blockers utilized in HCM have vasodilating properties and can worsen left ventricular outflow tract obstruction when used at high doses [29]. Sudden death has been reported when verapamil was used in patients with severe resting obstruction and advanced heart failure. Accordingly, calcium channel blockers should not be used in patients with congestive heart failure or those with elevated filling pressures and they should be avoided in patients with severe resting left ventricular outflow tract obstruction. Verapamil starting at low doses such as 40 mg three times a day or verapamil ER 120 mg daily can be titrated as needed up to 480 mg a day and may provide symptomatic relief of angina or shortness of breath by its negative inotropic and rate lowering effects. The lowest effective dose should always be used, and doses over 240 mg daily should be used with caution, with careful attention to whether such higher doses exacerbate or alleviate obstruction in a given patient. If patients have side effects from verapamil, especially constipation, then diltiazem can be used in similar doses to verapamil. Diltiazem has not been as well studied as

verapamil in patients with HCM, but diltiazem is a useful drug in observational experience to treat angina and shortness of breath in HCM patients.

There are no data to show that the combination of a beta–blocker with a calcium channel blocker is better than one drug alone. However, this combination may be useful in patients in whom uptitration of beta-blockers is not possible, such as asthmatics. The maintenance of even a low dose of a beta-blocker appears to reduce the risk of atrial arrhythmias, including atrial fibrillation, in some experience.

Disopyramide

Disopyramide is a Class I antiarrhythmic drug that has negative inotropic properties, making it a useful drug to treat patients with symptomatic obstructive HCM [30–33]. As opposed to beta-blockers and calcium channel blockers, disopyramide can reduce both resting and provocable obstruction. Disopyramide can successfully ameliorate symptoms of exertional shortness of breath, pre-syncope and syncope in up to two thirds of patients with hypertrophic obstructive cardiomyopathy who have a left ventricular outflow tract obstruction of at least 30 mmHg and whose symptoms are felt to be due to the outflow tract obstruction [26]. Disopyramide is well tolerated although its anticholinergic side effects can limit the tolerability of the drug. The commonest side effect is urinary retention, which can occur in both males and females. Dry mouth is also a common side effect. Pyridostigmine has been used in select patients to reverse these side effects, with variable effect. Disopyramide should always be given together with metoprolol, verapamil or diltiazem as the anticholinergic effects may enhance ventricular conduction and increase the ventricular rate during episodes of atrial fibrillation. Disopyramide may ameliorate angina, dizziness and shortness of breath by reducing the LVOT gradient by its negative inotropic properties.

Disopyramide should be initiated in a hospital with cardiac monitoring for potential arrhythmias and QT prolongation. The dose of disopyramide can range from 100 mg twice a day to 300 mg twice a day; all in controlled release formulation. The lowest effective dose should always be used. Patients should be started on 100 mg twice a day and then increased to 200 mg twice a day the following day. Telemetry monitoring for 48–72 h is appropriate and the clinical response of the patient can be assessed on a daily basis. Patients will usually notice an improvement in breathing and chest discomfort within 24–48 h. A maximum dose of 300 mg twice a day can be used if needed but anticholinergic side effects are dose related.

A non-randomized study showed no proarrythmia and a lower mortality in disopyramide treated patients [30]. An ECG should be performed at every visit to assess the conduction intervals especially the QT interval. An echocardiogram should assess the effectiveness of disopyramide in reducing the LVOT gradient but should only be ordered after several weeks of therapy to allow disopyramide to reach its maximal effectiveness. While inpatient initiation is recommended, patients have also been treated as outpatients, particularly those with prior ICD implantation; in such cases, starting the lowest dose and monitoring serial EKGs over several days to weeks may be reasonable.

Diuretics

Diuretics are useful to treat the volume-overloaded patient. Patients with long-standing HCM oftentimes are fluid overloaded, despite a relatively normal physical examination. In such cases a right heart catheterization may be helpful to determine the pulmonary capillary wedge pressure. Diuretics ranging from low dose thiazides to potent loop diuretics should be carefully chosen based on the patient's volume status, blood pressure, left ventricular outflow tract obstruction and clinical response. Diuretics should be carefully adjusted according to each patient's unique clinical characteristics. The cardiac history and physical examination are extremely important for assessing the need and response to diuretic therapy. For the volume overloaded patient with borderline blood pressure or a left ventricular outflow tract gradient above 50 mmHg, a low dose thiazide diuretic such as hydrochlorothiazide12.5–25 mg should be the first line diuretic. Aldosterone antagonists such as spironolactone and eplerenone are also useful diuretics to maintain euvolemia. For patients with more severe volume overload or if they respond poorly to thiazides, combinations such as dyazide, or escalating doses of loop diuretics such as furosemide should be titrated according to patient's needs. Torsemide is better absorbed and more potent that furosemide and can be used if more aggressive diuresis is needed. The addition of metalozone to furosemide or torsemide can significantly augment the effects of loop diuretics. However, HCM patients are sensitive to hypovolemia so these more powerful diuretic combinations should be used cautiously. Sodium, potassium and magnesium should always be closely monitored and should be kept at safe levels to prevent pro-arrhythmia.

Nitrates

Nitrates, which are commonly used to treat angina in patients with epicardial coronary artery diseases, may be very useful to treat angina in patients with HCM. There has always been a concern that nitrates could aggravate left ventricular

outflow obstruction and worsen hemodynamics in HCM patients; however if used sensibly, nitrates can provide significant symptomatic benefit for HCM patients with angina. Caution should be used especially in treating patients with high LVOT gradients and/or low blood pressures. Topical nitrates such as nitropaste or nitropatches are very useful in patients with HCM as they produce a small, somewhat controlled release of nitrates into the systemic circulation. Nitrates should be titrated according to patient's response and tolerance. It is important to note the variability in the use of nitrates in clinical practice, and that many experts do not use nitrates in HCM patients due to the aforementioned risks.

Adverse Effects of Medications

Patients may develop significant side effects from medications, especially from beta-blockers [34]. Symptoms such as fatigue or shortness of breath could be due to the adverse effects of medications and not from HCM. Up-titration of medications may alleviate obstructive physiology but increase symptoms of diminished cardiac output or reserve. Dyspnea on exertion can also be caused by the effects of sinus and AV nodal blocking drugs causing chronotropic incompetence, prolongation of the PR interval with impairment of LV filling, or high-degree heart block. Careful adjustment of the doses of drugs or switching to a different beta-blocker or to a calcium channel blocker can result in significant improvement in breathing and well-being [18, 24, 35, 36]. One should always consider the possibility that the patient's symptoms may be due to the side effects of their medications and not due to HCM.

Treatment of Specific Symptoms

Chest Pain

Chest discomfort is a common symptom in patients with HCM and is usually due to the unique pathophysiology in HCM. Hypertrophic cardiomyopathy patients have increased oxygen demand caused by left ventricular hypertrophy and adverse loading conditions. They also have compromised coronary blood flow due to medial hypertrophy of the coronary arteries and arterioles resulting in luminal narrowing and increased myocardial resistance to flow [37]. Myocardial bridging in which a segment of the left anterior descending coronary artery courses within the myocardium may be another cause for angina. Severe myocardial ischemia and infarction may occur in HCM due to the supply-demand mismatch [38, 39]. Atherosclerotic epicardial coronary artery disease should always be ruled out before one attributes chest pain or angina to HCM, especially in older patients or those with cardiovascular risk factors.

Beta-blockers should be the first line treatment for HCM patients with chest pain or angina. They improve oxygen supply-demand imbalance and reduce ischemia. If a beta-blocker does not control the chest discomfort or angina it should be weaned and discontinued. Verapamil starting at low does and titrated as needed up to 480 mg a day may provide symptomatic relief of angina by its negative inotropic and rate lowering effects; caution should be exercised in doses over 240 mg daily, as provocation of outflow tract obstruction may occur. If patients have side effects from verapamil, especially constipation, then diltiazem can be used in a similar dose as verapamil.

Patients with significant left ventricular outflow tract (LVOT) obstruction (resting or provocable gradient above 30 mm) who continue to complain of angina despite therapeutic doses of beta blockers or calcium channel blockers may also respond to disopyramide. Disopyramide may ameliorate angina by reducing the LVOT gradient by its negative inotropic properties. Patients will usually notice an improvement in breathing and chest discomfort within 24–48 h.

Nitrates, especially topical nitrates such as nitropaste or nitropatches may be very useful to treat angina in patients with HCM. Caution should be used especially in treating patients with high LVOT gradients and/or low blood pressures. Nitrates should be titrated according to patient's response and tolerance. There is no data regarding use of ranolazine in patients with HCM.

Shortness of Breath

Shortness of breath usually manifests as exertional dyspnea and can be caused by diastolic dysfunction [17, 18], mitral regurgitation, atrial fibrillation, dynamic LVOT obstruction, myocardial ischemia, pulmonary hypertension or vascular congestion. These pathophysiological abnormalities may combine to cause shortness of breath or cause shortness of breath as a discrete pathophysiology. Symptoms of diastolic heart failure, i.e. exertional shortness of breath, most frequently present themselves in middle-aged adults [1, 2, 18, 25, 40, 41]. The minority of patients, approximately 10–20 % will develop severe heart failure symptoms. [1, 2, 18, 25, 41] Functional limitation is usually gradual with long periods of stability and day-to-day variability. Women usually have more severe symptoms of heart failure, which often occur later in life [42].

Treatment of diastolic dysfunction is not well proven. Judicious use of diuretics is appropriate for patients with elevated filling pressures and volume overload. Diuretics should be carefully adjusted according to each patient's needs. The cardiac history and physical examination are extremely important for assessing the need and response to diuretic therapy. Symptoms of shortness of breath, orthopnea, PND and edema and clinical signs of elevated filling

pressures especially careful assessment of the jugular venous pressure will allow the clinician to titrate the appropriate diuretics.

The BNP is often elevated in exacerbations of congestive heart failure in HCM patients but the level of BNP is usually lower than in systolic heart failure and should not be relied upon to adjust diuretics.

Specific diuretics should be carefully chosen based on the severity of the volume overload, the blood pressure, the degree of left ventricular outflow tract obstruction and the renal function. For any patient who is volume overloaded regardless of the underlying pathophysiology, diuretics are the first line treatment. Patients should be diuresed until they are euvolemic before drugs such as beta blockers, calcium channel blockers or disopyramide are introduced. Careful adjustment of the doses of drugs or switching from a beta blocker to a calcium channel blocker can also result in significant improvement in breathing and well being. One should always consider the possibility that the patient's symptoms may be due to the side effects of their medications and not due to HCM. In particular, careful attention should be paid to over-diuresis, as this can stimulate obstruction and/or reduce cardiac output further.

If shortness of breath continues despite the patient being euvolemic, then beta-blockers should be the first line drugs. Beta-blockers may improve shortness of breath by improving oxygen-demand imbalance, by prolonging the diastolic filling period, by allowing more efficient inactivation of myocardial contractile proteins or by reducing the LVOT obstruction, especially the obstruction that may occur with exertion [43–45]. Beta-blockers can mitigate exercise provoked LVOT gradients thereby improving exertional dyspnea [20, 46]. The lowest effective dose of a beta-blocker should be used.

If beta-blockers are ineffective or cause significant side effects then verapamil or diltiazem can be used or added to treat shortness of breath. Verapamil and diltiazem should be used cautiously in patients with LVOT gradient above 50 mmHg at rest and/or bradycardic patients. Calcium channel blockers have a similar negative inotropic and rate lowering effect as beta blockers [47–51]. Verapamil and diltiazem can improve diastolic dysfunction by slowing the heart rate to allow for better atrial emptying. Verapamil and diltiazem have vasodilating properties and can worsen LVOT obstruction, especially at doses > 240 mg daily. They should be used cautiously in patients with congestive heart failure or elevated filling pressures and they should be avoided in patients with severe resting left ventricular outflow tract obstruction. They can aggravate congestive heart failure and cause sudden death [29].

Patients with LVOT gradients of at least 30 mmHg at rest or with provocation may have a significant improvement in shortness of breath with disopyramide. LVOT gradients are dynamic, characterized by spontaneous variability on a day to day (or even hourly) basis and are effected by various factors including dehydration, alcohol or heavy meals [20–22]. Disopyramide is the only drug with the potential for reducing LVOT gradients at rest. Disopyramide by its negative inotropic effects will reduce the LVOT gradient thereby improving diastolic dysfunction, reducing mitral regurgitation and improving shortness of breath. Up to 70 % of patients will have a significant improvement in their symptoms with disopyramide [30]. Disopyramide should always be given together with metoprolol, verapamil or diltiazem as the anticholinergic effects may enhance ventricular conduction and increase the ventricular rate if the patient develops atrial fibrillation.

Pulmonary Hypertension may develop in HCM patients due to severe diastolic dysfunction or due to secondary causes of pulmonary hypertension as seen in the general population. Patients with pulmonary hypertension should undergo an evaluation to determine whether the elevated pressures are passive (secondary) or primary; in long-standing HCM, secondary irreversible pulmonary hypertension may develop. Medications for pulmonary hypertension have not been studied in the HCM population. Patients with severe pulmonary hypertension might benefit from further pulmonary evaluation.

Dizziness, Presyncope and Syncope

Dizziness, presyncope and syncope have numerous possible causes in HCM patients similar to patients without HCM. Brady and tachyarrhythmias should always be excluded. If dizziness, presyncope or syncope is felt to be due to LVOT obstruction then a trial of beta-blockers should be initiated. Beta-blockers can reduce the LVOT obstruction especially the obstruction that may occur with exertion [20, 43, 46]. If beta-blockers are not helpful, then calcium channel blockers and/or disopyramide should be added. Disopyramide can improve dizziness, presyncope and syncope that is due to a high LVOT gradient by its negative inotropic effects on reducing the LVOT gradient [30]. Dizziness, presyncope and syncope may also be due to autonomic instability in a subset of patients; such patients may benefit from adequate hydration and other conservative measures and medications. More information may be found within the chapter on syncope.

Atrial Fibrillation

Atrial fibrillation occurs in about 20 % of HCM patients and can cause significant morbidity, including precipitation or aggravation of heart failure and stroke [7, 8, 17, 18, 52–55]. Paroxysmal atrial fibrillation can cause rapid clinical deterioration by reducing diastolic filling and cardiac output in the

patient dependent on atrial component of filling due to profound diastolic dysfunction, such as those with HCM. Chronic atrial fibrillation is often better tolerated especially if the heart rate is controlled. Atrial fibrillation that precipitates acute heart failure requires aggressive treatment including anticoagulation, rate control and urgent rhythm control. The risk of stroke for patients with HCM who develop atrial fibrillation and are not anticoagulated is 0.8 %/year and is more common in patients with LVOT obstruction [56, 57]. Susceptibility to atrial fibrillation is linked to aging and left atrial enlargement, usually > 50 mm [56, 57]. There is no evidence that atrial fibrillation is an independent determinant of sudden death in HCM patients [2, 33, 57, 58]. Disopyramide can be used for both its ability to reduce the LVOT gradient and to maintain sinus rhythm. Amiodarone is the most effective drug for controlling recurrences of atrial fibrillation [25, 57].

The CHADS2 score has not been validated in HCM [59]. Anticoagulation should be considered even in patients with only one episode of atrial fibrillation because of the high risk of recurrent atrial fibrillation and the high risk of embolic stroke [52, 56, 57]. Aspirin is reserved for patients who cannot or will not take warfarin or other anticoagulants but its efficacy in HCM is unproven. Anticoagulation with vitamin K antagonists, i.e. warfarin adjusted to an INR of 2.0–3.0, is indicated in HCM patients with paroxysmal, persistent or chronic atrial fibrillation. Anticoagulation with direct thrombin inhibitors such as dabigatran is an alternative to warfarin but data for HCM patients is not available [60]. Anticoagulation with factor Xa inhibitors such as rivoroxaban and apixaban is also an alternative but data for HCM patients are not available.

Clinical Pearls

- Use the lowest effective dose of a medication and assess the response after several weeks before titrating medications.
- Consider the possibility that medications are causing the patients symptoms. Shortness of breath, fatigue, dizziness and syncope can be side effects of beta-blockers and calcium channel blockers.
- Disopyramide may cause a dry mouth and/or urinary retention. Lowering the dose may help minimize the side effects. Pyridostigmine has been used to counteract these side effects in some patients.
- Nitroglycerin patches can be adjusted by patients and can be applied and removed according to complaints of chest pain and the development of side effects. Patches can be applied for as little as 30 min or as long as 12 h. Nitrates are usually well tolerated by most HCM patients, but many experts avoid nitrates altogether and prefer other agents for angina.
- The jugular venous pressure and abdominal jugular reflux are very useful for assessing elevated cardiac filling pressures, as well as the need for and the titration of diuretics.
- HCM patients with volume overload tolerate diuretics very well, including high doses of intravenous diuretics to achieve euvolemia.
- Patients with fluid retention should be taught how to titrate their oral diuretics at home. Daily weight recordings are often helpful.
- Beta-blockers, anticoagulants and contemplation of rhythm control methods should be the first line treatment for atrial fibrillation.
- Exertional syncope and/or dizziness due to a significant left ventricular outflow tract gradient respond well to beta-blockers alone or beta-blockers with disopyramide (Figs. 14.1 and 14.2).

Specific Forms of HCM

Key Points

- HCM can present with unusual clinical presentations including mid ventricular obstruction and apical aneurysms.
- Beta-blockers are the mainstay of treatment for mid ventricular obstruction.
- Apical aneurysms should be treated with warfarin.
- Echocardiograms should be performed at least every 1–2 years to assess for apical aneurysms and left ventricular systolic dysfunction.
- Left ventricular systolic dysfunction should be treated with angiotensin converting enzyme inhibitors, beta-blockers, aldosterone antagonists and diuretics.
- Tako-tsubo cardiomyopathy can affect patients with HCM.
- Patients without HCM can develop dynamic left ventricular outflow tract or mid ventricular obstruction in conditions causing left ventricular volume depletion, hyperdynamic left ventricular contractibility or focal left ventricular contractile disturbances (pseudo-HCM).
- Intravenous fluids are the first line treatment for hypotensive patients with HCM or pseudo-HCM. If they remain hypotensive despite adequate volumes of IV fluids, the drug of choice for hypotension is phenylephrine.

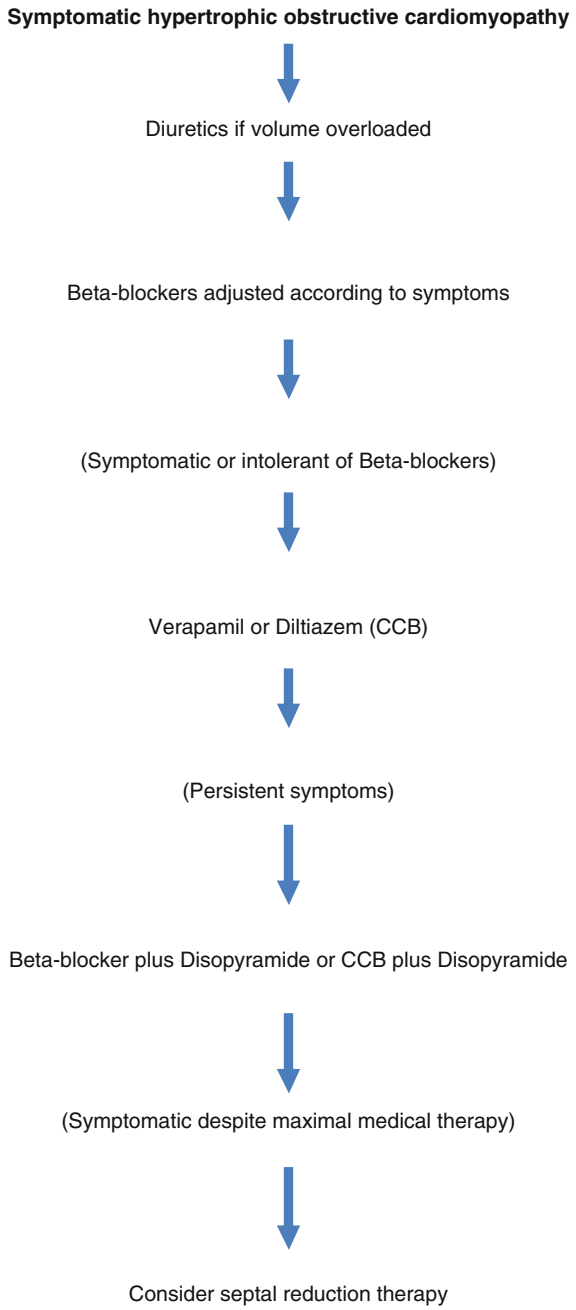

Fig. 14.1 Treatment of symptomatic hypertrophic obstructive cardiomyopathy

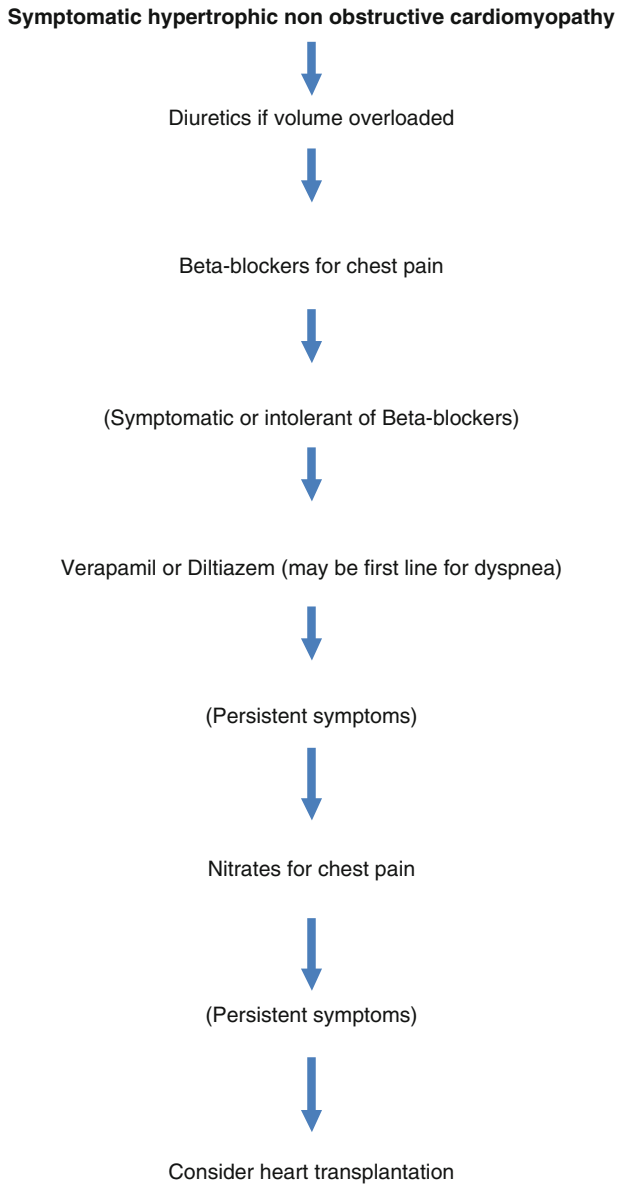

Fig. 14.2 Treatment of symptomatic hypertrophic non-obstructive cardiomyopathy

Apical Hypertrophic Cardiomyopathy

Apical hypertrophic cardiomyopathy is a phenotypic variant of HCM with hypertrophy predominantly affecting the cardiac apex. Patients with apical HCM comprise approximately 25 % of HCM patients in Asian populations and 1–10 % in non-Asian populations. Apical hypertrophic cardiomyopathy can cause chest pain, myocardial infarction, atrial fibrillation, strokes and sudden death. Although many afflicted patients have mild symptoms, some patients are severely debilitated due to profound diastolic dysfunction. It may be associated with apical pouches or apical aneurysms. In rare cases, concomitant abnormalities of the papillary muscles, or extention of hypertrophic myocardium to the mid-cavity can cause LVOT obstruction and a murmur. The treatment of apical HCM patients in general should include beta-blockers or verapamil for chest pain, anticoagulation as indicated for apical aneurysms, appropriate management of atrial fibrillation and risk stratification to determine the need for an ICD [61–66] (Fig. 14.3).

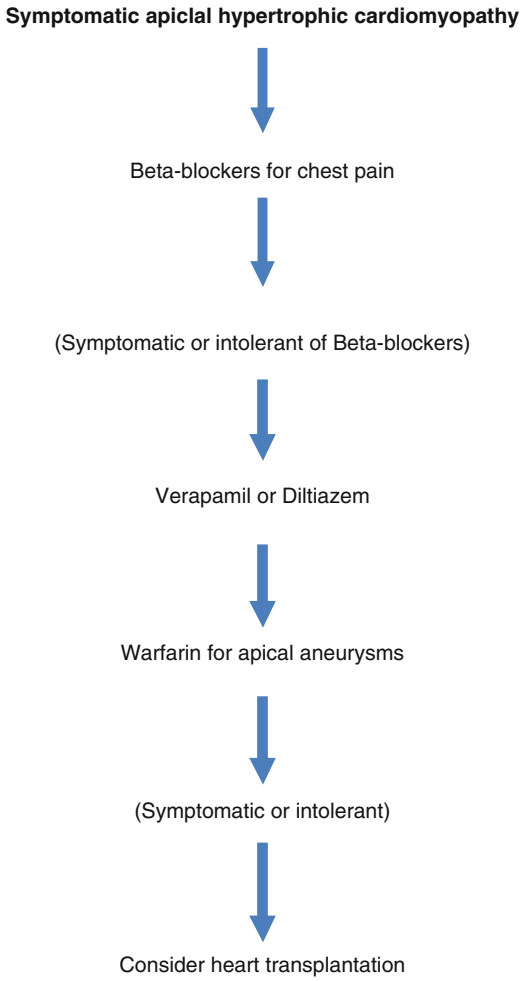

Fig. 14.3 Treatment of symptomatic apical hypertrophic cardiomyopathy

Hypertrophic Cardiomyopathy Associated with Mid Ventricular Obstruction

Mid ventricular obstruction is a distinct phenotype of HCM and occurs due to segmental mid-septal hypertrophy and hypercontractility of the lateral ventricular wall along with misplacement of the hypertrophied papillary muscles. It causes a mid cavity gradient. Mid cavity obstruction occurs in 9–13 % of HCM cohorts and appears to be more symptomatic than other phenotypes of HCM. Dyspnea is the most common symptom. Left ventricular apical aneurysm can develop in up to one quarter of patients with mid ventricular obstruction. The aneurysm is thought to develop due to the increased pressure load on the apical myocardium, the increased metabolic demand and reduced oxygen supply mainly by extra vascular compression of the coronary arteries. Progression to end stage HCM appears to occur more frequently than other HCM phenotypes. Mid ventricular obstruction appears also to be associated with a high risk of arrhythmias and sudden death. Treatment should include beta-blockers or verapamil to reduce the mid ventricular obstruction and thus improve shortness of breath. Anticoagulation should be considered for apical aneurysms. Patients should be monitored closely to detect ventricular arrhythmias and the need for an ICD. Yearly echocardiograms should be done to monitor for ventricular dilation and progression to a dilated cardiomyopathy [67–74].

End Stage Heart Failure

The discovery of a reduced ejection fraction occurs in approximately 3 % of HCM patients. Before attributing the reduced ejection fraction to the burnt out phase of HCM, other causes of left ventricular dysfunction should be evaluated such as coronary artery disease, valvular heart disease and metabolic disorders [40, 75]. The end stage disease is attributable to an irreversible process of extensive replacement scarring presumably due to microvascular ischemia [38, 75]. It is characterized by left ventricular remodeling with progressive wall thinning (due to myocardial necrosis), cavity enlargement and systolic dysfunction [75, 76]. A substantial portion have significant scar burden by MRI with late gadolinium enhancement.

The only known predictor of end stage HCM is a family history of end stage disease. The clinical course of end stage HCM is variable and unpredictable. Some patients remain well compensated for many years [75]. Treatment should be changed to standard therapeutic agents for systolic heart failure including diuretics, angiotension-converting-enzyme inhibitors (or angiotensin receptor blockers), beta blockers, digoxin and aldosterone inhibitors. Verapamil and disopyramide should be discontinued. Patients who fail to respond to treatment with beta blockers, diuretics, afterload reducing agents and ICDs with biventricular pacing should be considered for heart transplantation, depending on age and suitability [77].

A small percentage of patients who develop systolic heart failure may have reverse remodeling and revert back to the original phenotype with normal systolic function and left ventricular outflow tract obstruction. Medications will need to be readjusted to treat symptomatic hemodynamics that may redevelop. This may include reinitiating disopyramide. Thus, careful attention to the physical examination and serial echocardiograms, especially for changes in the exam or clinical status, are paramount.

Tako-tsubo Cardiomyopathy

Patients with hypertrophic cardiomyopathy may develop an acute form of tako-tsubo cardiomyopathy similar to patients with normal hearts. Excessive sympathetic stimulation, vascular abnormalities and metabolic disturbances have been suggested to be responsible [78]. Patients may develop transient acute severe systolic dysfunction, congestive heart

failure or cardiogenic shock [79]. These patients may need temporary hemodynamic support and will usually normalize their ventricular function within days to weeks. If they have left ventricular outflow tract obstruction and hypotension, they should be treated with phenylephrine for blood pressure support. Dobutamine and inotropes (including digoxin) should always be avoided in patients with dynamic left ventricular outflow tract obstruction. In rare cases, placement of ventricular assist device may prove necessary; due to its ability to assist in ejection of blood directly from the LV to the aorta, the Impella device may be ideal. An intra-aortic balloon pump, in contrast, is contraindicated in such patients due to the worsening of outflow tract obstruction produced by the drop in afterload.

Tako-tsubo Cardiomyopathy with HCM Features

There are a series of patients without HCM that present with Taka-tsubo cardiomyopathy and develop transient left ventricular outflow traction obstruction or dynamic intraventricular pressure gradients [80, 81]. These patients resemble hypertrophic obstructive cardiomyopathy patients because of their similar obstructive pathophysiology. The obstruction in these patients develops as a result of LV outflow tract obliteration secondary to mid and distal LV dyskinesis and compensatory basal wall hyperkinesia [81, 82]. It is imperative to recognize dynamic LV gradients because they require a different treatment approach than patients with acute systolic dysfunction alone. These patients are best treated by augmenting left ventricular (LV) volume, reducing LV ejection velocity and supporting the blood pressure with a combination of intravenous fluids, beta blockers and phenylephrine as indicated. Again, inotropes and digoxin are contraindicated. As with patients with HCM and secondary TakoTsubo cardiomyopathy, patients with continued hypotension despite the above measures may benefit from Impella ventricular assist device and avoidance of the intra-aortic balloon pump, in particular.

Clinical Pearls

- The clinical evaluation combined with detailed echocardiography is useful to diagnose unusual presentations of HCM and conditions mimicking HCM.
- Dobutamine can produce hemodynamic disturbances including left ventricular outflow tract obstruction and mid ventricular obstruction in normal patients. These patients should not be labeled as HCM patients.
- The treatment of choice for patients without HCM who develop left ventricular or midventricular obstruction is avoiding inotropes, increasing fluid administration and initiating a beta-blocker.
- Phenylephrine is a drug of choice for treating HCM patients with hypotension that is unresponsive to intravenous fluids. Use of ventricular assist devices that sit across the outflow tract may be considered. The IABP should be avoided in these settings.
- HCM patients who develop acute or chronic left ventricular systolic dysfunction can improve and normalize their systolic function.
- HCM patients who have persistent severe left ventricular systolic dysfunction after 1 year of appropriate medical treatment have a poor prognosis and cardiac transplantation should be considered.

References

1. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. JAMA. 2002;287:1308–20.
2. Maron BJ, McKenna WJ, Danielson GK, Task Force on Clinical Expert Consensus Documents, et al. A report of the American College of Cardiology Foundation Task Force on clinical expert consensus documents and the European Society of Cardiology committee for practice guidelines. J Am Coll Cardiol. 2003;42:1687–713.
3. Maron BJ, Casey SA, Poliac LC, Gohman TE, Almquist AK, Aeppli DM. Clinical course of hypertrophic cardiomyopathy in a regional United States cohort. JAMA. 1999;281:650–5.
4. Maron BJ, Casey SA, Hauser RG, Aeppli DM. Clinical course of hypertrophic cardiomyopathy with survival to advanced age. J Am Coll Cardiol. 2003;42:882–8.
5. Maron BJ, Casey SA, Haas TS, Kitner CL, Garberich RF, Lesser JR. Hypertrophic cardiomyopathy with longevity to 90 years or older. Am J Cardiol. 2012;109:1341–7.
6. Cannan CR, Reeder GS, Bailey KR. Natural history of hypertrophic cardiomyopathy: a population-based study. Circulation. 1995;92:2488–95.
7. Cecchi F, Olivotto I, Montereggi A. Hypertrophic cardiomyopathy in Tuscany: clinical course and outcome in an unselected regional population. J Am Coll Cardiol. 1995;26:1529–36.
8. Spirito P, Chiarella F, Carratino L. Clinical course and prognosis of hypertrophic cardiomyopathy in an outpatient population. N Engl J Med. 1989;320:749–55.
9. Shapiro LM, Zezulka A. Hypertrophic cardiomyopathy: a common disease with a good prognosis: five year experience of a district general hospital. Br Heart J. 1983;50:530–3.
10. Kofflard MJ, Waldstein DJ, Vos J, ten Cate FJ. Prognosis in hypertrophic cardiomyopathy observed in a large clinic population. Am J Cardiol. 1993;72:939–43.
11. Maron BJ, Spirito P. Impact of patient selection biases on the perception of hypertrophic cardiomyopathy and its natural history. Am J Cardiol. 1993;72:970–2.
12. Spirito P, Rapezzi C, Autore C, et al. Prognosis of asymptomatic patients with hypertrophic cardiomyopathy and nonsustained ventricular tachycardia. Circulation. 1994;90:2743–7.
13. Maron BJ, Mathenge R, Casey SA. Clinical profile of hypertrophic cardiomyopathy identified de novo in rural communities. J Am Coll Cardiol. 1999;33:1590–5.

14. Maron BJ, Chaitman BR, Ackerman MJ. Recommendations for physical activity and recreational sports participation for young patients with genetic cardiovascular diseases. Circulation. 2004;109: 2807–16.
15. Maron BJ, Lever H. In defense of antimicrobial prophylaxis for prevention of infective endocarditis in patients with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2009;54:2339–40.
16. Spirito P, Rapezzi P, Bellone P, et al. Infective endocarditis in hypertrophic cardiomyopathy: prevalence, incidence, and indications for antibiotics prophylaxis. Circulation. 1999;99:2132–7.
17. Wigle ED, Sasson Z, Henderson MA, et al. Hypertrophic cardiomyopathy: the importance of the site and the extent of hypertrophy: a review. Prog Cardiovasc Dis. 1985;28:1–83.
18. Wigle ED, Rakowski H, Kimball BP, Williams WG. Hypertrophic cardiomyopathy: clinical spectrum and treatment. Circulation. 1995;92:1680–92.
19. Geske JB, Sorajja P, Ommen SR. Left ventricular outflow tract gradient variability in hypertrophic cardiomyopathy. Clin Cardiol. 2009;32:397–402.
20. Braunwald E, Lambrew CT, Rockoff SD, Ross Jr J, Morrow AG. Idiopathic hypertrophic subaortic stenosis, I: a description of the disease based upon an analysis of 64 patients. Circulation. 1964;30:3–119.
21. Maron BJ, Maron MS, Wigle ED, Braunwald E. The 50-year history, controversy, and clinical implications of left ventricular outflow tract obstruction in hypertrophic cardiomyopathy: from idiopathic hypertrophic subaortic stenosis to hypertrophic cardiomyopathy. J Am Coll Cardiol. 2009;54:191–200.
22. Paz R, Jortner R, Tunick PA, et al. The effect of the ingestion of ethanol on obstruction of the left ventricular outflow tract in hypertrophic cardiomyopathy. N Engl J Med. 1996;335:938–41.
23. Melacini P, Maron BJ, Bobbo F, et al. Evidence that pharmacological strategies lack efficacy for the prevention of sudden death in hypertrophic cardiomyopathy. Heart. 2007;93:708–10.
24. Maron BJ, Bonow RO, Cannon III RO, Leon MB, Epstein SE. Hypertrophic cardiomyopathy: interrelations of clinical manifestations, pathophysiology, and therapy. N Engl J Med. 1987;316: 780–9, 844.
25. Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA guidelines for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/ American Heart Association Task Force on practice guidelines. J Am Coll Cardiol. 2011;58:212–60.
26. Louie EK, Edwards III LC. Hypertrophic cardiomyopathy. Prog Cardiovasc Dis. 1994;36:275–308.
27. Adelman AG, Shah PM, Gramiak R, et al. Long-term propranolol therapy in muscular subaortic stenosis. Br Heart J. 1970;32: 804–11.
28. Flamm MD, Harrison DC, Hancock EW. Muscular subaortic stenosis. Prevention of outflow obstruction with propranolol. Circulation. 1968;38:846–58.
29. Epstein SE, Rosing DR. Verapamil: its potential for causing serious complications in patients with hypertrophic cardiomyopathy. Circulation. 1981;64:437–41.
30. Sherrid MV, Barac I, McKenna WJ, et al. Multicenter study of the efficacy and safety of disopyramide in obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol. 2005;45:1251–8.
31. Pollick C, Detsky A, Ogilvie RI, et al. Disopyramide versus propranolol in hypertrophic cardiomyopathy: double-blind randomized trial. Circulation. 1985;72:155.
32. Pollick C, Kimball B, Henderson M, et al. Disopyramide in hypertrophic cardiomyopathy I. Hemodynamic assessment after intravenous administration. Am J Cardiol. 1988;62:1248–51.
33. Sherrid M, Delia E, Dwyer E. Oral disopyramide therapy for obstructive hypertrophic cardiomyopathy. Am J Cardiol. 1988;62: 1085–8.
34. Gilligan DM, Chan WL, Stewart RA, Oakley CM. Adrenergic hypersensitivity after beta-blocker withdrawal in hypertrophic cardiomyopathy. Am J Cardiol. 1991;68:766–72.
35. Rosing DR, Kent KM, Maron BJ, Epstein SE. Verapamil therapy: a new approach to the pharmacologic treatment of hypertrophic cardiomyopathy. II. Effects on exercise capacity and symptomatic status. Circulation. 1979;60:1208–13.
36. Gilligan DM, Chan WL, Joshi J, et al. A double-blind, placebo controlled crossover trial of nadolol and verapamil in mild and moderately symptomatic hypertrophic cardiomyopathy. J Am Coll Cardiol. 1993;21:1672–9.
37. Maron BJ, Wolfson JK, Epstein SE. Intramural ("small vessel") coronary artery disease in hypertrophic cardiomyopathy. J Am Coll Cardiol. 1986;8:545–57.
38. Maron MS, Olivotto I, Maron BJ, et al. The case for myocardial ischemia in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2009;54:866–75.
39. Cannon III RO, Rosing DR, Maron BJ. Myocardial ischemia in patients with hypertrophic cardiomyopathy: contribution of inadequate vasodilator reserve and elevated left ventricular filling pressures. Circulation. 1985;71:234–43.
40. Melacini P, Basso C, Angelini A, et al. Clinicopathological profiles of progressive heart failure in hypertrophic cardiomyopathy. Eur Heart J. 2010;31:2111–23.
41. Spirito P, Seidman CE, McKenna WJ, Marion BJ. The management of hypertrophic cardiomyopathy. N Engl J Med. 1997;336:775–85.
42. Olivotto I, Maron MS, Adabag AS, et al. Gender-related differences in the clinical presentation and outcome of hypertrophic cardiomyopathy. J Am Coll Cardiol. 2005;46:480–7.
43. Sherrid MV, Pearle G, Gunsburg DZ. Mechanism of benefit of negative inotropes in obstructive hypertrophic cardiomyopathy. Circulation. 1998;97:41–7.
44. Alvares RF, Goodwin JF. Non-invasive assessment of diastolic function in hypertrophic cardiomyopathy on and off beta adrenergic blocking drugs. Br Heart J. 1982;48:204–12.
45. Bourmayan C, Razavi A, Fournier C. Effect of propranolol on left ventricular relaxation in hypertrophic cardiomyopathy: an echographic study. Am Heart J. 1985;109:1311–6.
46. Nistri S, Olivotto I, Maron MS, et al. B blockers for prevention of exercise-induced left ventricular outflow tract obstruction in patients with hypertrophic cardiomyopathy. Am J Cardiol. 2012; 110:715–9.
47. Bonow RO, Dilsizian V, Rosing DR. Verapamil-induced improvement in left ventricular diastolic filling and increased exercise tolerance in patients with hypertrophic cardiomyopathy: short and long-term effects. Circulation. 1985;72:853–64.
48. Bonow RO, Frederick TM, Bacharach SL. Atrial systole and left ventricular filling in hypertrophic cardiomyopathy: effect of verapamil. Am J Cardiol. 1983;51:1386–91.
49. Bonow RO, Ostrow HG, Rosing DR. Effects of verapamil on left ventricular systolic and diastolic function in patients with hypertrophic cardiomyopathy: pressure-volume analysis with nonimaging scintillation probe. Circulation. 1983;68:1062–73.
50. Bonow RO, Vitale DF, Maron BJ. Regional left ventricular asynchrony and impaired global left ventricular filling in hypertrophic cardiomyopathy: effect of verapamil. J Am Coll Cardiol. 1987;9: 1108–16.
51. Kass DA, Wolff MR, Ting CT. Diastolic compliance of hypertrophied ventricle is not acutely altered by pharmacologic agents influencing active processes. Ann Intern Med. 1993;119:466–73.
52. Robinson K, Frenneaux MP, Stockins B, Karatasakis G, Poloniecki JD, McKenna WJ. Atrial fibrillation in hypertrophic cardiomyopathy: a longitudinal study. J Am Coll Cardiol. 1990;15:1279–85.
53. McKenna WJ, England D, Doi YL, Deanfield JE, Oakley CM, Goodwin JF. Arrhythmia in hypertrophic cardiomyopathy. I. Influence on prognosis. Br Heart J. 1981;46:168–72.

54. Furlan AJ, Craciun AR, Raju NR, Hart N. Cerebrovascular complications associated with idiopathic hypertrophic subaortic stenosis. Stroke. 1984;15:282–4.
55. Spirito P, Lakatos E, Maron BJ. Degree of left ventricular hypertrophy in patients with hypertrophic cardiomyopathy and chronic atrial fibrillation. Am J Cardiol. 1992;69:1217–22.
56. Olivotto I, Cecchi F, Casey SA, Dolara A, Traverse JH, Maron BJ. Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. Circulation. 2001;104:2517–24.
57. Maron BJ, Olivotto I, Bellone P, et al. Clinical profile of stroke in 900 patients with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2002;39:301–7.
58. Maron BJ. Contemporary insights and strategies for risk stratification and prevention of sudden death in hypertrophic cardiomyopathy. Circulation. 2010;121:445–56.
59. Fang MC, Go AS, Chang Y, Borowsky L, Pomernacki NK, Singer DE, ATRIA study group. Comparison of risk stratification schemes to predict thromboembolism in people with nonvalvular atrial fibrillation. J Am Coll Cardiol. 2008;51:810–5.
60. Connolly SJ, Ezekowitz MD, Yusuf S. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1139–51.
61. Klarich KW, Attenhofer Jost CH, Binder J, Connolly HM, Scott CG, Freeman WK, Ackerman MJ, Nishimura RA, Tajik AJ, Ommen SR. Risk of death in long-term follow-up of patients with apical hypertrophic cardiomyopathy original research article. J Am Coll Cardiol. 2013;12:1784–91.
62. Eriksson MJ, Sonnenberg B, Woo A, Rakowski P, Parker TG, Wigle E, Rakowski H. Long-term outcome in patients with apical hypertrophic cardiomyopathy. J Am Coll Cardiol. 2002;39(4):638–45.
63. Sakamoto T, Tei C, Murayama M, Ichiyasu H, Hada Y. Giant T wave inversion as a manifestion of asymmetrical apical hypertrophy (AAH) of the left ventricle. Echocardiographic and ultrasonocardiotomographic study. Jpn Heart J. 1976;17:611–29.
64. Yamaguchi H, Ishimura T, Nishiyama S, Nagasaki S, Nagasaki F, Takatsu T, Nishijo T, Umeda KM. Hypertrophic nonobstructive cardiomyopathy with giant negative T waves (apical hypertrophy): ventriculographic and echocardiographic features in 30 patients. Am J Cardiol. 1979;44:401–12.
65. Klues HG, Schiffers A, Maron BJ. Phenotypic spectrum and patterns of left ventricular hypertrophy in hypertrophic cardiomyopathy: morphologic observations and significance as assessed by two-dimensional echocardiography in 600 patients. J Am Coll Cardiol. 1995; 26:1699–708.
66. Moon J, Shim CY, Ha JW, Cho IJ, Kang MK, Yang WI, Jang Y, Chung N, Cho SY. Clinical and echocardiographic predicators of outcomes in patients with apical hypertrophic cardiomyopathy original research articles. J Am Coll Cardiol. 2011;108:1614–9.
67. Falicov RE, Resnekov L, Bharati S, Lev M. Mid-ventricular obstruction: a variant of obstructive cardiomyopathy. Am J Cardiol. 1976;37:432–7.
68. Minami Y, Kajimoto K, Terajima Y, Yashiro B, Okayam D, Haruki S, et al. Clinical implications of midventricular obstruction in patients with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2011;57:2346–55.
69. Fighali S, Krajcer Z, Edelman S, Leachman RD. Progression of hypertrophic cardiomyopathy into a hypokinetic left ventricle: high incidence in patients with midventricular obstruction. J Am Coll Cardiol. 1987;9:288–94.
70. DeGregoria C. Left ventricular dynamic obstruction by atypical papillary muscle morphology: is this finding so unusual in clinical practice. J Am Soc Echocardiogr. 2007;20:100–1.
71. Nakamura T, Matsubara K, Furukawa K, Azuma A, Sugihara H, Katsume H, et al. Diastolic paradoxic jet flow in patients with hypertrophic cardiomyopathy: evidence of concealed apical asynergy with cavity obliteration. J Am Coll Cardiol. 1992;19:516–24.
72. Maron MS, Finley JJ, Bos JM, Hauser TH, Manning WJ, Haas TS, et al. Prevalence, clinical significance, and natural history of left ventricular apical aneurysms in hypertrophic cardiomyopathy. Circulation. 2008;118:1541–9.
73. Shah A, Duncan K, Winson G, Chaudhry FA, Sherrid MV. Severe symptoms in mid and apical hypertrophic cardiomyopathy. Echocardiography. 2009;26:922–33.
74. Efthimiadis GK, Pagourelias ED, Parcharidou D, Gossios T, Kamperidis V, Theofilogiannakos EK, Pappa Z, Meditskou S, Hadjimiltiades S, Pliakos C, Karvounis H, Styliadis IH. Clinical characteristics and natural history of hypertrophic cardiomyopathy with midventricular obstruction. Circ J. 2013;77:2366–74.
75. Spirito P, Maron BJ. Absence of progression of left ventricular hypertrophy in adult patients with hypertrophic cardiomyopathy. J Am Coll Cardiol. 1987;9:1013–7.
76. Spirito P, Maron BJ, Bonow RO, Epstein SE. Occurrence and significance of progressive left ventricular wall thinning and relative cavity dilatation in hypertrophic cardiomyopathy. Am J Cardiol. 1987;60:123–9.
77. Shirani J, Maron BJ, Cannon III RO, Shanin S, Roberts WC. Clinicopathologic features of hypertrophic cardiomyopathy managed by cardiac transplantation. Am J Cardiol. 1993;72:434–40.
78. Dorfman TA, Aqel R, Mahew M, Iskandrian AE. Tako-tsubo cardiomyopathy: a review of the literature. Curr Cardiol Rev. 2007; 3:137–42.
79. Tsuchihashi K, Ueshima K, Uchida T, Oh-mura N, Kimura K, et al. Transient left ventricular apical ballooning without coronary artery stenosis: a novel heart syndrome mimicking acute myocardial infarction. J Am Coll Cardiol. 2001;38:11–8.
80. Gianni M, Dentali F, Grandi AM, Sumner G, Hiralal R, et al. Apical ballooning syndrome or takotsubo cardiomyopathy: a systematic review. Eur Heart J. 2006;27:1523–9.
81. Villareal RP, Achari A, Wilansky S, Wilson JM. Anteroapical stunning and left ventricular outflow tract obstruction. Mayo Clin Proc. 2001;76:79–83.
82. Bybee KA, Kara T, Prasad A, Lerman A, Barsness GW, et al. Systematic review: transient left ventricular apical ballooning: a syndrome that mimics ST-segment elevation myocardial infarction. Ann Intern Med. 2004;141:858–65.

Indications and Outcome of PPM and ICD Placement

15

Joseph J. Germano, Joshua R. DeLeon, Daniel R. Zakhary, and Mark E. Josephson

Abstract

The use of synchronized atrioventricular (AV) pacing devices and implantable cardioverter-defibrillators (ICDs) plays a critical role in the management of hypertrophic cardiomyopathy (HCM). Indications for pacing and defibrillators follow the standard guidelines for treatment of conduction disease and arrhythmias in the general population, with distinct additional indications for HCM patients based on the potential to mitigate diastolic dysfunction and outflow tract gradients, and the potential for life-threatening ventricular arrhythmia and sudden cardiac death. ICDs can be a life-saving therapy in high-risk HCM patients, but the early placement of these devices in younger patients may expose them to a higher lifetime risk of complications. Given the unique nature of HCM, specific procedural and programming considerations should be taken into account.

Keywords

Hypertrophic cardiomyopathy • Pacemaker • Implantable-cardioverter defibrillator • Device programming • Sudden cardiac death • Appropriate implantable-cardioverter defibrillator • Inappropriate implantable-cardioverter defibrillator

Key Points

- Devices for the management of conduction disease and arrhythmias play an important role in the treatment of hypertrophic cardiomyopathy (HCM).
- Beyond standard conduction disease indications, pacemakers may be used to treat heart failure or syncope symptoms associated with HCM. However, pacemaker placement to reduce outflow tract obstruction or increase ventricular filling through optimization of atrio-ventricular delay has been downgraded in recent guidelines.
- Implantable cardioverter-defibrillators (ICDs) have been used to prevent sudden cardiac death (SCD) in HCM, and appear effective in defined high-risk HCM patients, but this has been based on limited data from observational outcome studies, with recommendations primarily derived from expert consensus.

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- In patients with HCM, specific procedural and programming considerations should be taken into account.
- Complications of device placement, both procedural and long-term, may be increased in patients with HCM. These include mechanical complications as well as electrophysiologic complications. Accordingly, the decision to place a device requires careful and individualized assessment of the risk to benefit ratio.

Introduction and Overview

The use of synchronized atrioventricular (AV) or DDD pacing has been an important component in the management of HCM. Dual-chamber pacing, utilizing right atrial and right ventricular (RV) leads, has been the method used. Indications for device placement in HCM patients follow the standard indications as in the non-HCM population, with distinct additional indications based on the potential to mitigate diastolic dysfunction and outflow tract gradients. More recently, reports of biventricular pacemaker placement to reduce outflow tract gradients have also been reported. ICDs have been proven to be a life-saving therapy in subsets of HCM patients, particularly those who meet defined high-risk criteria. However, the oftentimes early placement of these devices within the lifetime of the average HCM patient means that they will be susceptible to a higher risk of complications over the ensuing decades.

In this chapter, we will examine the data supporting the indications for pacing and defibrillation in HCM patients, and review the clinical and practical application of these therapies. Synchronized atrioventricular pacing in HCM is used primarily for conduction disease, heart rate support, and more controversially, symptom alleviation due to outflow tract obstruction and/or diastolic dysfunction. However, the recommendation for pacemaker placement to reduce outflow tract obstruction or increase ventricular filling through optimization of AV delay has been downgraded in recent guidelines. It is now clear that AV pacing is not very helpful in patients with non-obstructive HCM, no symptoms, or symptoms well controlled on medical therapy, nor is it helpful in patients who are candidates for septal reduction therapy. Also, pacing is not indicated for mortality benefit or to change the natural history of the underlying disease process. As already mentioned, ICDs have been used to prevent sudden cardiac death (SCD) in HCM, and appear effective in defined high-risk HCM patients, but this has been based on limited outcome studies and recommendations derived primarily from expert consensus. Furthermore, in the past some have recommended that all patients with HCM receive an ICD; this, however, is controversial and not supported by either the recent AHA/ACC guidelines or the prior ACC/ESC guidelines.

Complications of device placement, both procedural and long-term, may be increased in patients with HCM. These include mechanical as well as electrophysiologic complications. When deciding on the appropriateness of implantation, it is necessary to recognize the complex relationship between hemodynamic parameters, specifics of device programming, and the impact of lead position. Accordingly, the decision to place a device requires careful and individualized assessment of the risk to benefit ratio.

Once the decision to implant a device has been made, there are several procedural considerations that must be addressed. RV pacing leads should be placed in the distal RV apex rather than on the RV septum to effectively reduce the left ventricular outflow tract (LVOT) gradient without affecting cardiac output. ICD leads should also be placed apically for defibrillation threshold (DFT) optimization (which is usually higher in HCM), and may be challenging due to increased trabeculations and a bulging intraventricular septum in these patients. Reported annual rates of appropriate ICD therapy are increased in HCM patients (ranging from 3.3 to 6.8 %), which may be due to predisposing factors such as prior cardiac arrest or sustained ventricular arrhythmia, male gender, young age, and a history of atrial fibrillation. Lead complications are more common specifically in HCM patients given more vigorous muscular contractions of the hyperdynamic heart that could provoke lead fracture. Inappropriate ICD therapies are particularly problematic in HCM patients of young age due to faster heart rates, and generally due to the increased incidence of atrial fibrillation, higher incidence of lead fracture, and T-wave over sensing. Both dual- and single-chamber ICD devices are safe and effective for detecting and treating life-threatening ventricular tachyarrhythmias; however, it is unclear whether dual-chamber devices offer any benefit over single-chamber devices in detection of supraventricular tachycardia (SVT) and the prevention of inappropriate therapies.

This chapter will therefore discuss the data supporting the indications for pacing and defibrillation in HCM patients, the clinical and practical application of these therapies, and the risks of procedural and long-term complications, both mechanical and electrophysiologic. Special populations, such as patients following alcohol septal ablation or surgical myomectomy, will also be further discussed.

Device Indications Specific to HCM

Pacemakers

Synchronized atrioventricular pacing in HCM has been used for three major indications: (1) conduction disease, (2) heart rate support, and (3) reduction in symptoms due to

Table 15.1 Pacing recommendations for patients with HCM

Class of recommendation	Recommendation	Level of evidence
Class I	*None*	
Class IIa	Relief of symptoms attributable to LVOT obstruction in patients with an existing dual-chamber device (implanted for non-HCM indications).	B
Class IIb	Medically refractory symptomatic patients with obstructive HCM who are suboptimal candidates for septal reduction therapy.	B
Class III	Pacemaker implant should not be performed to reduce LVOT gradient in patients with HCM who are asymptomatic or whose symptoms are medically controlled.	C
	Pacemaker implant should not be performed for symptom relief as a first-line therapy in patients who are candidates for septal reduction.	B

Based on Gersh et al. [1].
Abbreviations: *HCM* hypertrophic cardiomyopathy

outflow tract obstruction and/or diastolic dysfunction. Table 15.1 summarizes the ACCF/AHA Guidelines published in 2011 [1].

The first category includes traditional indications such as sinus node dysfunction as well as AV conduction disturbances unrelated to the diagnosis of HCM. In instances such as post septal myomectomy or alcohol septal ablation, there is a higher incidence of complete heart block, especially in those of advanced age or with baseline conduction disease. Advanced conduction disease in this setting represents a clear indication for dual-chamber pacing.

The second major indication has been to provide heart rate support for medical therapy (beta-adrenergic blockers, calcium channel blockers, or antiarrhythmic medications) used to treat the symptoms associated with HCM. As the number and/or doses of beta-blockers or calcium-channel blockers typically required in the management of outflow tract obstruction may reach or exceed traditional maximal doses, heart rate support becomes an important indication, especially in elderly patients, prior to contemplation of invasive techniques such as alcohol septal ablation or surgical myomectomy.

The third and most controversial indication for pacing in patients with HCM is symptom alleviation. Conceptually, it has been suggested that dual-chamber pacing reduces LVOT gradients and improves symptoms in obstructive forms of HCM by various proposed mechanisms, the most important of which include: paradoxical septal motion [2, 3]; asynchronous ventricular septal activation [3–5]; influence on myocardial perfusion [6]; increase left ventricular dimensions [7]; negative inotropic effect [7]; decrease in LV ventricular thickness [8]; and, decrease in mitral valve systolic anterior motion and the resultant mitral regurgitation [2, 3]. In addition, optimizing AV delay, which typically requires a shorter interval but is unique to each patient, may improve ventricular filling. This improves cardiac output both by increasing end-diastolic volume and by secondary reductions in outflow tract gradient.

Reduction in dynamic LVOT gradient with dual-chamber pacing has often been impressive but inconsistently observed and is extremely variable, with resting gradient reduction ranging from 25 to 72 %. Symptomatic improvement has been reported in various trials, but many of these trials were observational, and placebo (i.e. no ventricular pacing) and "training" (initial symptomatic improvement of patients undergoing DDD pacing) effects could not be eliminated [2–5, 9, 10].

The M-PATHY trial [10] was a landmark randomized, double-blind, cross-over study examining the role of pacing in reducing LVOT gradient, peak oxygen consumption, and symptoms in patients with obstructive HCM. Forty-eight symptomatic HCM patients with ≥50 mmHg resting gradient, and who were refractory to drug therapy were randomized to 3 months each of DDD pacing and pacing backup (AAI-30) in a double-blind, crossover study design, followed by an uncontrolled and unblinded 6-month pacing trial. No significant differences were evident between pacing and no pacing for subjective or objective measures of symptoms or exercise capacity, including NYHA functional class, quality of life score, treadmill exercise time or peak oxygen consumption. After 6 additional months of unblinded pacing, functional class and quality of life score were improved compared with baseline, but peak oxygen consumption was unchanged. The majority of patients showed up to a 40 % reduction in LVOT gradient. At 12 months, 6 patients (12 %) showed improved functional capacity; all were 65–75 years of age. Overall, Left ventricular wall thicknesses in the study group showed no remodeling between baseline and 12 months. The authors concluded that despite the majority of patients showing a modest improvement in LVOT gradient, pacing cannot be regarded as a primary treatment for obstructive HCM. They also noted a perceived symptomatic improvement, which was most consistent with a substantial placebo effect with randomization. The authors advised caution in interpreting symptomatic improvements with longer, uncontrolled pacing periods given these subjective findings were unaccompanied by objective improvement in cardiovascular performance. A small, but potentially important, subset (12 %) of patients ≥65 years of age showed a clinical response, suggesting that DDD pacing could be a therapeutic option for some elderly patients. This study represents the

primary data supporting PPM utilization for symptom reduction in elderly patients, even though this was a *post hoc* analysis. As a result, most institutions (and the guidelines) suggest moving to invasive therapies (i.e. alcohol septal ablation or surgical myomectomy) once symptoms are refractory to optimal medical therapy, rather than employing a trial of PPM. This is especially true for younger and middle-age patients, while elderly patients may have an option of a trial of pacing, based on their individualized risks of instead proceeding to septal reduction therapy.

Qintar et al. also analyzed the effects of LVOT gradient reduction in a recent analysis of randomized controlled trials of either parallel group (placebo-controlled) or crossover design, which examined the benefits and/or harmful effects of pacing in drug refractory or drug intolerant HCM patients [11]. In the crossover studies, active pacing was achieved by DDD pacing. In non-active pacing groups, backup AAI at 30 beats per minute was generally used. Both children and adults of either sex were included in this analysis. Primary outcomes were all-cause mortality, exercise capacity, symptomatic improvement as measured by New York Heart Association (NYHA) functional class and/or exercise capacity, and quality of life as measured by recognized scales. Secondary outcomes evaluated in this analysis were LVOT obstruction gradient, NYHA functional classification, LV wall thickness, peak oxygen consumption, complications related to device implantation, and cost-effectiveness. At the time of this publication only five studies met the inclusion criteria and all patients were adults. There was insufficient data to assess all-cause mortality, cost-effectiveness, quality of life, and peak oxygen consumption. Symptoms and NYHA class tended to improve in the studies that reported this data. However, given the small numbers of patients analyzed and the inconsistent reporting of these data, results were equivocal. Only one of these trials assessed exercise capacity time, which appeared to improve in the pacing arm, albeit not impressively. The results of quality-of-life questionnaires were extremely variable and impossible to interpret. LV wall thickness was evaluated in only one study and was found to be unchanged with pacing. In that study, LVOT gradient, as in some prior studies, improved; however, as stated above, this is a physiologic measure and not a clinical outcome. Complications appeared to be in line with expected numbers. The authors summarized that review of the data showed no convincing evidence to support or refute the use of active pacing in patients with HCM [4, 9, 10, 12, 13].

Cheng et al. focused on the structural impact of pacing in 37 patients with obstructive HCM [8]. Patients were followed for up to 4 years after dual-chamber pacemaker implantation. They specifically followed programming parameters and echocardiographic findings in these patients, who were paced greater than 98 % of the time. They found statistically significant declines in interventricular septal size, LVOT peak velocity, LVOT peak gradient, and an increase in LVOT diameter compared with pre-pacing measurements. Other parameters, including pulmonary artery systolic pressure and LV ejection fraction (LVEF), did not change. The authors concluded that beneficial cardiac structural changes can be derived from chronic dual-chamber pacing, and assumed that their findings indicated an improvement in the pathophysiology of HCM. Unfortunately, there are significant limitations to this study, and no confident conclusions can be drawn from this report.

Silva et al. reported on 39 HCM patients with heterogeneous indications, including both patients with and without LVOT obstruction, as well as AV block [14]. These patients were followed for up to 17 years, representing the longest follow-up period for HCM patients receiving pacemaker therapy published. Of note, only 13 of the 39 patients received a device for gradient related symptoms. Programming and stimulation mode were variable as well. The authors reported symptomatic and functional class improvement only in patients with obstruction. They concluded that pacing may be beneficial in drug treatment refractory obstructive HCM, but could not exclude that clinical improvement may have been attributable to co-interventions, such as myomectomy, frequently present in these patients. This study therefore, while reporting information on long-term outcomes of HCM patients receiving a pacemaker, provides little supportive or directive data with regard to device use.

Of note, Berruezo et al. reported beneficial structural changes as well as functional improvements in a small number of patients receiving biventricular pacemakers [15]. In this pilot study, nine patients had successful implantation of a biventricular device. The optimal pacing mode was biventricular in six, LV-only in 2, and RV-only in one. With biventricular pacing, functional capacity and quality of life progressively improved as demonstrated by a reduction in NYHA functional class, increase in 6-minute walk test distance, and quality of life improvement. The authors also showed an incremental and progressive reduction in LV outflow gradient in the year after implant utilizing biventricular pacing over the other pacing configurations (LV only and RV only). Gradient reduction was associated with diminished peak longitudinal displacement of the LV septum and earlier displacement of the lateral wall. The authors theorized that these findings might be due to a reduction in systolic anterior motion of the mitral valve resulting in a progressive reduction in mitral regurgitation. Another novel finding in this study was LV reverse remodeling (i.e. progressive reduction of LV mass) seen predominantly in the interventricular septum with biventricular pacing. Although this study was a small pilot study, the findings are thought provoking and require further investigation. Nonetheless, despite these find-

ings, given the extensive interpretive limitations found in the literature on long-term use of pacing in HCM, it is clear that conclusive recommendations cannot yet be made, and additional randomized studies of larger cohorts of patients are needed.

Knyshov et al. proposed a differentiated approach to the treatment of patients with obstructive HCM based on what they consider to be the three major pathogenic mechanisms underlying the development of HCM: hypertrophy of the myocardium, electromechanical disturbance of spatial activation and contraction, and pathology of the valvular and chordal apparatus of the mitral valve [16]. In a retrospective study of 194 patients, they divided patients into three treatment groups, and addressed specifically the 91 patients that had obstructive HCM. This study demonstrated that in these patients with drug-refractory symptomatic disease, surgical myomectomy, transcoronary alcohol septal ablation and dual-chamber DDD-mode pacing were equally effective at reducing left ventricular outflow tract obstruction, and each lead to similar subjective improvements in functional capacity. However, surgical myomectomy was most effective in improving objective NYHA functional class.

They concluded from their research that the positive effects they observed in their patients from implantation of pacemakers were attributable to positive results from temporary DDD stimulation performed prior to device implant. They propose the following mechanism of benefit based on the assumption that LVOT peak gradient and mitral regurgitation are similarly dependent on the LV excitation sequence and the LV pre-excitation efficacy of DDD-mode pacing, and conforming to the pathogenic mechanisms noted above. Genetically determined abnormalities of myofibril and myocyte orientation lead to hypertrophy of the basal septum, resulting in narrowing of the LVOT and changes in the sequence of LV electrical excitation. These delays in excitation occur at the LV apex and the papillary muscle associated with the anterior mitral leaflet, and the authors assume that this leads to papillary muscle dysfunction and systolic anterior motion of the anterior mitral leaflet. This exacerbates the LVOT gradient and leads to mitral regurgitation. This in turn increases myocyte work and triggers secondary hypertrophy, creating a self-augmenting cycle. The authors report evidence that LV apex pre-excitation leads to earlier papillary muscle activation, producing less mitral regurgitation and lower LVOT gradients. They propose that in selected patients, therefore, DDD pacing will be effective in the early phases of the disease. Consistent with this approach, they applied alcohol septal ablation therapy to those patients with LVOT gradients who did not demonstrate electromechanical disturbances of spatial activation and contraction or pathologic changes of the mitral valve. Surgical myomectomy was selected for patients with LVOT gradient and significant mitral valve pathology.

Employing this therapeutic framework, they propose several indications for the use of dual-chamber pacing in HCM patients, based on results of temporary DDD-mode pacing evaluation. Most importantly, the indications include a reduction of the LVOT gradient of at least 30 % and a residual gradient of less than 50 mmHg, as well as contraindications (either relative or absolute) to ablation or surgery. The authors note several important limitations to this study and the therapeutic approach that is derived from their findings, including small numbers in some subgroups, lack of randomization, and selection bias. Nonetheless, using a differentiated approach to patient selection based on assessing and understanding the pathogenesis of the hemodynamic derangements found for each individual patient may lead to clearer identification of those patients who will benefit from dual-chamber pacing.

As mentioned above, the M-PATHY trial [10] identified a subset of patients greater than 60–65 years of age that may derive specific benefit with respect to symptom improvement from pacing. Additionally, this group tends to include less than ideal candidates for septal reduction therapy [10, 17]. This was supported by a recent study which suggested that older patients (average age of 62 years) with more advanced NYHA functional class (class III-IV) and with significant resting LVOT gradients (>50 mmHg) may have a sustainable decrease in LVOT gradient as well as a persistent reduction in NYHA symptoms at up to 10 years of follow-up after pacing. However, this study was limited to 50 patients treated at a single center, the study was not randomized, and it did not use crossover or placebo pacing protocols (all patients were fully paced in the ventricle) [17].

Overall, data supporting symptom improvement is generally lacking or limited and suggests that pacemaker implantation should be reserved for patients who have medically refractory symptoms and who are not candidates for septal reduction therapy. Specifically, DDD pacing is not helpful in patients with non-obstructive HCM, those with no symptoms or symptoms controlled with medical therapy, or for patients who are candidates for septal reduction therapy [4, 9, 10, 18]. It is, however, reasonable to try dual chamber pacing in HCM patients who already have a pacemaker implanted for other indications [1].

Another factor tempering the utilization of DDD pacing (i.e. RV pacing), is that RV pacing has been shown to cause an increased incidence of congestive heart failure and atrial fibrillation. Whether or not this is applicable to patients with HCM is unknown [19]. Pacing should also not be used for mortality benefit or to change the natural history of the underlying disease process, as there is no data to propose these benefits [2, 10, 11]. Table 15.1 summarizes the ACCF/AHA Guidelines published in 2011 [1]. Importantly, there are no Class 1 indications for Pacing specific to HCM. In fact, the committee presented a total of five indications for

pacing, two of which are Class 3, identifying them as no benefit in HCM.

Lastly, in making a decision regarding the appropriateness of pacemaker implantation, it is necessary to recognize and recall the complex interrelationship between the hemodynamics of HCM, the specifics of pacemaker programming (discussed later in the chapter), and the impact of lead position. It is necessary to thoroughly understand the role of each of these factors in order to determine if any benefit from pacemaker implantation may be achieved. Given the variety of currently available options, therapy should be individualized to the patient.

Defibrillators

A subset of patients with HCM has an increased risk of SCD [20–23]. This risk may be dissociated from the degree of symptoms and exercise intolerance the patient may be suffering from, and indeed even asymptomatic patients may have a significant incidence of SCD. As such, screening for SCD is recommended for all patients with HCM [1], as it has been shown that ICDs are effective in aborting SCD in HCM patients [22]. In the past, some experts have recommended ICD implantation in all patients with a diagnosis of HCM. However, this universal recommendation is controversial and no longer supported by either the recent AHA/ACC guidelines or the prior ACC/ESC guidelines, especially considering that currently available SCD risk stratification strategies in this population do not always correctly identify all patients at risk, complication rates are high [24, 25] and the risk of SCD in the overall HCM population may be only minimally elevated [26]. In our HCM Center, where guidelines are strictly followed, ICD implantation is indicated in roughly 1 out of every 3 patients.

Results of recently reported clinical outcomes in a reasonably large cohort of patients continue to highlight important issues related to patient selection for an ICD [27], specifically those related to inappropriate shocks or implant complications. Thus, there is a continued need for focused patient selection algorithms for ICD implantation and accurate ICD programming methodologies to be developed to ensure the creation of appropriate implantation criteria. These issues are particularly difficult in the pediatric population with HCM, where there are additional technical difficulties associated with device implantation, high rates of inappropriate shocks and procedural complications, and particular psychiatric issues associated with the presence of a device, especially when aggregated over the lifetime of these young patients [28].

The subset of HCM patients with reduced LVEF and congestive heart failure are difficult to risk stratify. First, the etiology (or etiologies) responsible for developing the cardiomyopathy (CMP) is unclear and may be multiple. Diminished LVEF in HCM patients may result from standard pathologic processes seen in patients without HCM, such as CAD. Additionally, processes specific to HCM, such as chronic LVOT obstruction or myocyte abnormalities may result in decreased contractile force, i.e. “end-stage” or “burnt-out” HCM. Secondly, HCM patients have not been included in the primary prevention trials of SCD in patients with coronary disease or other forms of CMP. Therefore, it is difficult to extrapolate data from those trials to the HCM population. Accordingly, we treat HCM patients with ICDs as we do in the non-HCM patient population, assuming their risk is similar, but have no definitive or comparable data. In summary, in reduced LVEF HCM patients, it is reasonable to utilize any and all therapies useful for primary (or secondary) prevention established for other reduced LVEF heart failure patients, including ICD therapy. Importantly, some experts recommend ICD implantation for EF < 50 %, indicating any degree of systolic dysfunction, while others utilize the more standard threshold of 30–35 % seen in the general population. Further studies fine-tuning this approach will be necessary.

Table 15.2 summarizes the ACCF/AHA Guidelines published in 2011 [1]. Despite the creation of these formalized guidelines, most of the specific recommendations are based on expert consensus rather than clinical trials. Therefore, it is especially important to consider the risks associated with long-term ICD therapy prior to implantation.

With regard to outcomes in this population, there are no randomized trials demonstrating a mortality benefit attributable to ICDs. In the studies that do show “benefit,” appropriate ICD therapies are used as a surrogate endpoint for SCD, which does not control for differences in programmed device parameters and other variables, limiting their clinical utility [21, 27, 29–31]. In addition, it is well-known that roughly half of appropriate shocks would not have resulted in death, and thus this surrogate while helpful is not entirely accurate. Consistent with this, Germano et al. analyzed seven major ICD trials that randomized patients to ICD vs. medical therapy [29]. Appropriate ICD therapy rates equaled or exceeded control group all-cause mortality in six of seven of these trials. In studies that included death as an endpoint, appropriate ICD therapies outnumbered the incidence of sudden death in the control group by a factor of 2–3. The authors stated that appropriate ICD shocks cannot be equated with aborted sudden cardiac death, as has been done in the interpretation of various nonrandomized series of ICDs. In addition, they observed that the occurrence of appropriate therapies and effective shocks does not constitute proof that ICDs are superior to alternative management strategies, because not all VT and VF treated by ICDs would have resulted in sudden death.

Maron et al. conducted a retrospective analysis of HCM patients with ICDs [21]. The authors reported a 23 % rate of

Table 15.2 ICD implantation recommendations for patients with HCM

Class of recommendation	Recommendation	Level of evidence
Class I	ICD implantation should follow a thorough discussion of the strength of evidence, benefits, and risks to allow the informed patient's active participation in decision-making, as well as the application of individual clinical judgment.	C
	HCM patients with prior documented cardiac arrest, VF, or hemodynamically significant VT	B
Class IIa	First-degree relative with SCD presumably caused by HCM.	C
	Maximum LV wall thickness ≥ 30 mm	C
	One or more recent, unexplained syncopal episodes	C
	NSVT (particularly those <30 years of age) in the presence of other SCD risk factors or modifiers	C
	Abnormal blood pressure response with exercise in the presence of other SCD risk factors[a] or modifiers[b]	C
	High-risk children with HCM, based on unexplained syncope, massive LV hypertrophy, or family history of SCD, after taking into account the relatively high complication rate of long-term ICD implantation	C
Class IIb	Isolated bursts of NSVT in the absence of any other SCD risk factors or modifiers	C
	Abnormal blood pressure response with exercise in the absence of any other SCD risk factors or modifiers, particularly in the presence of significant outflow obstruction	C
Class III	Routine strategy in patients with HCM without an indication of increased risk	C
	Strategy to permit patients with HCM to participate in competitive athletics	C
	Identified HCM genotype in the absence of clinical manifestations of HCM	C

Based on Gersh et al. [1].
Abbreviations: *HCM* hypertrophic cardiomyopathy, *Hg* mercury, *ICD* implantable cardioverter-defibrillator, *LV* left ventricular, *mm* millimeters, *NSVT* nonsustained ventricular tachycardia, *SCD* sudden cardiac death, *VF* ventricular fibrillation, *VT* ventricular tachycardia
[a]Established risk factors: personal history of sustained VT/VF; family history of SCD; syncope; NSVT; LV wall thickness ≥30 mm; abnormal blood pressure response to exercise
[b]Potential SCD risk modifiers: resting LVOT gradient of ≥30 mmHg; late gadolinium enhancement on cardiac magnetic resonance imaging; LV apical aneurysm; genetic mutations

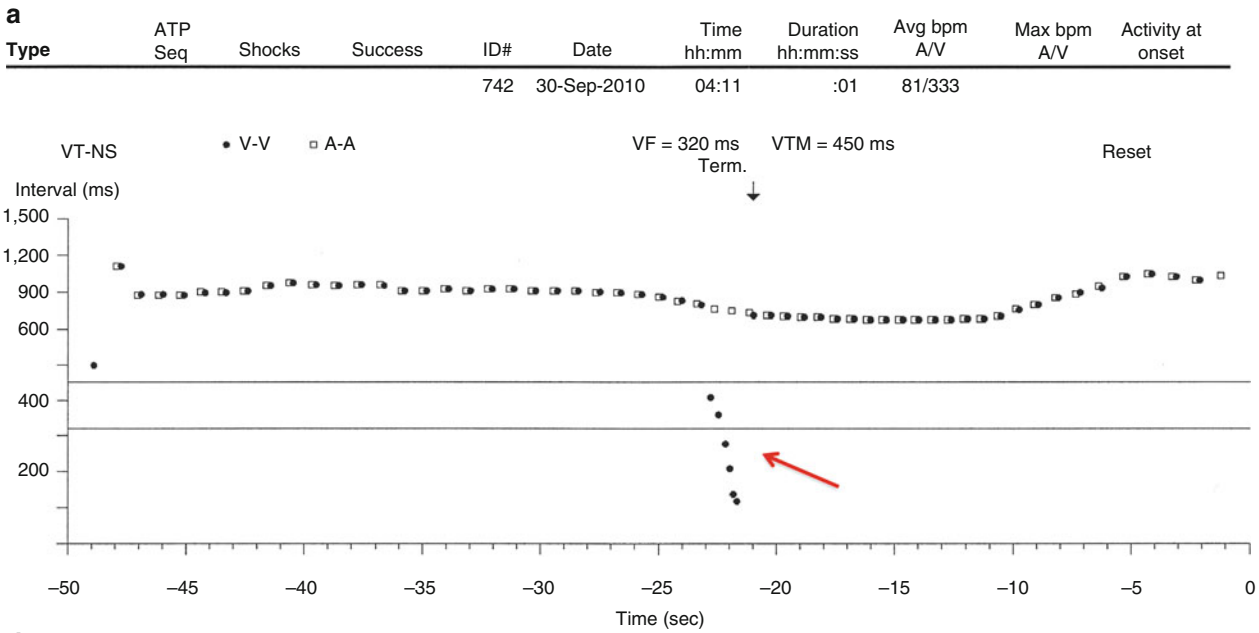
appropriate ICD therapy and correlate that to a reduction in sudden cardiac death. As it was a retrospective study, there was no control for device detection and therapy parameters, which clearly affect the incidence of appropriate ICD therapies. This represents an example of the potentially exaggerated benefit of ICD therapy, as it is likely that not all ICD therapies would have resulted in sudden death. Despite the fact that the magnitude of ICD benefit may be exaggerated, the occurrence of VT and VF in high-risk HCM patients and the efficacy of ICD therapy in terminating them cannot be ignored.

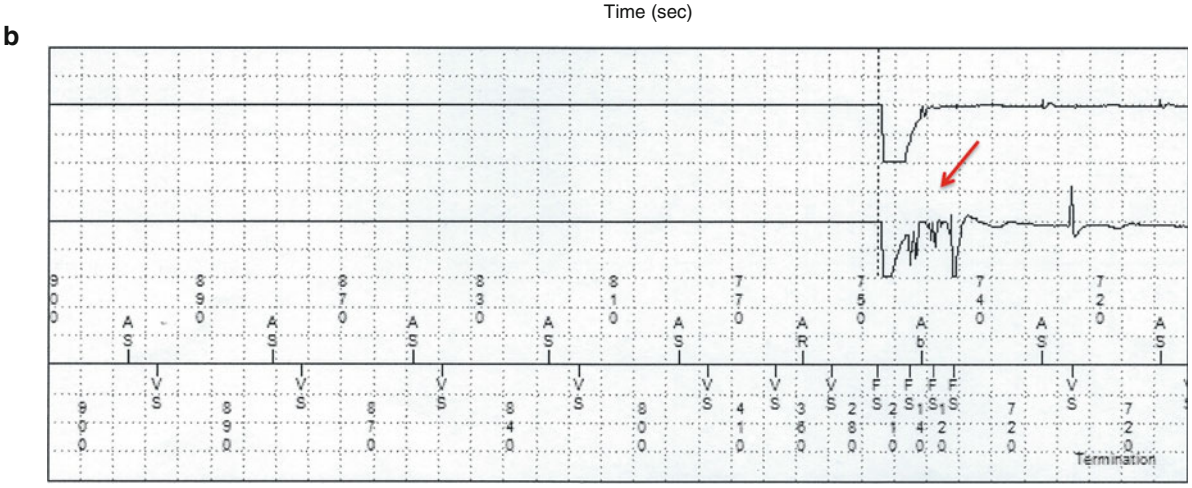
Procedural Considerations and Device Complications

Once the decision to implant a pacemaker has been made, there are various procedural considerations that must be addressed. RV pacing leads should be placed in the distal RV apex rather than on the RV septum. RV apical pacing has been shown to reduce the LVOT gradient without affecting cardiac output, which is not the case with RV septal pacing [32]. Preliminary data from at least one small study suggests that biventricular pacing may offer an even more substantial LVOT gradient reduction, implying that the mechanism of gradient reduction is complex and based on more than ventricular pre-excitation [33].

ICD leads are also placed in the RV apex both for pacing as well as defibrillation threshold (DFT) optimization. Apical placement is often more challenging in HCM due to increased trabeculations and the bulging intraventricular septum, which frequently obstructs the RV as well as the LV. Apical placement is important as HCM patients have been shown to have higher DFTs, which generally increases with increasing LV wall thickness [34]. For this reason, DFT testing at implant should be strongly considered at the time of lead placement.

Device-related complications (not including ICD therapies) have been reported to be in the range of 15–40 % in studies that followed patients for longer periods of time (up to 4 years). The most common complications included lead malfunction or displacement requiring revision as well as system infection. Lead problems are more common specifically in HCM patients given the more vigorous muscular contraction of the hyperdynamic heart provoking lead fracture in this group. HCM patients are also typically younger than other patients with ICDs, which may lead to issues of discomfort at the ICD site due to the muscularity of these patients and the fact that they are typically more physically active than older patients. These factors also contribute to lead fracture. Figure 15.1 shows various clinical





c

Sensing integrity counter

(if >300 counts, check for sensing issues)

Since 07-Sep-2010

Short V-V Intervals 501

d

RV pacing impedance

At implant	528 ohms	Highest	528 ohms
Last	1,520 ohms	Lowest	368 ohms

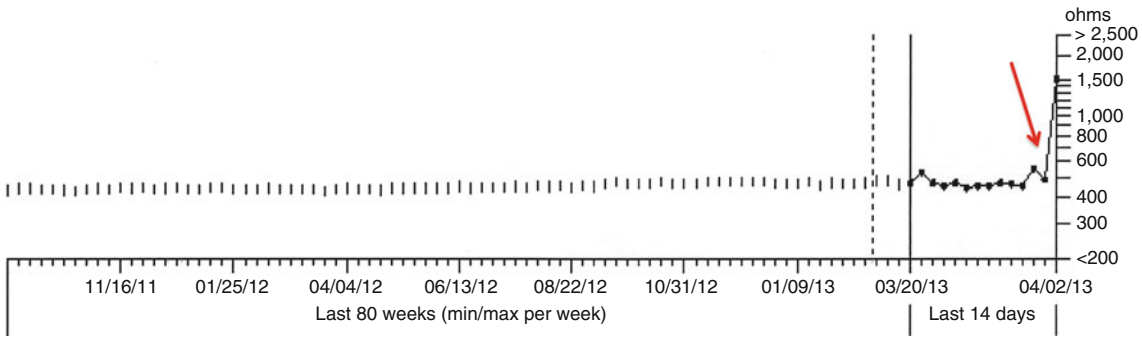


Fig. 15.1 Manifestations of ICD lead fracture. This figure shows the various manifestations of ICD lead fracture. Panel (**a**) depicts artifact representing "noise" on the ICD channel is shown by the outlying short V-V intervals (*red arrow*) with no change in the A-A intervals. This is confirmed in Panel (**b**), where "noise" and not VF is apparent (*red arrow*). Panel (**c**) shows the sensing integrity counter, which tracks non-physiologically short V-V intervals, indicating "noise." When >300 of these episodes are detected (assuming routine 3 month ICD interrogations), a lead fracture should be strongly considered. In this case, 501 episodes were noted. Panel (**d**) demonstrates another typical finding associated with lead fracture, a change in lead impedance. The *red arrow* demonstrates a rapid rise in lead impedance consistent with conductor fracture of the ICD lead

manifestations of ICD lead fractures. Shown are examples of "noise" and impedance changes, both typical findings in ICD lead fractures. The serious procedural complications of pneumothorax or cardiac tamponade have also been reported, but are relatively infrequent. Data on serious complications are inconsistent, due to variability in the clinical status of patients and disparities in reporting methods [35–37].

Inappropriate ICD therapies are a particular problem in HCM patients due to their young age (faster heart rates), increased incidence of atrial fibrillation, higher incidence of lead fracture, and T-wave over sensing (TWO). These issues are discussed in detail later in this chapter.

The decision as to whether to implant a single-chamber or dual-chamber ICD in HCM will vary based on clinical factors such as age, pacing indications, prior supraventricular arrhythmias and physician choice. Intuition would suggest that young patients and those with no pacing indications would most likely benefit from a single-chamber device to minimize complications associated with an additional lead, and those with prior SVT or AF and pacing indications would benefit from a dual-chamber device to achieve AV synchrony, potentially reduce outflow tract gradient, and improve supravnetricular tachycardia (SVT)/ventricular tachycardia (VT) discrimination. Dual chamber also allows better monitoring of subsequent events, including the frequency of AF.

As expected, however, in patients ≤30 years of age, dual-chamber devices have not demonstrated superior arrhythmia discrimination [38]. Further support for single-chamber devices is provided by analysis of the National Cardiovascular Data Registry (NCDR) in patients receiving ICDs for primary prevention without indications for pacing. These data demonstrate that the use of dual-chamber devices was associated with a higher risk of device-related complications [39, 40], increased in-hospital mortality [39], and similar 1-year mortality and hospitalization rates [40]. However, these data are not derived from randomized trials, are not unique to HCM, and selection bias for various clinical variables affecting mortality and morbidity cannot be eliminated. Arrhythmia discrimination was also not evaluated in this analysis from the NCDR. A small randomized trial showed that dual-chamber functionality resulted in less clinically significant adverse events than single-chamber functionality [41].

Both dual- and single-chamber devices have been shown to be safe and effective for detecting and treating life-threatening ventricular tachyarrhythmias [42]; however, discrepancy exists as to whether dual-chamber devices offer benefit over single-chamber devices with regard to detection of SVT and subsequent prevention of inappropriate therapies [42–44]. In one study, dual-chamber ICDs allowed better rhythm classification, but the applied detection algorithms did not offer benefits in avoiding inappropriate therapies during SVT. This was due to inadequacy of the algorithms themselves and atrial sensing errors [42]. Nevertheless, retrospective physician adjudication of arrhythmic events is likely enhanced with dual-chamber detection and may aide in programming to prevent future inappropriate episodes.

An important consideration in device selection is that the typical ICD patient has either an ischemic or nonischemic CMP (diminished LVEF), but the typical HCM patient has preserved LVEF. This is important because dual-chamber devices are generally associated with increased RV pacing, which is a more ominous phenomenon in CMP associated with low LVEF than in HCM. This makes morbidity and mortality analysis and comparisons between these two groups extremely difficult.

Device Monitoring

Recommendations for pacemaker interrogation are every 3–12 months, and every 3–6 months for ICDs. During these interrogations, information typically recorded includes battery longevity; system integrity and function; detected arrhythmia episodes; and device therapies. Interrogations in person or via remote monitoring are acceptable methods. The exact monitoring interval should be based on individual patient factors such as indication for implantation and clinical status. No distinct recommendations are made beyond these for HCM patients [45].

Reported annual rates of appropriate ICD therapy range from 3.3 to 6.8 %. Factors identified as predictive of appropriate ICD therapies in HCM patients include NSVT, history of prior cardiac arrest or sustained ventricular arrhythmia, male gender, young age (usually defined as patient age <30 years) and a history of AF [35–37, 46, 47].

Rates of inappropriate ICD therapy are reported to be 3.7–6.9 % per year. The majority of inappropriate therapies are a result of rapid ventricular rates associated with AF and sinus tachycardia. Other common causes are lead noise due to lead failure/fracture and TWO. TWO is a phenomenon commonly seen in HCM patients, given the increased frequency of large T-waves in these patients. These T-waves are mistakenly interpreted as additional R-waves, artificially classifying sinus rhythm as ventricular rhythms [35–37, 46, 47]. Figure 15.2 shows a HCM patient with TWO noted on routine interrogation. This is traditionally managed by decreasing the maximum R-wave sensitivity. However, this adjustment has the potential risk of underdetection of future ventricular fibrillation (VF) given the variable sensitivity standard on ICDs to accommodate detection of R-waves for purposes of pacing and defibrillation. Some ICD manufacturers have proprietary algorithms to prevent this phenomenon. A full description of these algorithms is beyond the scope of this text. However, it is essential to perform defibrillation testing in patients after VF detection parameters are changed to ensure proper detection and effective treatment of VF.

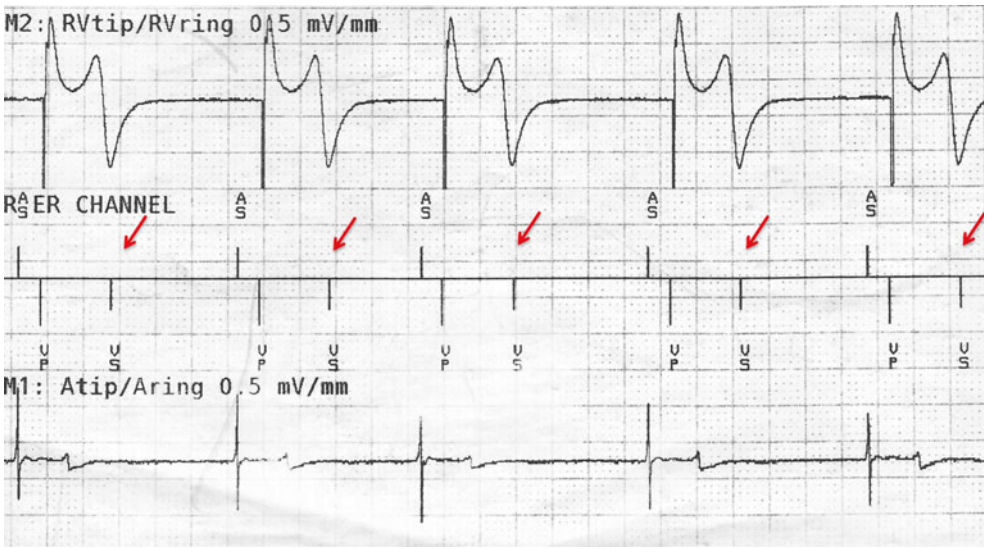


Fig. 15.2 T-wave oversensing. This figure depicts a phenomenon known as T-wave oversensing. The T-wave is inappropriately sensed as another R-wave (QRS complex) due to the large magnitude of the T-wave, common in patients with massive hypertrophy seen in HCM (depicted by *arrows*). This phenomenon can lead to double counting (counting both the R-wave and T-Wave) resulting in inappropriate ICD therapies due to falsely perceived high ventricular rates

Defibrillation threshold testing should also be performed when adding antiarrhythmic agents that can increase the defibrillation threshold (e.g. amiodarone). This should be done after an adequate loading dose of the antiarrhythmic drug has been administered. Defibrillation testing should also be considered when any cardiac structural changes have occurred, such as increased LV thickening, change in LV ejection fraction, myocardial infarction, and potentially after myomectomy and alcohol septal ablation, depending on the extent of the septal injury.

Rates of ICD therapies (both appropriate and inappropriate) are influenced by numerous variables and include: the subset of HCM patients being studied; the type of device used (single vs. dual-chamber); the use of SVT discriminators; and programmed ICD detection and therapy parameters. As such, careful attention to programming ICD parameters can help avoid unnecessary ICD therapies (see below).

Contemporary pacemakers and ICDs have expanded memory and diagnostic capabilities. These diagnostics have become a routine part of device interrogation, both at the bedside and via remote monitoring, and are important for subclinical arrhythmia detection and for alerting to device and lead malfunction or therapies. It is common to observe subclinical atrial fibrillation and atrial flutter. This detection capability is important as it may identify patients at increased risk of a future thromboembolic event, and as such should prompt a discussion about rate/rhythm control and anticoagulation. Data from the TRENDS study [48] suggests that thromboembolic risk is a quantitative function of AF burden. AF burden ≥5.5 hours on any of 30 prior days appeared to double thromboembolic risk. Similarly, the ASSERT trial [49] showed that subclinical atrial tachyarrhythmias (atrial rate >190 beats per minute for >6 minutes) detected on pacemakers and ICDs in patients over 65 years of age with hypertension and no history of atrial fibrillation were associated with a 2.5-fold increased risk of ischemic stroke or systemic embolism. Additional studies are needed to more precisely investigate the relationship between stroke risk and AF burden in patients with and without devices. An additional benefit of AF monitoring is the potential discontinuation of anticoagulation in patients who are AF-free for a period of time. This strategy is controversial and can lead to an increased risk of stroke, but may be helpful in certain clinical scenarios [50].

The use of proprietary algorithms to determine intrathoracic impedance to assess fluid status (i.e. congestive heart failure) has been utilized in HCM patients although data is limited. In our center, we use this measurement as an adjunctive tool to manage patients with HCM and CHF. Figure 15.3 demonstrates a patient in our practice with CHF and HCM, in which a rise in the fluid accumulation index preceded the development of clinical signs of CHF. Diuretic therapy improved the patient's symptoms and resulted in a decrease in the fluid accumulation index [51]. Note the variations in thoracic impedance over several months, which changed with clinical status and diuresis.

Device Programming

Pacemaker Programming

Pacemaker programming in HCM will depend on the indication for pacing. If the pacemaker was implanted for sinus node dysfunction, AV conduction disturbances, or to allow optimization of medical therapy for symptom control (traditional indications), the pacemaker is programmed accordingly. In patients in which the pacemaker was placed to treat symptomatic LVOT obstruction or in those where symptom alleviation is desired, short AV delays are generally used to ensure complete ventricular capture at both rest and with

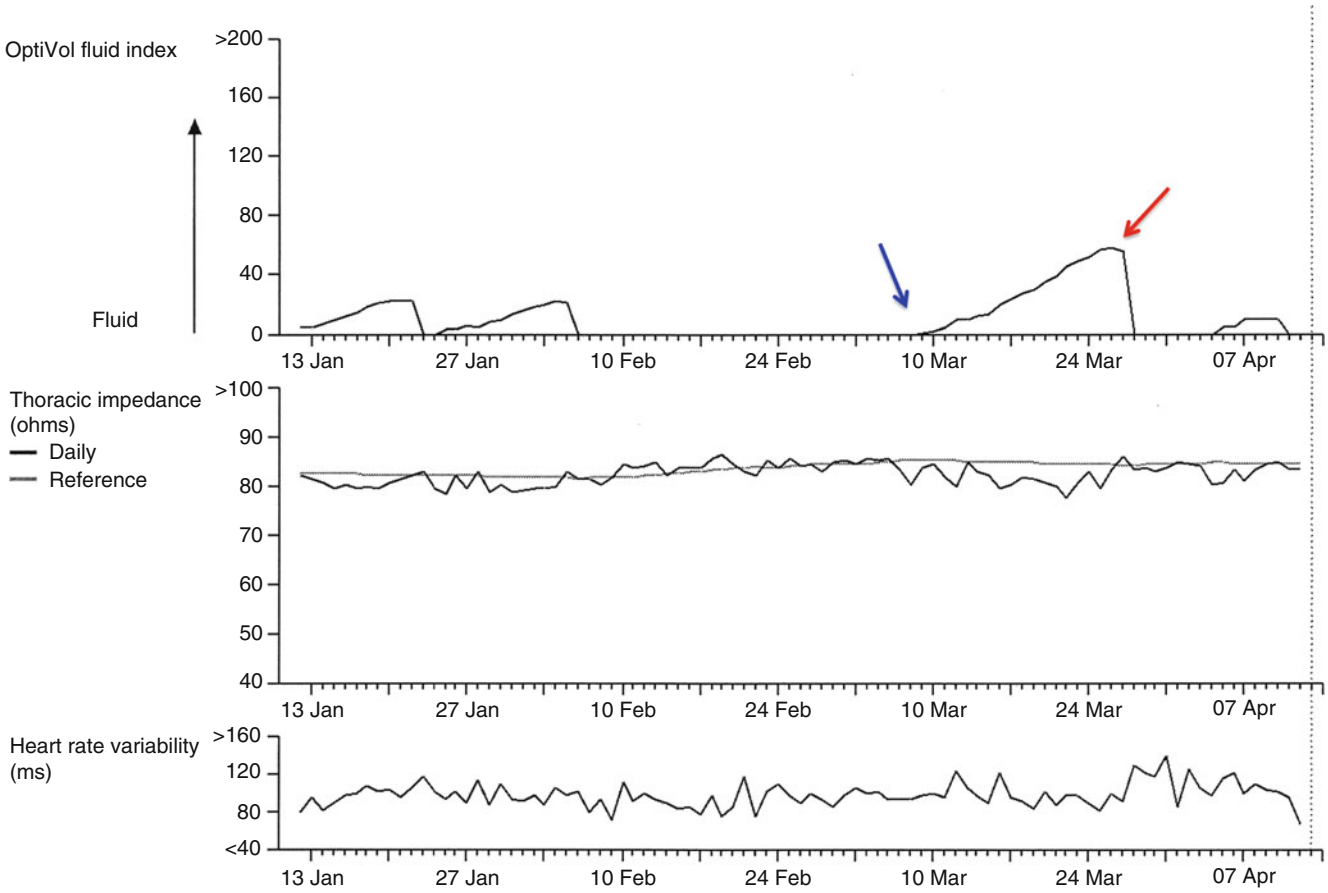


Fig. 15.3 Transthoracic impedance metrics in HCM and CHF. This figure demonstrates the variations in thoracic impedance in a patient with HCM and congestive heart failure seen over several months. The *blue arrow* shows the beginning of a period of fluid accumulation (increased fluid index), manifest as a drop in impedance. The *red arrow* shows the initiation of diuretic therapy and a return of fluid levels to baseline. Note that the fluid index is inversely related the thoracic impedance, i.e. a decrease in thoracic impedance corresponds to an increase in fluid accumulation

exertion, and to optimize ventricular filling. In most cases, the optimal AV delay has been identified as the longest AV interval that results in complete ventricular pre-excitation (i.e. ventricular pacing. This AV delay often results in deterioration in both systolic and diastolic function but to a lesser magnitude than pacing at the shortest AV intervals [52]. In addition, when dual-chamber pacing is desired, rate-adaptive AV delays should be used to ensure RV pacing with exertion.

As with non-HCM patients, rate response should be considered in patients with significant baseline bradycardia whether due to sinus node dysfunction and/or medical therapy. After device implantation, heart rate variability should be assessed by device histograms and rate response modes and settings should be programmed accordingly.

ICD Programming

As noted earlier, inappropriate shocks are a particular problem in HCM. Efforts should be made to avoid these shocks using careful ICD programming. One method is to use higher detection intervals. Fortunately, this can usually be accomplished safely as slow monomorphic VT is rare in HCM, allowing higher programmed detection rates without the risk of neglecting slower VT [22]. Another method is to prolong detection intervals. Several recent studies have shown this to be a successful way to prevent inappropriate shocks without increasing the risk of mortality or syncope [53–55]. Utilization of antitachycardia pacing has been shown to be a safe and effective strategy in HCM [56]; however, this is generally not expected to be a major strategy utilized in HCM, as most ventricular arrhythmias are VF or polymorphic VT [22]. Various other proprietary algorithms are available to assist in differentiating VT and SVT, as well as to prevent TWO, and should generally be employed. A discussion of each of these is beyond the scope of this text.

In most primary prevention trials, therapy zones often identify a ventricular rate of 188 beats per minute as the first VF (or VT) detection zone [57]. This will obviously vary with the specific clinical scenario and other factors, such as patient age. In our practice, we generally program older

patients with therapy zones that are lower than 188 beats per minute and younger patients with zones that are higher than 188 beats per minute. We also employ a monitor zone in almost all patients, generally at 150 beats per minute. However, both monitor and therapy zones need to be individualized for all patients.

Device Malfunction and Recall

Pacemaker pulse generator and lead performance has always been good, and has improved since the 1990s. However, ICD system malfunction has become an area of growing concern. While ICD pulse generator function appears to be excellent and malfunction rates are very low, high-voltage-capability ICD lead failure rates have become an issue with the advent of recent recalls. Generally speaking, ICD leads fail at a rate of 0.5–1 % per year. However, despite having been shown to be safe and effective in HCM patients, ICD leads fail at a higher rate (1.4 %) in the younger more active population of HCM patients. These failures appear to be due more to faulty lead design than patient characteristics. Nevertheless, the contribution of a hyperdynamic heart and physical activity cannot be excluded as a precipitant in eliciting these defects [46, 58–62].

Managing device system malfunction, advisories, and recalls are complex issues that are largely beyond the scope of this chapter; however, there are some important considerations specific to the HCM patient. First, as a group, this is a younger population of patients that may require device therapy for many decades. Given the increased length of time they are exposed to this therapy, their hyperdynamic LV systolic function, and increased physical activity, they will almost certainly have system issues at some point. These issues should be discussed with patients before device implantation. Communication of all the issues associated with device implantation is particularly critical in these patients.

Clinical Pearls

- Pacemakers are commonly used in HCM, most often for traditional indications rather than because of the presence of HCM, but also to allow sufficient medical therapy for symptom control. Use of pacemakers for symptom control is not routinely beneficial, but may have a role in elderly patients.
- Apical lead placement is essential in HCM patients for both pacing and defibrillation applications.
- Defibrillation threshold is often higher in the HCM population and care must be taken to ensure proper programming.
- Attention must be paid to T-waves at implant, as TWO can be a significant issue in these patients.
- ICD patient selection is important. Most patients, even with clear indications, will never receive ICD therapies. Complications, which include inappropriate therapies, system malfunction, and other issues, are frequently higher in this population, and may importantly affect the risk to benefit analysis. Therefore, patients should be counseled accordingly prior to device implantation.

References

1. Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2011;58:e212–60.
2. Fananapazir L, Epstein ND, Curiel RV, Panza JA, Tripodi D, McAreavey D. Long-term results of dual-chamber (DDD) pacing in obstructive hypertrophic cardiomyopathy. Evidence for progressive symptomatic and hemodynamic improvement and reduction of left ventricular hypertrophy. Circulation. 1994;90:2731–42.
3. Jeanrenaud X, Goy JJ, Kappenberger L. Effects of dual-chamber pacing in hypertrophic obstructive cardiomyopathy. Lancet. 1992;339:1318–23.
4. Nishimura RA, Trusty JM, Hayes DL, et al. Dual-chamber pacing for hypertrophic cardiomyopathy: a randomized, double-blind, crossover trial. J Am Coll Cardiol. 1997;29:435–41.
5. Slade AK, Sadoul N, Shapiro L, et al. DDD pacing in hypertrophic cardiomyopathy: a multicentre clinical experience. Heart. 1996;75:44–9.
6. Posma JL, Blanksma PK, Van Der Wall EE, Vaalburg W, Crijns HJ, Lie KI. Effects of permanent dual chamber pacing on myocardial perfusion in symptomatic hypertrophic cardiomyopathy. Heart. 1996;76:358–62.
7. Pak PH, Maughan WL, Baughman KL, Kieval RS, Kass DA. Mechanism of acute mechanical benefit from VDD pacing in hypertrophied heart: similarity of responses in hypertrophic cardiomyopathy and hypertensive heart disease. Circulation. 1998;98:242–8.
8. Yue-Cheng H, Zuo-Cheng L, Xi-Ming L, et al. Long-term follow-up impact of dual-chamber pacing on patients with hypertrophic obstructive cardiomyopathy. Pacing Clin Electrophysiol. 2013;36:86–93.
9. Kappenberger L, Linde C, Daubert C, et al. Pacing in hypertrophic obstructive cardiomyopathy. A randomized crossover study. PIC Study Group. Eur Heart J. 1997;18:1249–56.
10. Maron BJ, Nishimura RA, McKenna WJ, Rakowski H, Josephson ME, Kieval RS. Assessment of permanent dual-chamber pacing as a treatment for drug-refractory symptomatic patients with obstructive hypertrophic cardiomyopathy. A randomized, double-blind, crossover study (M-PATHY). Circulation. 1999;99:2927–33.
11. Qintar M, Morad A, Alhawasli H, et al. Pacing for drug-refractory or drug-intolerant hypertrophic cardiomyopathy. Cochrane Database Syst Rev. 2012;5:CD008523.
12. Gao YC, Li Y, Han ZH, Zhang XL, Zhao H, Jiang TY. Transcoronary ablation of septal hypertrophy versus dual-chamber cardiac pacing for the treatment of aged patients with hypertrophic obstructive

cardiomyopathy. Zhonghua Xin Xue Guan Bing Za Zhi. 2007;35:333–6.
13. Mickelsen S, Bathina M, Hsu P, Holmes J, Kusumoto FM. Doppler evaluation of the descending aorta in patients with hypertrophic cardiomyopathy: potential for assessing the functional significance of outflow tract gradients and for optimizing pacemaker function. J Interv Card Electrophysiol. 2004;11:47–53.
14. Silva LA, Fernandez EA, Martinelli Filho M, et al. Cardiac pacing in hypertrophic cardiomyopathy: a cohort with 24 years of follow-up. Arq Bras Cardiol. 2008;91(250–6):74–80.
15. Berruezo A, Vatasescu R, Mont L, et al. Biventricular pacing in hypertrophic obstructive cardiomyopathy: a pilot study. Heart Rhythm. 2011;8:221–7.
16. Knyshov G, Lazoryshynets V, Rudenko K, et al. Is surgery the gold standard in the treatment of obstructive hypertrophic cardiomyopathy? Interact Cardiovasc Thorac Surg. 2013;16:5–9.
17. Galve E, Sambola A, Saldana G, et al. Late benefits of dual-chamber pacing in obstructive hypertrophic cardiomyopathy: a 10-year follow-up study. Heart. 2010;96:352–6.
18. Cannon 3rd RO, Tripodi D, Dilsizian V, Panza JA, Fananapazir L. Results of permanent dual-chamber pacing in symptomatic non-obstructive hypertrophic cardiomyopathy. Am J Cardiol. 1994;73:571–6.
19. Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices): developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. Circulation. 2008;117:e350–408.
20. Elliott PM, Gimeno Blanes JR, Mahon NG, Poloniecki JD, McKenna WJ. Relation between severity of left-ventricular hypertrophy and prognosis in patients with hypertrophic cardiomyopathy. Lancet. 2001;357:420–4.
21. Maron BJ, Shen WK, Link MS, et al. Efficacy of implantable cardioverter-defibrillators for the prevention of sudden death in patients with hypertrophic cardiomyopathy. N Engl J Med. 2000;342:365–73.
22. Maron BJ, Spirito P, Shen WK, et al. Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy. JAMA. 2007;298:405–12.
23. Teare D. Asymmetrical hypertrophy of the heart in young adults. Br Heart J. 1958;20:1–8.
24. Maron BJ, Maron MS, Lesser JR, et al. Sudden cardiac arrest in hypertrophic cardiomyopathy in the absence of conventional criteria for high risk status. Am J Cardiol. 2008;101:544–7.
25. Thaman R, Gimeno JR, Reith S, et al. Progressive left ventricular remodeling in patients with hypertrophic cardiomyopathy and severe left ventricular hypertrophy. J Am Coll Cardiol. 2004;44:398–405.
26. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. JAMA. 2002;287:1308–20.
27. O'Mahony C, Lambiase PD, Quarta G, et al. The long-term survival and the risks and benefits of implantable cardioverter defibrillators in patients with hypertrophic cardiomyopathy. Heart. 2012;98:116–25.
28. Ostman-Smith I. Hypertrophic cardiomyopathy in childhood and adolescence – strategies to prevent sudden death. Fundam Clin Pharmacol. 2010;24:637–52.
29. Germano JJ, Reynolds M, Essebag V, Josephson ME. Frequency and causes of implantable cardioverter-defibrillator therapies: is device therapy proarrhythmic? Am J Cardiol. 2006;97:1255–61.
30. Maron BJ, Haas TS, Shannon KM, Almquist AK, Hodges JS. Long-term survival after cardiac arrest in hypertrophic cardiomyopathy. Heart Rhythm. 2009;6:993–7.
31. Maron BJ, Spirito P, Ackerman MJ, et al. Prevention of sudden cardiac death with implantable cardioverter-defibrillators in children and adolescents with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2013;61:1527–35.
32. Gadler F, Linde C, Juhlin-Dannfeldt A, Ribeiro A, Ryden L. Influence of right ventricular pacing site on left ventricular outflow tract obstruction in patients with hypertrophic obstructive cardiomyopathy. J Am Coll Cardiol. 1996;27:1219–24.
33. Lenarczyk R, Wozniak A, Kowalski O, et al. Effect of cardiac resynchronization on gradient reduction in patients with obstructive hypertrophic cardiomyopathy: preliminary study. Pacing Clin Electrophysiol. 2011;34:1544–52.
34. Roberts BD, Hood RE, Saba MM, Dickfeld TM, Saliaris AP, Shorofsky SR. Defibrillation threshold testing in patients with hypertrophic cardiomyopathy. Pacing Clin Electrophysiol. 2010;33:1342–6.
35. Schinkel AF, Vriesendorp PA, Sijbrands EJ, Jordaens LJ, ten Cate FJ, Michels M. Outcome and complications after implantable cardioverter defibrillator therapy in hypertrophic cardiomyopathy: systematic review and meta-analysis. Circ Heart Fail. 2012;5:552–9.
36. Syska P, Przybylski A, Chojnowska L, et al. Implantable cardioverter-defibrillator in patients with hypertrophic cardiomyopathy: efficacy and complications of the therapy in long-term follow-up. J Cardiovasc Electrophysiol. 2010;21:883–9.
37. Lin G, Nishimura RA, Gersh BJ, et al. Device complications and inappropriate implantable cardioverter defibrillator shocks in patients with hypertrophic cardiomyopathy. Heart. 2009;95:709–14.
38. Lawrence D, Von Bergen N, Law IH, et al. Inappropriate ICD discharges in single-chamber versus dual-chamber devices in the pediatric and young adult population. J Cardiovasc Electrophysiol. 2009;20:287–90.
39. Dewland TA, Pellegrini CN, Wang Y, Marcus GM, Keung E, Varosy PD. Dual-chamber implantable cardioverter-defibrillator selection is associated with increased complication rates and mortality among patients enrolled in the NCDR implantable cardioverter-defibrillator registry. J Am Coll Cardiol. 2011;58:1007–13.
40. Peterson PN, Varosy PD, Heidenreich PA, et al. Association of single- vs dual-chamber ICDs with mortality, readmissions, and complications among patients receiving an ICD for primary prevention. JAMA. 2013;309:2025–34.
41. Almendral J, Arribas F, Wolpert C, et al. Dual-chamber defibrillators reduce clinically significant adverse events compared with single-chamber devices: results from the DATAS (Dual chamber and Atrial Tachyarrhythmias Adverse events Study) trial. Europace. 2008;10:528–35.
42. Theuns DA, Klootwijk AP, Goedhart DM, Jordaens LJ. Prevention of inappropriate therapy in implantable cardioverter-defibrillators: results of a prospective, randomized study of tachyarrhythmia detection algorithms. J Am Coll Cardiol. 2004;44:2362–7.
43. Deisenhofer I, Kolb C, Ndrepepa G, et al. Do current dual chamber cardioverter defibrillators have advantages over conventional single chamber cardioverter defibrillators in reducing inappropriate therapies? A randomized, prospective study. J Cardiovasc Electrophysiol. 2001;12:134–42.
44. Friedman PA, McClelland RL, Bamlet WR, et al. Dual-chamber versus single-chamber detection enhancements for implantable defibrillator rhythm diagnosis: the detect supraventricular tachycardia study. Circulation. 2006;113:2871–9.
45. Tracy CM, Epstein AE, Darbar D, et al. 2012 ACCF/AHA/HRS focused update of the 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Heart Rhythm. 2012;9:1737–53.
46. Hauser RG, Maron BJ, Marine JE, et al. Safety and efficacy of transvenous high-voltage implantable cardioverter-defibrillator

leads in high-risk hypertrophic cardiomyopathy patients. Heart Rhythm. 2008;5:1517–22.
47. Woo A, Monakier D, Harris L, et al. Determinants of implantable defibrillator discharges in high-risk patients with hypertrophic cardiomyopathy. Heart. 2007;93:1044–5.
48. Glotzer TV, Daoud EG, Wyse DG, et al. The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk: the TRENDS study. Circ Arrhythm Electrophysiol. 2009;2:474–80.
49. Healey JS, Connolly SJ, Gold MR, et al. Subclinical atrial fibrillation and the risk of stroke. N Engl J Med. 2012;366:120–9.
50. Corley SD, Epstein AE, DiMarco JP, et al. Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study. Circulation. 2004;109:1509–13.
51. Silva JN, VON Bergen NH, Dubin AM, et al. Assessment of intrathoracic impedance algorithm in the pediatric and adult congenital population. Pacing Clin Electrophysiol. 2014;37:1174–1180
52. Nishimura RA, Hayes DL, Ilstrup DM, Holmes Jr DR, Tajik AJ. Effect of dual-chamber pacing on systolic and diastolic function in patients with hypertrophic cardiomyopathy. Acute Doppler echocardiographic and catheterization hemodynamic study. J Am Coll Cardiol. 1996;27:421–30.
53. Wilkoff BL, Williamson BD, Stern RS, et al. Strategic programming of detection and therapy parameters in implantable cardioverter-defibrillators reduces shocks in primary prevention patients: results from the PREPARE (Primary Prevention Parameters Evaluation) study. J Am Coll Cardiol. 2008;52:541–50.
54. Wilkoff BL, Ousdigian KT, Sterns LD, Wang ZJ, Wilson RD, Morgan JM. A comparison of empiric to physician-tailored programming of implantable cardioverter-defibrillators: results from the prospective randomized multicenter EMPIRIC trial. J Am Coll Cardiol. 2006;48:330–9.
55. Wathen MS, DeGroot PJ, Sweeney MO, et al. Prospective randomized multicenter trial of empirical antitachycardia pacing versus shocks for spontaneous rapid ventricular tachycardia in patients with implantable cardioverter-defibrillators: Pacing Fast Ventricular Tachycardia Reduces Shock Therapies (PainFREE Rx II) trial results. Circulation. 2004;110:2591–6.
56. Cha YM, Gersh BJ, Maron BJ, et al. Electrophysiologic manifestations of ventricular tachyarrhythmias provoking appropriate defibrillator interventions in high-risk patients with hypertrophic cardiomyopathy. J Cardiovasc Electrophysiol. 2007;18:483–7.
57. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med. 2005;352:225–37.
58. Maisel WH. Pacemaker and ICD generator reliability: meta-analysis of device registries. JAMA. 2006;295:1929–34.
59. Hauser RG, Kallinen LM, Almquist AK, Gornick CC, Katsiyiannis WT. Early failure of a small-diameter high-voltage implantable cardioverter-defibrillator lead. Heart Rhythm. 2007;4:892–6.
60. Maisel WH. Transvenous implantable cardioverter-defibrillator leads: the weakest link. Circulation. 2007;115:2461–3.
61. Maisel WH. Semper fidelis–consumer protection for patients with implanted medical devices. N Engl J Med. 2008;358:985–7.
62. Kleemann T, Becker T, Doenges K, et al. Annual rate of transvenous defibrillation lead defects in implantable cardioverter-defibrillators over a period of >10 years. Circulation. 2007;115:2474–80.

Management of Arrhythmia: Medications, Electrophysiology Studies and Ablation

16

Daniel R. Zakhary, Joseph J. Germano, and Mark E. Josephson

Abstract

In patients with hypertrophic cardiomyopathy (HCM), arrhythmias including atrial fibrillation (AF), supraventricular tachycardia (SVT), and ventricular tachycardia (VT) are common. Many of these arrhythmias are asymptomatic, especially if of short duration, but some can precipitate syncope, palpitations, hemodynamic collapse or sudden cardiac death (SCD). Therefore, the evaluation of such arrhythmias, both proactively and reactively, and their clinical significance in patients with HCM is of paramount importance. In this chapter, we will discuss the incidence, diagnosis, medical management, and role of invasive testing and ablation for arrhythmias in HCM patients.

Keywords

Hypertrophic cardiomyopathy • Atrial fibrillation • Supraventricular tachycardia • Ventricular tachycardia • Sudden cardiac death • Ablation

Key Points

- Ambulatory electrocardiogram (ECG) monitoring should be used annually and when new symptoms potentially referable to arrhythmias arise, both to screen and diagnose arrhythmic disease in HCM patients, as arrhythmias are more frequent and significant in this population.
- Electrophysiology studies (EPS) are probably not helpful as a risk stratification tool in HCM, and are thus not routinely recommended.
- Atrial fibrillation (AF) is usually poorly tolerated in HCM patients, and sinus rhythm should be maintained when possible.
- Stroke risk in HCM patients with AF is high and most data suggest they should be anticoagulated irrespective of the presence or absence of other risk factors for thromboembolism.
- Radiofrequency ablation for AF can be beneficial in patients with HCM who have refractory symptoms or who cannot tolerate or are poor candidates for antiarrhythmic drugs.
- In HCM patients with two or more major risk factors for sudden cardiac death (SCD), the annual incidence of SCD approaches 4–5 %, warranting prophylactic implantable cardioverter defibrillator (ICD) therapy; in those with 1 major risk factor, and depending on the actual risk factor, ICD should be strongly considered. Patients with minor risk factors may also warrant ICD consideration on a case-by-case basis.

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- The amount of late gadolinium enhancement by MRI may be related to a higher risk of sudden cardiac death, and may prove to be an important predictor of high-risk among HCM patients; further studies are necessary.
- Although data remain limited, and the procedure challenging to perform, VT ablation in HCM appears associated with good long-term outcome.

Introduction and Overview

In patients with hypertrophic cardiomyopathy (HCM), all arrhythmias including atrial fibrillation (AF), supraventricular tachycardia (SVT), and ventricular tachycardia (VT) are common and the general prevalence increases with age. The diagnosis of arrhythmias in HCM may be suggested clinically based on symptoms such as palpitations or syncope, but it generally requires further testing. Ambulatory ECG monitoring is important for screening, as arrhythmias are usually of greater significance in the HCM population. All patients should also be screened with echocardiography mainly to assess the degree of LVH, as it is directly related to an increased risk for sudden cardiac death (SCD). Implantable loop recorders or ambulatory event monitors may be particularly helpful in patients with recurrent unexplained symptoms, especially prior to contemplation of ICD implantation.

There are important genetic associations in HCM with several pre-excitation syndromes. HCM has been described in patients with mutations in the PRKAG2 or LAMP2 genes [1, 2]. The proteins encoded by these genes are involved in carbohydrate metabolism rather than sarcomere structure like the other HCM mutations, emphasizing the genetic heterogeneity of the disease. Progressive conduction system disease requiring pacemaker implantation is common with PRKAG2 mutations while progression to end-stage HF in early adulthood is common with LAMP2 mutations. In addition, the association of WPW syndrome with autosomal dominant familial hypertrophic cardiomyopathy is well established in the literature. Recently, the genetic substrate linking hypertrophic cardiomyopathy to WPW syndrome has been identified; ventricular pre-excitation and hypertrophic cardiomyopathies were shown to segregate as a single autosomal dominant disorder by genetic linkage analyses to chromosome7q3 [3, 4].

However, limited data exists regarding the significance and treatment of these SVTs. For patients with AV nodal reentry tachycardia (AVNRT), high dose AVN blockers are usually sufficient, but it may be reasonable to pursue electrophysiology studies (EPS) and ablation in poorly tolerated or difficult to control cases. For patients with Wolff-Parkinson-White (WPW) syndrome, there is a risk of maintaining patients on AVN blocking monotherapy without the use of concurrent antiarrhythmic medications, due to the underlying potential to develop atrial or ventricular tachyarrhythmias. Overall, evidence suggests WPW should be identified and treated with radiofrequency ablation (RFA) ablation when found.

Atrial fibrillation is poorly tolerated in HCM, and as with all patients with AF, HCM patients can be managed with either a rate control (controlling the ventricular rate while allowing the patient to remain in AF) or a rhythm control strategy (using cardioversion, antiarrhythmic drugs, and/or procedures to maintain sinus rhythm). Stroke risk is high in this population and, consequently, anticoagulation is the cornerstone of AF treatment. All patients with HCM should be anticoagulated, even after a first or short-lived episode, because the likelihood of further (oftentimes subclinical) episodes is high. AF is frequently eliminated by pulmonary vein isolation (ablation), which disrupts the electrical activity between tissues containing these arrhythmogenic triggers and substrate and the left atria. Ablation can be successful in restoring long-term sinus rhythm and improving symptomatic status in most HCM patients with refractory AF, but may require multiple lesion delivery and repeat procedures, with the risk of increased complications. In addition, whether the frequency of non pulmonary vein triggers is higher in HCM patients remains unknown, but may contribute to higher recurrence. Accordingly, there may be a role for novel convergent (combined surgical and percutaneous) procedures to achieve successful ablation, especially in refractory cases or when non-PV triggers are found in the hypertrophied and disorganized myocardium. In summary, AF ablation is useful but may require a more aggressive approach and/or repeat procedures in HCM patients.

The recommendations for management of ventricular arrhythmias in HCM patients are less clear than for atrial arrhythmias. Although non-sustained VT (NSVT) is a common finding and is associated with an increased risk of SCD, suppression does not necessarily lead to a reduction in SCD or increased survival. Accordingly, NSVT is given a Class IIb recommendation in the current guidelines when it occurs in isolation, meaning that ICD implantation may be considered. In patients with sustained monomorphic VT in the setting of structural heart disease such as HCM, ICD therapy is generally the standard of care. Patients with recurrent sustained episodes of ventricular arrhythmias or firing of their ICD should be treated with adjunctive antiarrhythmics. VT mapping and catheter ablation is important especially in cases of medically refractory VT and VT storm, and can be a safe and successful method for eliminating VT in these patients.

The guidelines for ICD implantation for SCD prevention in HCM are continuously evolving based on incomplete data, and thus rely heavily on expert consensus. High-risk HCM patients should have ICD placement for primary prevention. Clinical factors and noninvasive testing continue to

be the cornerstone of risk assessment, although there is an obvious need for further risk stratification protocols, especially in intermediate risk patients. The role of EPS is heavily debated as a risk-stratifying tool based on the rationale that ventricular arrhythmias are a common cause of syncope and/or SCD in HCM, but routine EPS is not recommended in the current guidelines. EPS may however be useful in identifying electrophysiological abnormalities and selecting prophylactic antiarrhythmic therapy.

Incidence of Arrhythmia

In patients with hypertrophic cardiomyopathy, the general prevalence of all arrhythmias, especially atrial fibrillation (AF), increases with age. In one series, AF was present in approximately 5 % of patients at the time of diagnosis of HCM and developed in an additional 10 % during a 5- year follow-up period [5]. In another series of HCM patients followed for 9 years, AF occurred in 22 % of patients, giving an annual incidence of approximately 2 % per year [6]. In these series, AF was paroxysmal about two-thirds of the time. Overall, although the reported incidence of AF in HCM is low, it is approximately five-fold higher than that of the general population. Ambulatory ECG monitoring demonstrates that SVT is common in HCM patients (between 25 and 37 %), and occurs more commonly in patients with left ventricular outflow tract obstruction [7, 8]. The majority of these events are asymptomatic and self-limited, however, rarely requiring therapy.

Accessory atrioventricular pathways, which are responsible for pre-excitation syndromes such as atrioventricular reciprocating tachycardia and WPW, are thought to result from developmental failure to eradicate remnants of the atrioventricular connections during cardiogenesis, resulting in abnormal anatomical and electrical continuity [9]. WPW is one of the most common congenital cardiac abnormalities with a general prevalence of 0.15–3 per 1,000 adults [10, 11]. However, the prevalence of accessory pathways in HCM is markedly increased, with approximately 5 % of HCM patients having ventricular pre-excitation [12].

While HCM is commonly associated with SVT, the presence of ventricular arrhythmias is more concerning. Premature ventricular contractions (PVCs) and NSVT are relatively common in patients with HCM (Fig. 16.1). Evidence from ambulatory ECG monitoring has shown that PVCs are present in 88 % of patients with HCM [7].

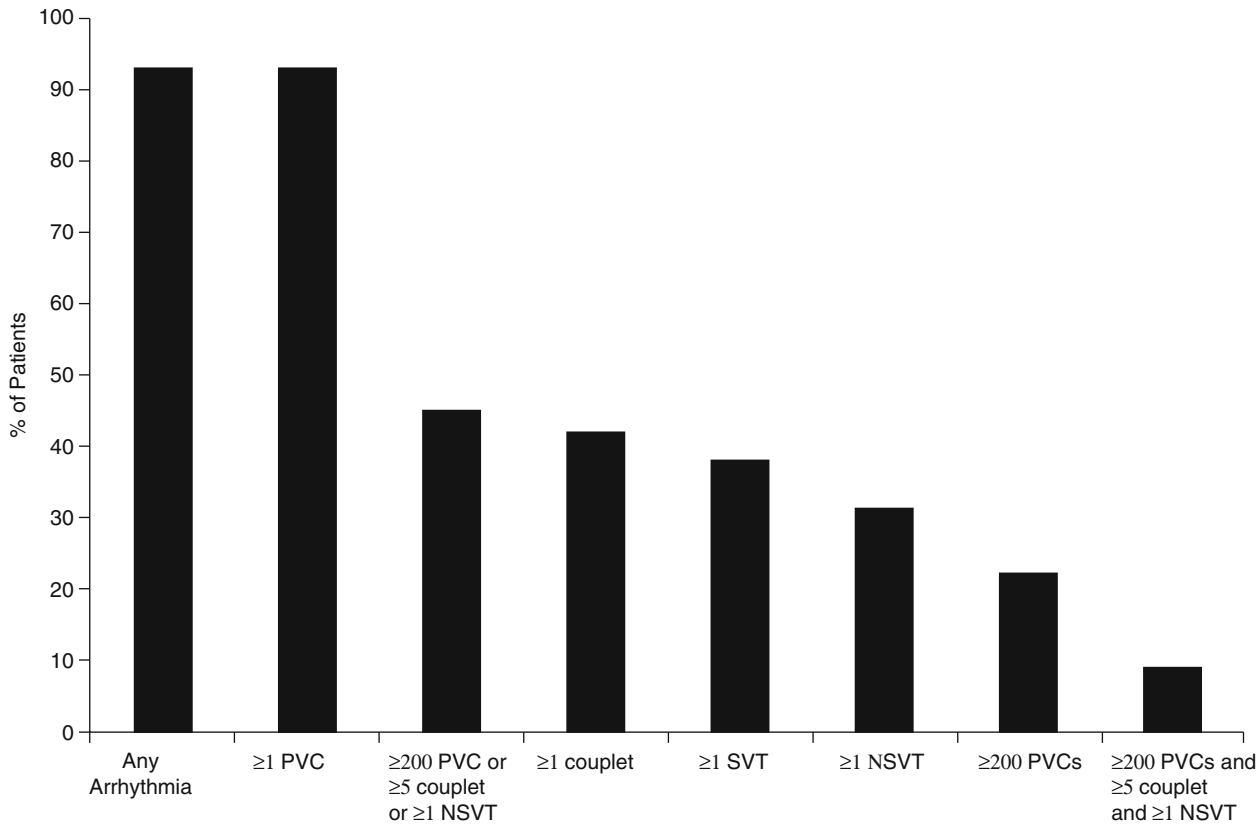

Fig. 16.1 Prevalence of ventricular and supraventricular arrhythmias on ambulatory electrocardiogram monitoring in patients with hypertrophic cardiomyopathy. *NSVT* nonsustained ventricular tachycardia, *PVC* premature ventricular complex, *SVT* supraventricular tachycardia (Figure from Adabag et al. [3])

However, frequent PVCs did not appear to necessarily lead to an increased incidence of sustained VT. In another study, the incidence of NSVT (defined as ≥3 beats of VT at 120 beats per minute) was approximately 15–30 % [13] on ECG monitoring. NSVT is more likely in patients with greater degrees of left ventricular hypertrophy (LVH) and New York Heart Association (NYHA) class III or IV symptoms. It is well established that NSVT is associated with an increased risk for SCD in patients with HCM [8, 13–16]. This increased risk is greatest in younger patients and those with symptoms; however, there is no clear relation to prognosis in terms of the duration, frequency, or rate of the NSVT episodes.

Data from HCM patients who received appropriate ICD firing indicate that the underlying rhythm is polymorphic VT, VT leading to VF, and less commonly sustained monomorphic VT [17]. Overall, the annual incidence of these malignant events is approximately 6–11 % [17, 18]. Caution must be taken in equating appropriate ICD therapies to SCD, as appropriate device therapy has been shown to roughly double true SCD in most studies [19]. The development of these ventricular arrhythmias is likely from a combination of physiological events in addition to the pro-arrhythmic substrate of the hypertrophied myocardium and intramyocardial scar. This is evidenced by the abnormal hemodynamic and autonomic responses during or soon after mild to moderate exercise in these patients, which may also provoke the underlying arrhythmogenic substrate [20, 21].

SCD is the most feared complication of HCM, and the annual incidence of SCD is approximately 1 % [22]. Although this overall rate is not dissimilar from the general population of non-HCM patients, a subset of HCM patients have significantly higher rates of SCD, whereas others are at lower risk; hence, in the population as a whole a normal average life expectancy can be expected, and efforts to evaluate the risk of SCD in HCM patients necessarily focus on mechanisms to identify those at highest risk.

Sustained VT, either resuscitated or aborted, without any known inciting factors is a major risk factor for SCD and requires an ICD for secondary prevention [17]. A family history of SCD in HCM patients, especially if a first-degree relation, is associated with an increased risk of sudden death in other affected family members, and this risk is particularly high for multiple SCD events, or those occurring in younger members [8]. Other major risk factors include massive myocardial thickening >3 cm, recurrent unexplained syncope despite optimal medical therapy, and abnormal blood pressure or arrhythmia response to exercise treadmill testing. In general, the risk of sudden death in HCM parallels the number of patient risk factors, approaching approximately 60 % for patients with 3 or more risk factors (Fig. 16.2).

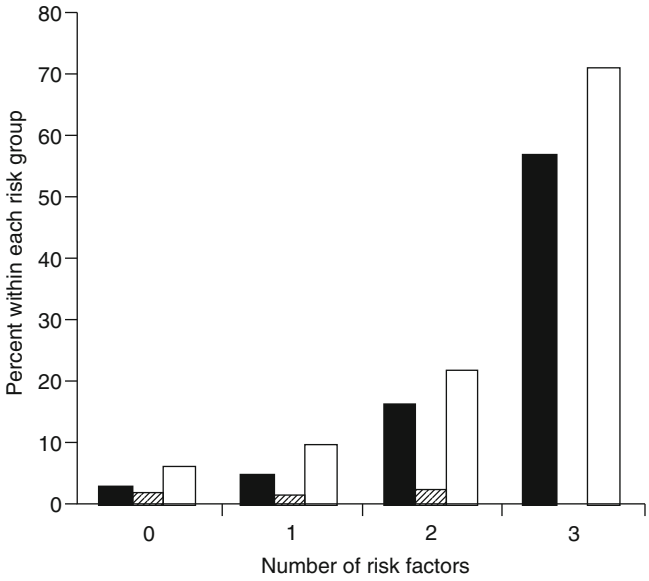

Fig. 16.2 Sudden cardiac death in hypertrophic cardiomyopathy. Bar graph showing the percentage of each risk factor group (zero, one, two and three risk factors) in which patients died during follow-up (sudden deaths = black bars, overall deaths = white bars, hatched bars = congestive heart failure or transplant) (Figure from Elliott et al. [19])

Diagnosis of Arrhythmia

The diagnosis of arrhythmias in HCM may be suggested clinically based on symptoms such as palpitations or syncope, but generally requires further testing. Distinct from hemodynamic syncope caused by left ventricular outflow tract (LVOT) obstruction or autonomic insufficiency, SVT and VT may be involved in the etiology of syncope or decompensation in HCM patients, and are important predictors of sudden cardiac death [23, 24]. Atrial tachyarrhythmias may be more common in middle-aged patients, and programmed atrial stimulation can be a useful means to identify this etiology of syncope [25]. The development of ventricular tachyarrhythmias is related to several predisposing factors, including myocardial fibrosis and ischemia [26, 27], myocyte disarray, and autonomic disturbances. The degree of myocardial fibrosis as it relates to the arrhythmic substrate can be assessed by late gadolinium enhancement on cardiac MRI [28] to predict events in HCM [29]. Myocyte disarray is histologically characterized by an irregular arrangement of abnormal shaped myocytes that contain bizarre nuclei and surrounding areas of increased connective tissue. Interstitial fibrosis can cause dispersion of activation and result in myocardial fibers having differential conduction velocities and refractory periods, thereby leading to reentry.

Noninvasive Testing

All patients with HCM should be screened with ECGs and echocardiography. An ECG should be performed at every patient visit, as subclinical arrhythmias may be captured in this manner (Fig. 16.3). The majority of patients with SVT have sporadic brief episodes of tachycardia that may be difficult to capture on a standard 12-lead electrocardiogram. Although ambulatory monitoring may be useful in patients with frequent runs of SVT to ascertain the frequency and duration of events, it is perhaps less useful in establishing a diagnosis, since only several channels are typically used making it difficult to discriminate between SVT mechanisms. In one study using Holter monitoring of such events, the result was an incorrect SVT diagnosis in 55 % of cases [30]. In patients with WPW, ambulatory monitoring may be useful in risk assessment. In one case series, patients with intermittent pre-excitation had EPS consistent with lower risk of ventricular fibrillation (VF) compared with those with persistent pre-excitation [31]. Longer monitoring, such as event monitors, 30-day monitors or loop recorders may be considered in patients with infrequent yet worrisome symptoms.

Ventricular arrhythmias may also be diagnosed by ambulatory monitoring. Studies examining the prevalence and prognostic significance of ventricular and supraventricular arrhythmias showed they were frequent and demonstrated a broad spectrum on ambulatory ECG monitoring. Ventricular tachyarrhythmias were shown to have a low positive and relatively high negative predictive value for sudden death in this HCM population [7]. Nevertheless, according to the ACC/AHA practice guidelines for ambulatory ECG monitoring, for patients with idiopathic hypertrophic cardiomyopathy, there is only a IIb indications for routine ambulatory ECG monitoring to detect arrhythmias and to assess the risk of cardiac events in patients without symptoms [32].

Several studies indicate that the degree of LVH by echocardiography is directly related to an increased risk for SCD, and therefore echocardiography remains a vital component to the diagnosis and workup of arrhythmias. In particular, the incidence of SCD almost doubles for each 5 millimeters increase in wall thickness, implicating sustained VT or VF [33]. However, not all studies have confirmed the association between massive LVH (greater than 3 centimeters) and SCD, and overall it has a low positive predictive value [34]. Thus, as with the other major risk factors, massive LVH is most useful when considered within the full context of the clinical history, although many experts consider this risk factor as sufficient to warrant ICD placement in amenable patients.

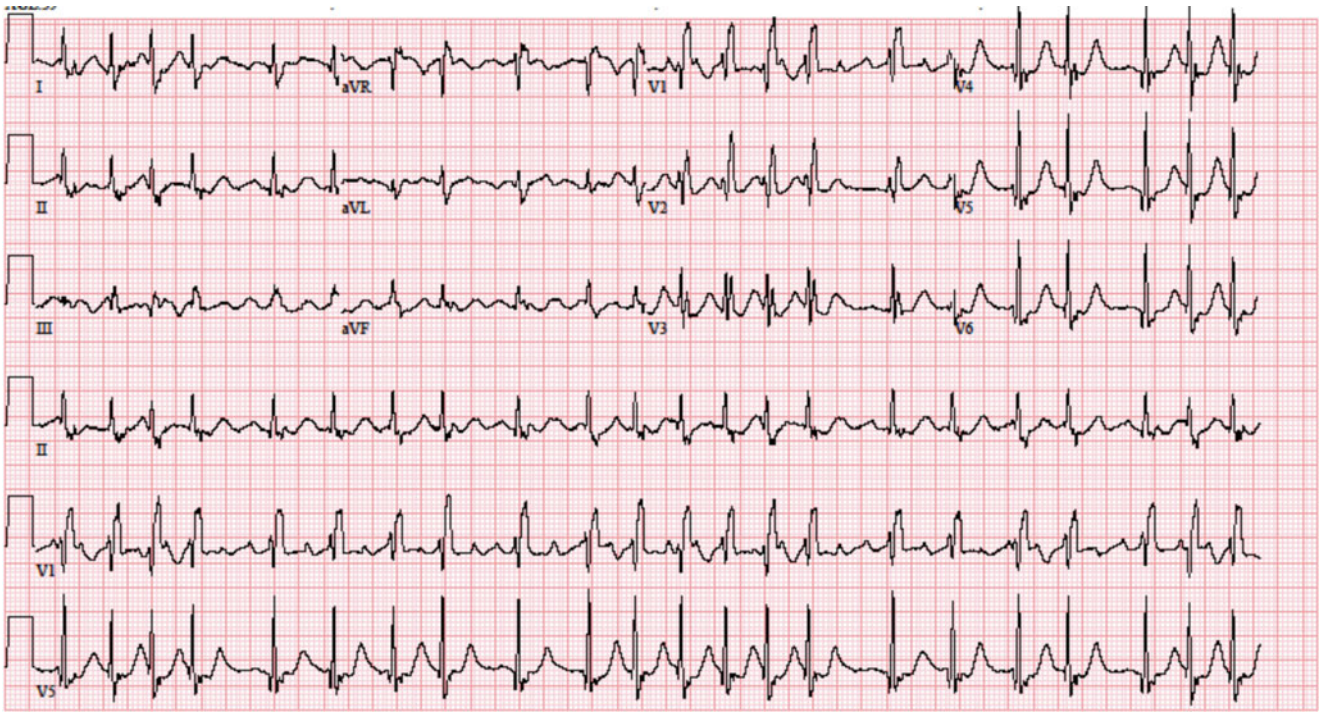

Fig. 16.3 ECG from an asymptomatic young patient with advanced HCM prior to AF ablation. Atrial activity is seen as irregular fibrillary waves suggesting atrial fibrillation. Right bundle branch block is present potentially obscuring left ventricular hypertrophy

Patients suspected of arrhythmia should also undergo full evaluation for markers of hemodynamic and electrical instability such as symptom-limited upright exercise testing. Approximately 30 % of HCM patients cannot appropriately increase their baseline blood pressure during exercise, and in some patients the blood pressure actually falls below baseline values. This abnormal blood pressure response during maximal exercise is associated with an increased risk for SCD, especially in patients younger than 40 years of age and those with a family history of premature SCD [35, 36]. It is not clear whether this abnormal response is due to the development of outflow tract obstruction, abnormal autonomic vascular response, or changes in diastolic dysfunction with exertion. See chapter on risk stratification of sudden cardiac death for more discussion.

Invasive Testing

Clinical factors and noninvasive testing (as discussed above) have and continue to be the cornerstone of risk assessment, but there is an obvious need for further risk stratification, especially in intermediate risk patients. The role of EPS has been heavily debated as a risk-stratifying tool based on the rationale that ventricular arrhythmias are a common cause of syncope and/or SCD in HCM. EPS may be useful in identifying an electrophysiologic abnormality and selecting prophylactic antiarrythmic therapy [37]. However, EPS that demonstrate inducible ventricular arrhythmias have not been shown to be a reliable predictor of SCD, even though properties of the septum that are consistent with arrhythmogenic scarring (such as reduced voltage and conduction delay) can be found [15]. This may be due in part to varying substrate, unrelated factors such as vascular and hemodynamic responses (as previously discussed), and/or other poorly understood mechanisms. Accordingly, there is limited (if any) value of invasive electrophysiology testing for diagnosis and clinical decision making in patients with HCM to justify the risk of complications associated with these procedures. As a result, invasive EPS has been removed from the guidelines as a tool for risk stratification.

WPW may be an exception to this general rule. Affected individuals with both pre-excitation and hypertrophy often exhibit high grade AV block, which is usually regarded as an uncommon phenomenon in HCM [38–40]. The syndrome of WPW is typically recognized by the characteristic changes on the surface electrocardiogram; however definitive diagnosis of pre-excitation may require electrophysiologic testing. In particular, EPS can be used in patients with WPW syndrome to determine several important electrophysiologic properties including conduction capability and refractory periods of the accessory pathway and the behavior of the AV nodal and His Purkinje conduction system [41, 42]. In addition, EPS can evaluate the number and locations of accessory pathways (necessary for catheter ablation) and/or the response to pharmacologic or ablation therapy.

Management

SVT

AVNRT can be managed using beta-blockers or calcium channel blockers as first line therapy for these patients with HCM since these agents are advantageous to concomitantly treat diastolic dysfunction and LVOT obstruction. In addition, although high dose AVN blockers will probably be sufficient in the majority of patients with SVT, it may be reasonable to pursue EPS/catheter ablation in poorly tolerated or difficult to control cases.

Treatment of WPW is based on AV nodal blocking medications to slow AV nodal conduction and antiarrhythmic drugs to slow accessory pathway conduction, in addition to radiofrequency ablation of the accessory pathway. Radiofrequency catheter ablation has practically eliminated surgical ablation in the vast majority of WPW patients, except in patients with failure of repeated RFA attempts and possibly also patients undergoing concomitant cardiac surgery for other indications.

For HCM patients with WPW (in contrast to AVNRT), there may be an earlier indication for ablation since they are often difficult to manage medically and patients may be more susceptible to associated SCD. It is important to recognize the risks of maintaining patients with HCM plus WPW on monotherapy with beta-blockers or calcium channel blockers without the use of other antiarrhythmics. This may be due to an increased risk of subsequent AF and/or VF in the absence of other background agents. At our center, patients with HCM and WPW typically undergo ablation in order to be able to maximize AVN blockers and prevent associated SCD, as the incidence of AF in their lifetime is high.

AF and Atrial Flutter

As with all patients with AF, HCM patients can be managed with either a rate control (controlling the ventricular rate while allowing the patient to remain in AF) or a rhythm control strategy (using cardioversion, antiarrhythmic drugs, and/or procedures to maintain sinus rhythm). Selecting the proper strategy must take into account individual characteristics and must weigh symptoms and hemodynamic tolerance of AF against risks associated with antiarrhythmic medications and procedural complications (Fig. 16.4). Given the specific hemodynamic derangements associated with HCM and these arrhythmias (namely, the loss of atrial con-

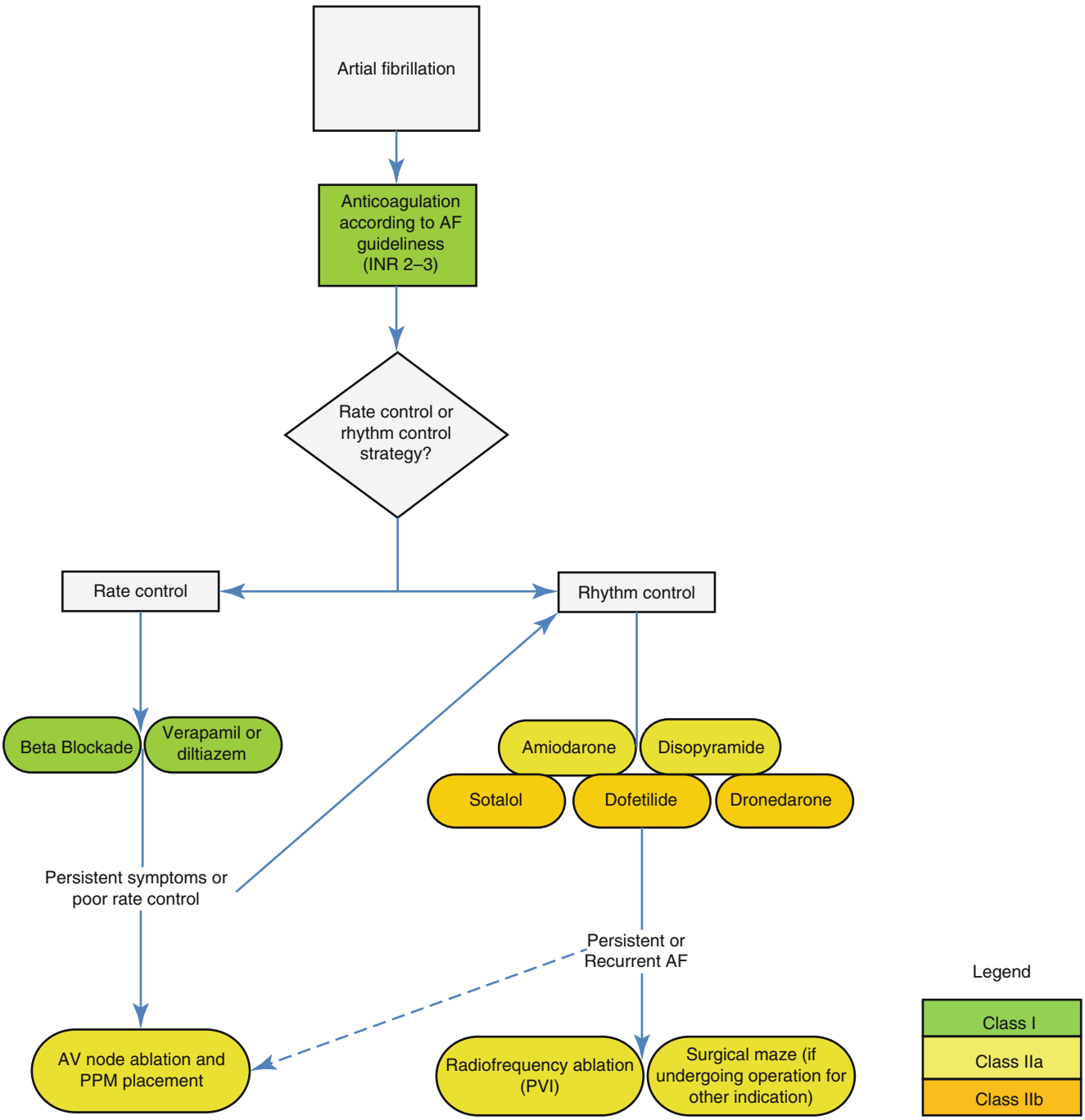

Fig. 16.4 Flowchart for general management strategies of AF in the setting of HCM. *AF* indicates atrial fibrillation, *AV* atrioventricular, *INR* international normalized ratio, *PPM* permanent pacemaker and *PVI* pulmonary vein isolation (From 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy, Writing Committee Members et al. Circulation. *J Am Coll Cardiol*. 58.25 (2011): e212–e260)

traction and rapid irregular ventricular rates discussed above) as well as the more common association with symptoms, a rhythm control strategy is more frequently utilized in HCM patients with AF than similar patients with AF but without HCM. In most respects, rhythm control in HCM patients is similar to patients without HCM, with a few important differences.

Chemical or electrical cardioversion is often needed to restore sinus rhythm, frequently with adjuvant antiarrhythmic therapy. As for patients with unknown duration of AF in the non-HCM population, a transesophageal echocardiogram (TEE) is often required to exclude left atrial appendage thrombus. Importantly, patients with HCM oftentimes have abundant trabeculae, which may also be present in the left atrial

appendage. Careful attention to these, which may be mistaken for thrombus, must be undertaken. Flow velocities in the appendage may assist in differentiating the two. In difficult cases, cardiac MRI or CT may be useful to definitively exclude appendage thrombus if a rhythm control strategy is needed. The treatment of atrial flutter in HCM is similar to AF in terms of medical management, as well as transesophageal evaluation, with select patients being good candidates for ablation.

The choice of antiarrhythmic agents is limited by significant LVH, but also the lack of clinical experience (refer to the 2011 HCM guidelines) [47, 48]. Of the antiarrhythmic drugs available, amiodarone has been found to be the most effective. Disopyramide may also be used, but because of the concern for accelerated AV conduction, it should only be given in combination with an AV nodal blocking agent, such as a beta-blocker or a non-dihydropyridine calcium channel blocker [47, 49]. Patients with significant concomitant outflow tract obstruction may be best served by an initial trial of disopyramide, as opposed to amiodarone, given the former drugs effect on inotropy and reduced gradients. In addition, although amiodarone is effective in reducing the incidence of recurrent AF or heart rate in AF, its use is limited by long-term toxicity, which can be significant in the oftentimes younger HCM patient population who might require therapy for decades. Efficacy data in HCM patients with AF is limited (see discussion below).

In the instances when rate control is chosen (i.e. failure to maintain sinus rhythm, lack of symptoms associated with AF, and/or hemodynamic stability), beta-blockers and calcium channel blockers are the preferred agents. Digoxin should be avoided, as it may worsen LV outflow obstruction and diastolic function due to its positive inotropic effects. If rate control is not possible, AV nodal ablation with placement of a permanent pacemaker is an effective treatment option. In such cases dual chamber pacemakers are required to reconnect the atria with the ventricles, given the heavy reliance on atrial contraction in this patient population. In addition, a short AV delay and apical pacing may aid in optimizing ventricular filling and reducing outflow tract obstruction, respectively.

Anticoagulation

Anticoagulation is the cornerstone of AF treatment, and is especially important in patients with HCM [50]. All patients with HCM should be anticoagulated as described in the 2011 HCM guidelines, even after a first or short-lived episode, because the likelihood of future subclinical episodes and the association with stroke is high. In the largest cohort of HCM patients with AF studied, 22 % of 480 outpatients with HCM developed AF during a 9-year follow-up period (incidence of approximately 2 % per year). The occurrence of non-fatal ischemic stroke overall was 14 % and stroke-related death was 7 %, which was independent of whether AF was exclusively paroxysmal or chronic [6]. In addition, in these HCM patients ischemic strokes were 8 times more frequent among AF patients than among those in sinus rhythm, and the annual HCM-related mortality was 3 % in AF patients compared to 1 % in sinus rhythm.

Anticoagulation can be achieved with warfarin for a goal INR of 2.0–3.0. Newer agents such as direct thrombin inhibitors, or factor Xa inhibitors, can also be used, although these agents have not been studied specifically in the population of HCM patients. In large randomized trials of patients who are at intermediate or high risk for clinical thromboembolism, compared to warfarin, anticoagulation with each of the novel oral anticoagulant agents (NOACs) leads to similar or lower rates both of ischemic stroke and major bleeding. Three meta-analyses regarding pooled results from the RELY (dabigatran), ROCKET-AF (rivaroxaban) and ARISTOTLE (apixaban) trials have confirmed these results, although it is unclear whether any patients with HCM were included in these trials [51–53].

Patients with AF often have an AF burden that improves after surgical myectomy or alcohol ablation, likely due to unloading of the left atrium and overall ventricular remodeling. Although there is no consensus as to the optimal duration of anticoagulation post AF ablation, it is likely reasonable to continue full anticoagulation for a short time (e.g., 1 year) provided there has been no documented recurrence. At our center, select patients may come off anticoagulation, as long as vigorous monitoring for recurrence of AF continues.

AF Ablation

There are limited data for ablation of atrial fibrillation specifically in the HCM population. Several obstacles to treating AF with antiarrhythmic drugs include limited choices (due to insufficient data, contraindications, or the extended duration of therapy), variable efficacy in maintaining sinus rhythm, and frequent medication side effects. Catheter ablation can therefore be used as an effective alternative, especially for refractory cases. AF is usually eliminated by pulmonary vein isolation, which disrupts the electrical activity between tissues containing these arrhythmogenic triggers and substrate (the antral and ostial portions of the pulmonary veins) and the left atria. Atrial tissue can also be directly ablated using the MAZE procedure concomitantly in HCM patients undergoing septal myomectomy. Although pulmonary vein isolation is effective in eliminating AF in other patient populations, results in patients with HCM are less well established. One study confirmed successful PVI ablation using 3D electroanatomical mapping in a population of HCM patients [54]. Recurrence rates after the first pulmonary vein isolation were shown to be higher in patients with HCM. It is possible that atrial tissue itself may be more arrhythmogenic in this patient population, leading to a high incidence of non-PV triggers and hence a higher failure rate after PV isolation. Additionally, the thick myocardium may make the creation of transmural lesions more difficult. In terms of substrate,

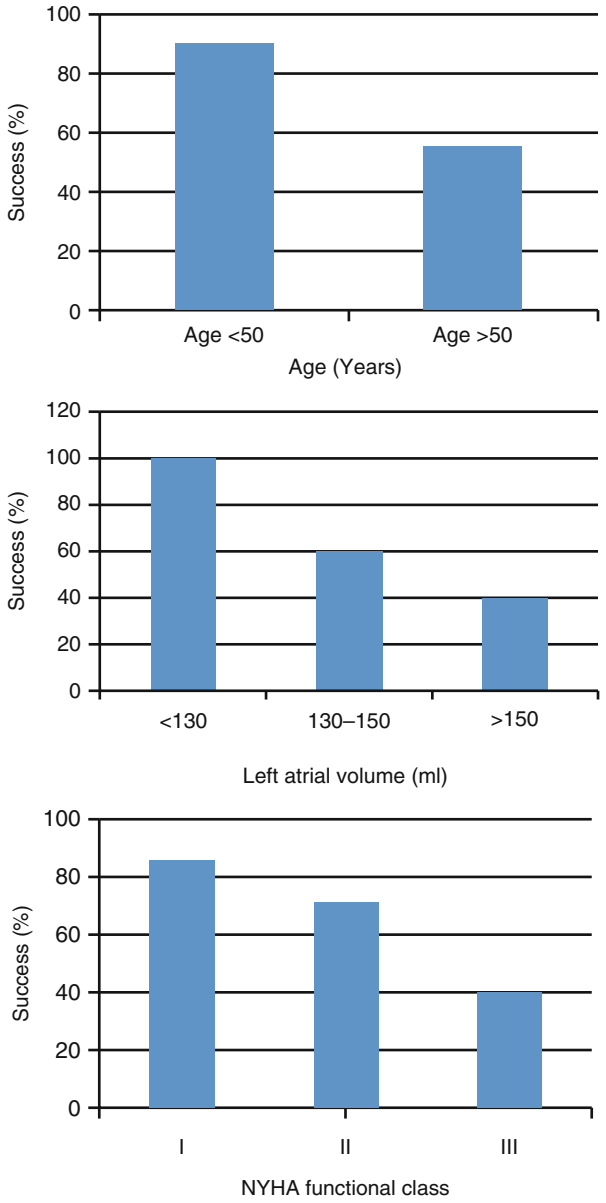

Fig. 16.5 RFA success in HCM patients based on age, left atrial volume, and NYHA functional class. Vertical bars represent the proportion of HCM patients in sinus rhythm (success rate) after the ablation (Adapted from Di Donna et al. [52])

the degree of heart failure, left atrial size, and patient age were shown to be important predictors of success or failure [55, 56] (Fig. 16.5). The best candidates were younger HCM patients with a small atrial size (indicative of less atrial remodeling) and those with mild symptoms. Those patients with sarcomere gene mutations often required repeat procedures. However, after repeated ablation procedures, long-term cure was achieved in a significant percentage of patients [57]. Overall, results show that ablation can be successful in restoring long-term sinus rhythm and improving symptomatic status in most HCM patients with refractory AF, but it requires multiple lesion delivery and repeat procedures, with the risk of significant complications.

The newer methodologies for eliminating atrial fibrillation (AF) have been shown to have fewer potential complications than standard radiofrequency ablation [58]. The STOP AF trial recently demonstrated that cryo balloon ablation is a safe and effective alternative with risks within accepted standards for ablation therapy [59]. However, balloon based ablation therapies have not been studied specifically in HCM patients. There is also a role for novel convergent (combined surgical and percutaneous) procedures to achieve successful ablation, especially in refractory cases, or when non-pulmonary vein triggers in the hypertrophied and disorganized myocardium are found. These combined electrophysiologic and cardiothoracic surgical procedures can offer a viable treatment alternative for atrial fibrillation patients who have failed other ablations or who have enlarged atria (>4.5 cm) secondary to structural heart disease such as HCM. In this procedure, a comprehensive bi-atrial lesion pattern on the outside of the heart is created surgically using a trans-diaphragmatic approach, while in the same setting catheter ablation is used to complete the lesion pattern endocardially and diagnostically check that all reentrant circuits have been interrupted (electrical isolation of the pulmonary veins). Taken together, therefore, the overall outcome of AF ablation for HCM patients is relatively favorable.

Ventricular Arrhythmias

The recommendations for management of ventricular arrhythmias in HCM patients are less clear than for atrial arrhythmias, and much of the evidence comes from previous trials in post-MI patients. Asymptomatic VPCs do not require therapy, but beta-blockers may be effective in symptomatic patients. NSVT is a common finding and is associated with an increased risk of SCD; [23] however, the decision to treat HCM patients for NSVT and the antiarrhythmics of choice remain controversial. The CAST trial demonstrated that treating NSVT with antiarrhythmic agents actually lead to an increase in sudden death and total cardiovascular mortality [60], but these data were based on ischemic patients using Vaughan-Williams class Ic antiarrhythmic agents such as flecainide and encainide, and did not involve patients with HCM. Furthermore although NSVT, among other risk factors, is associated with increased SCD in HCM patients, suppression with chronic amiodarone therapy did not necessarily lead to a reduction in SCD or increased survival [61]. In summary, it is unclear whether suppression of NSVT is related to improved outcomes in HCM patients. Accordingly, NSVT is instead treated by heightening the consideration for ICD implantation. However, due to the poor correlation with SCD when this risk factor is present in

isolation, it was given a Class IIb recommendation in the recent guidelines, meaning that ICD implantation may be considered but is not routinely recommended.

Guidelines for ICD implantation for SCD prevention in HCM are constantly evolving due to incomplete data, and therefore rely heavily on expert consensus. Commonly, patients with NSVT as their sole risk factor for SCD are monitored more frequently for additional risk factors, such as extent of LV thickening, presence and extent of outflow tract obstruction, response to exercise testing, or presence of significant late gadolinium enhancement, the presence of any of which might elevate the recommendation for ICD implantation. In patients with sustained monomorphic VT, however, in the setting of structural heart disease such as HCM, ICD therapy is generally the standard of care. Patients with recurrent sustained episodes of ventricular arrhythmias or firing of their ICD should be treated with adjunctive antiarrhythmics, preferably amiodarone [62]. Antiarrhythmics are indicated as an alternative to ICD implantation in patients who are not candidates or refuse the procedure [63].

Adjunctive therapy with catheter ablation is sometimes offered to patients with ICD to improve symptoms and quality of life, but is usually not performed without prior ICD placement. Also, a significant percentage of patients ultimately require concomitant therapy with antiarrhythmic drugs to decrease the recurrence of ventricular arrhythmia and the frequency of ICD shocks [64]. Catheter ablation of VT in patients with HCM is important in cases of medication refractory VT and VT storm. In patients without an ICD, VT storm has been defined as the presence of two or more ventricular tachyarrhythmias within 24 hours, VT occurring immediately after termination, or sustained and non-sustained VT resulting in a total number of ventricular ectopic beats greater than sinus beats in a 24-hours period [65]. Recent evidence suggests that VT mapping and ablation can be a safe and successful method for eliminating VT in these patients [66–68].

It is well established that endocardial ablation almost always fails if the VT originates from a deep intramural or epicardial source, as may be the case in HCM. The data is limited, but studies using a combination of voltage-based substrate mapping and activation, entrainment, and late/fractionated potential mapping suggest that standard endocardial mapping and ablation alone cannot fully target the involved VT circuits in HCM patients [69, 70]. Combined with MRI data regarding fibrosis and scarring [71], this suggests that the VT circuits in HCM involve the epicardium, a thick myocardium, as well as the endocardium [72]. Additionally, the arrhythmogenic substrate may be atypical and extremely variable in this specific patient population. An epicardial approach may be needed to overcome the thick ventricular wall and characteristic midcavitary obliteration [73]. Fortunately, long-term outcomes of combined epicardial and endocardial ablation have been shown to be successful in patients with HCM-related monomorphic VT. In one study, 78 % of patients who underwent ablation alone had freedom from recurrent ICD shocks at a median 3 year follow up [69].

Most studies using catheter ablation therapy for VT are based on RF ablation, but the success depends on whether or not there is concomitant structural heart disease [74]. Few studies have been performed on the specific population of HCM patients [66] demonstrating safety and effectiveness. As a result, all patients should receive an aggressive trial of antiarrhythmic medication therapy and an adequate trial of ATP pacing beforehand. Overall, catheter ablation of VT is an effective option to consider for HCM patients who fail aggressive trials of antiarrhythmic medications and anti-tachycardia pacing.

Clinical Pearls

- Ambulatory ECG monitoring is important for screening in HCM, as arrhythmias are usually of greater significance in this population. Implantable loops or event monitors may be especially helpful in patients with recurrent unexplained symptoms, especially prior to contemplation of ICD implantation.
- AF is a significant problem in HCM. Rhythm control is often needed in this population with diastolic dysfunction and outflow tract obstruction.
- TEE may not adequately differentiate left atrial appendage trabeculae in HCM from thrombus; given the need for maintenance of sinus rhythm in these patients, further testing with cardiac MRI or CT may be needed to exclude thrombus.
- If rate control is not achieved with medications, and rhythm control is not a viable option, patients should undergo AV nodal ablation with placement of a permanent dual chamber pacemaker for definitive rate control and assurance of atrial kick.
- Stroke risk is high in this population. Patients with HCM and AF/AFL should be anticoagulated irrespective of the CHADS2/CHADS-VASC score. If there is reason to believe that AF burden or incidence has decreased (e.g., after septal reduction therapy or antiarrhythmic therapy), and is supported by documentation on monitoring or implanted devices, select patients may come off anticoagulation, as long as vigorous monitoring for recurrence continues.
- NSVT is common in HCM and associated with increased risk of SCD, but benefits of treating NSVT are uncertain. ICD implantation for NSVT alone is a class IIb recommendation; most experts require additional risk factors to warrant ICD implantation and its concomitant acute and long-term risks.

- High-risk HCM patients should have ICD placement for primary prevention. The number of major risk factors to warrant ICD placement is still debatable; all experts consider the presence of 2 major risk factors an indication, while some experts will consider one risk factor as sufficient, especially when it is a first-degree relative with SCD, spontaneous VT/SCD in the index patient, or massive LVH > 3 centimeters.
- VT catheter ablation may be a useful emerging therapy in the HCM population, but foci for arrhythmia may be deeper in the myocardium or epicardial.
- AF ablation may be useful, but might require more aggressive approach and repeat procedures, due to non-PV triggers in a subset of patients.
- WPW should be identified and treated with RF ablation when found, given the high lifetime incidence of concomitant AF.

References

1. Murphy RT, Mogensen J, McGarry K, et al. Adenosine monophosphate-activated protein kinase disease mimicks hypertrophic cardiomyopathy and Wolff-Parkinson-White syndrome natural history. J Am Coll Cardiol. 2005;45:922–30.
2. Arad M, Maron BJ, Gorham JM, et al. Glycogen storage diseases presenting as hypertrophic cardiomyopathy. N Engl J Med. 2005;352:362–72.
3. MacRae CA, Ghaisas N, Kass S, et al. Familial Hypertrophic cardiomyopathy with Wolff-Parkinson-White syndrome maps to a locus on chromosome 7q3. J Clin Invest. 1995;96:1216.
4. Gollob MH, Green MS, Tang ASL, et al. Identification of a gene responsible for familial Wolff–Parkinson–White syndrome. N Engl J Med. 2001;344:1823–31.
5. Robinson K, Frenneaux MP, Stockins B, Karatasakis G, Poloniecki JD, Mckenna WJ. Atrial fibrillation in hypertrophie cardiomyopathy: a longitudinal study. J Am Coll Cardiol. 1990;15:1279–85.
6. Olivotto I, Cecchi F, Casey SA, Dolara A, Traverse JH, Maron BJ. Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. Circulation. 2001;104:2517–24.
7. Adabag AS, Casey SA, Kuskowski MA, Zenovich AG, Maron BJ. Spectrum and prognostic significance of arrhythmias on ambulatory Holter electrocardiogram in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2005;45:697–704.
8. McKenna WJ, England D, Doi YL, Deanfield JE, Oakley CM, Goodwin JF. Arrhythmia in hypertrophic cardiomyopathy. I: Influence on prognosis. Br Heart J. 1981;46:168–72.
9. Anderson RH, Davies MJ, Becker AE. Atrioventricular ring specialized tissue in normal heart. Eur J Cardiol. 1974;2:219–30.
10. Newman BJ, Donoso E, Friedberg CK. Arrhythmias in the Wolff-Parkinson-White syndrome. Prog Cardiovasc Dis. 1966; 9:147–65.
11. Vidaillet Jr HJ, Pressley JC, Henke E, Harrell Jr FE, German LD. Familial occurrence of accessory atrioventricular pathways (preexcitation syndrome). N Engl J Med. 1987;317:65–9.
12. Fananapazir L, Tracy CM, Leon MB, et al. Electrophysiologic abnormalities in patients with hypertrophic cardiomyopathy. A consecutive analysis in 155 patients. Circulation. 1989;80:1259–68.
13. Spirito P, Rapezzi C, Autore C, et al. Prognosis of asymptomatic patients with hypertrophic cardiomyopathy and nonsustained ventricular tachycardia. Circulation. 1994;90:2743–7.
14. Maron BJ, Savage DD, Wolfson JK, Epstein SE. Prognostic significance of 24 hour ambulatory electrocardiographic monitoring in patients with hypertrophic cardiomyopathy: a prospective study. Am J Cardiol. 1981;48:252–7.
15. Fananapazir L, Chang AC, Epstein SE, McAreavey D. Prognostic determinants in hypertrophic cardiomyopathy. Prospective evaluation of a therapeutic strategy based on clinical, Holter, hemodynamic, and electrophysiological findings. Circulation. 1992;86: 730–40.
16. Monserrat L, Elliott PM, Gimeno JR, Sharma S, Penas-Lado M, McKenna WJ. Non-sustained ventricular tachycardia in hypertrophic cardiomyopathyan independent marker of sudden death risk in young patients. J Am Coll Cardiol. 2003;42:873–9.
17. Maron BJ, Shen W-K, Link MS, et al. Efficacy of implantable cardioverter–defibrillators for the prevention of sudden death in patients with hypertrophic cardiomyopathy. N Engl J Med. 2000; 342:365–73.
18. Primo J, Geelen P, Brugada J, et al. Hypertrophic cardiomyopathy: role of the implantable cardioverter-defibrillator. J Am Coll Cardiol. 1998;31:1081–5.
19. Germano JJ, Reynolds M, Essebag V, Josephson ME. Frequency and causes of implantable cardioverter-defibrillator therapies: is device therapy proarrhythmic? Am J Cardiol. 2006;97:1255–61.
20. Frenneaux MP, Counihan PJ, Caforio AL, Chikamori T, McKenna WJ. Abnormal blood pressure response during exercise in hypertrophic cardiomyopathy. Circulation. 1990;82:1995–2002.
21. Frenneaux MP. Assessing the risk of sudden cardiac death in a patient with hypertrophic cardiomyopathy. Heart. 2004;90:570–5.
22. Elliott PM, Gimeno JR, Thaman R, et al. Historical trends in reported survival rates in patients with hypertrophic cardiomyopathy. Heart. 2006;92:785–91.
23. Elliott PM, Poloniecki J, Dickie S, et al. Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. J Am Coll Cardiol. 2000;36:2212–8.
24. Priori SG, Aliot E, Blomstrom-Lundqvist C, et al. Task force on sudden cardiac death of the European Society of Cardiology. Eur Heart J. 2001;22:1374–450.
25. Brembilla-Perrot B, Jacquot A, Beurrier D, Jacquemin L. Hypertrophic cardiomyopathy: Value of atrial programmed electrical stimulation in patients with or without syncope with special reference to the role of atrial arrhythmias. Int J Cardiol. 1997;59:47–56.
26. Basso C, Thiene G, Corrado D, Buja G, Melacini P, Nava A. Hypertrophic cardiomyopathy and sudden death in the young: pathologic evidence of myocardial ischemia. Hum Pathol. 2000;31: 988–98.
27. Choudhury L, Mahrholdt H, Wagner A, et al. Myocardial scarring in asymptomatic or mildly symptomatic patients with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2002;40:2156–64.
28. Moon JCC, Reed E, Sheppard MN, et al. The histologic basis of late gadolinium enhancement cardiovascular magnetic resonance in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2004;43:2260–4.
29. Marsan NA, Bax JJ. Cardiomyopathies: myocardial fibrosis assessed by CMR to predict events in HCM. Nat Rev Cardiol. 2010;7:604–6.
30. Jaeggi ET, Gilljam T, Bauersfeld U, Chiu C, Gow R. Electrocardiographic differentiation of typical atrioventricular node reentrant tachycardia from atrioventricular reciprocating tachycardia mediated by concealed accessory pathway in children. Am J Cardiol. 2003;91:1084–9.
31. Klein GJ, Gulamhusein SS. Intermittent preexcitation in the Wolff-Parkinson-White syndrome. Am J Cardiol. 1983;52:292–6.

32. Crawford MH, Bernstein SJ, Deedwania PC, et al. ACC/AHA guidelines for ambulatory electrocardiography: executive summary and recommendations a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the Guidelines for Ambulatory Electrocardiography) developed in collaboration with the North American Society for Pacing and Electrophysiology. Circulation. 1999;100:886–93.
33. Spirito P, Bellone P, Harris KM, Bernabò P, Bruzzi P, Maron BJ. Magnitude of left ventricular hypertrophy and risk of sudden death in hypertrophic cardiomyopathy. N Engl J Med. 2000;342:1778–85.
34. Elliott PM, Gimeno Blanes JR, Mahon NG, Poloniecki JD, McKenna WJ. Relation between severity of left-ventricular hypertrophy and prognosis in patients with hypertrophic cardiomyopathy. Lancet. 2001;357:420–4.
35. Olivotto I, Maron BJ, Montereggi A, Mazzuoli F, Dolara A, Cecchi F. Prognostic value of systemic blood pressure response during exercise in a community-based patient population with hypertrophic cardiomyopathy. J Am Coll Cardiol. 1999;33:2044–51.
36. Sadoul N, Prasad K, Elliott PM, Bannerjee S, Frenneaux MP, McKenna WJ. Prospective prognostic assessment of blood pressure response during exercise in patients with hypertrophic cardiomyopathy. Circulation. 1997;96:2987–91.
37. Kowey PR, Eisenberg R, Engel TR. Sustained arrhythmias in hypertrophic obstructive cardiomyopathy. N Engl J Med. 1984;310: 1566–9.
38. Massumi RA. Familial Wolff-Parkinson-White syndrome with cardiomyopathy. Am J Med. 1967;43:951–5.
39. Khair GZ, Soni JS, Bamrah VS. Syncope in hypertrophic cardiomyopathy. II. Coexistence of atrioventricular block and Wolff-Parkinson-White syndrome. Am Heart J. 1985;110:1083–6.
40. Westlake RE, Cohen W, Willis WH. Wolff-Parkinson-White syndrome and familial cardiomegaly. Am Heart J. 1962;64:314–20.
41. Calkins H, Sousa J, El-Atassi R, et al. Diagnosis and cure of the Wolff-Parkinson-White syndrome or paroxysmal supraventricular tachycardias during a single electrophysiologic test. N Engl J Med. 1991;324:1612–8.
42. Pappone C, Vicedomini G, Manguso F, et al. Risk of malignant arrhythmias in initially symptomatic patients with Wolff-Parkinson-White syndrome results of a prospective long-term electrophysiological follow-Up study. Circulation. 2012;125:661–8.
43. Fuster V. ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation) (vol 114, pg e257, 2006). Circulation 2007;116:E138-E.
44. Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in collaboration with the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2011;58:2703–38.
45. Spirito P, Seidman CE, McKenna WJ, Maron BJ. The management of hypertrophic cardiomyopathy. N Engl J Med. 1997;336:775–85.
46. Hematpour K, Steinberg JS. Treatment of atrial fibrillation in hypertrophic cardiomyopathy. Anadolu Kardiyol Derg. 2006;6:44–8.
47. Dentali F, Riva N, Crowther M, Turpie AGG, Lip GYH, Ageno W. Efficacy and safety of the novel oral anticoagulants in atrial fibrillation a systematic review and meta-analysis of the literature. Circulation. 2012;126:2381–91.
48. Adam SS, McDuffie JR, Ortel TL, Williams JW. Comparative effectiveness of warfarin and new oral anticoagulants for the management of atrial fibrillation and venous thromboembolism a systematic review. Ann Intern Med. 2012;157:796–807.
49. Ntaios G, Papavasileiou V, Diener H-C, Makaritsis K, Michel P. Nonvitamin-K-antagonist oral anticoagulants in patients with atrial fibrillation and previous stroke or transient ischemic attack a systematic review and meta-analysis of randomized controlled trials. Stroke. 2012;43:3298–304.
50. Liu X, Ouyang F, Mavrakis H, et al. Complete pulmonary vein isolation guided by three-dimensional electroanatomical mapping for the treatment of paroxysmal atrial fibrillation in patients with hypertrophic obstructive cardiomyopathy. Europace. 2005;7: 421–7.
51. Bunch TJ, Munger TM, Friedman PA, et al. Substrate and procedural predictors of outcomes after catheter ablation for atrial fibrillation in patients with hypertrophic cardiomyopathy. J Cardiovasc Electrophysiol. 2008;19:1009–14.
52. Di Donna P, Olivotto I, Delcrè SDL, et al. Efficacy of catheter ablation for atrial fibrillation in hypertrophic cardiomyopathy: impact of age, atrial remodelling, and disease progression. Europace. 2010;12:347–55.
53. Kilicaslan F, Verma A, Saad E, et al. Efficacy of catheter ablation of atrial fibrillation in patients with hypertrophic obstructive cardiomyopathy. Heart Rhythm. 2006;3:275–80.
54. Burkhardt JD, Natale A. New technologies in atrial fibrillation ablation. Circulation. 2009;120:1533–41.
55. Packer DL, Kowal RC, Wheelan KR, et al. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation first results of the North American Arctic Front (STOP AF) pivotal trial. J Am Coll Cardiol. 2013;61:1713–23.
56. Echt DS, Liebson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo: the Cardiac Arrhythmia Suppression Trial. N Engl J Med. 1991;324: 781–8.
57. Cecchi F, Olivotto I, Montereggi A, Squillatini G, Dolara A, Maron BJ. Prognostic value of non-sustained ventricular tachycardia and the potential role of amiodarone treatment in hypertrophic cardiomyopathy: assessment in an unselected non-referral based patient population. Heart. 1998;79:331–6.
58. McKenna WJ, Oakley CM, Krikler DM, Goodwin JF. Improved survival with amiodarone in patients with hypertrophic cardiomyopathy and ventricular tachycardia. Br Heart J. 1985;53:412–6.
59. Gregoratos G, Abrams J, Epstein AE, et al. ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices—summary article a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE Committee to Update the 1998 Pacemaker Guidelines). J Am Coll Cardiol. 2002;40: 1703–19.
60. Strickberger SA, Man KC, Daoud EG, et al. A prospective evaluation of catheter ablation of ventricular tachycardia as adjuvant therapy in patients with coronary artery disease and an implantable cardioverter-defibrillator. Circulation. 1997;96:1525–31.
61. Zipes DP, Camm AJ, Borggrefe M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). J Am Coll Cardiol. 2006;48:e247–346.

62. Santangeli P, Di Biase L, Lakkireddy D, et al. Radiofrequency catheter ablation of ventricular arrhythmias in patients with hypertrophic cardiomyopathy: safety and feasibility. Heart Rhythm. 2010;7:1036–42.
63. Rodriguez LUZ, Smeets JLRM, Timmermans C, et al. Radiofrequency catheter ablation of sustained monomorphic ventricular tachycardia in hypertrophic cardiomyopathy. J Cardiovasc Electrophysiol. 1997;8:803–6.
64. Lim KK, Maron BJ, Knight BP. Successful catheter ablation of hemodynamically unstable monomorphic ventricular tachycardia in a patient with hypertrophic cardiomyopathy and apical aneurysm. J Cardiovasc Electrophysiol. 2009;20:445–7.
65. Dukkipati SR, d'Avila A, Soejima K, et al. Long-term outcomes of combined epicardial and endocardial ablation of monomorphic ventricular tachycardia related to hypertrophic cardiomyopathy. Circ Arrhythm Electrophysiol. 2011;4:185–94.
66. Inada K, Seiler J, Roberts-Thomson KC, et al. Substrate characterization and catheter ablation for monomorphic ventricular tachycardia in patients with apical hypertrophic cardiomyopathy. J Cardiovasc Electrophysiol. 2011;22:41–8.
67. Adabag AS, Maron BJ, Appelbaum E, et al. Occurrence and frequency of arrhythmias in hypertrophic cardiomyopathy in relation to delayed enhancement on cardiovascular magnetic resonance. J Am Coll Cardiol. 2008;51:1369–74.
68. Kwon DH, Setser RM, Popović ZB, et al. Association of myocardial fibrosis, electrocardiography and ventricular tachyarrhythmia in hypertrophic cardiomyopathy: a delayed contrast enhanced MRI study. Int J Cardiovasc Imaging. 2008;24:617–25.
69. Bordignon S, Chun KJ, Schmidt B. Epicardial ablation of monomorphic ventricular tachycardia storm in hypertrophic cardiomyopathy. Europace. 2013;15:346.
70. Blanck Z, Dhala A, Deshpande S, Sra J, Jazayeri M, Akhtar M. Catheter ablation of ventricular tachycardia. Am Heart J. 1994;127:1126–33.

Indications for and Individualization of Septal Reduction Therapy

17

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Abstract

The importance of left ventricular outflow tract obstruction in a large subset of patients with HCM and drug-refractory symptoms, as well as the value of septal reduction therapy (surgical myectomy or alcohol septal ablation), has been demonstrated. However, determining the precise cause of symptoms in the HCM patient, and specifically implicating outflow tract obstructive physiology, can be quite challenging. Accordingly, a detailed and comprehensive morphologic and physiologic evaluation of the HCM patient is of paramount importance to determine which patients may benefit from septal reduction therapy. Patients should be considered for septal reduction therapy when (a) symptoms are clearly and primarily attributed to obstructive HCM despite optimal medical therapy, (b) symptoms encompass severe heart failure or angina (NYHA or CCS class III/IV), recurrent obstruction-related syncope, or recurrent clinical decompensation due to refractory paroxysmal atrial fibrillation, (c) a gradient ≥50 mmHg can be demonstrated on optimal medical therapy, and (d) obstruction is clearly dynamic and subvalvular, resulting mainly from septum-to-anterior mitral leaflet contact. Surgical myectomy has been the traditional gold-standard invasive therapy. Alcohol septal ablation (ASA) is a minimally invasive catheter-based alternative with less patient discomfort and more rapid recovery; however, only patients with certain anatomic criteria are candidates. Evidence from non-randomized studies suggests that ASA and surgical myectomy result in similar short- and long-term outcomes with respect to hemodynamic and functional improvements, with greater propensity for pacemaker placement with septal ablation. Based on comprehensive assessment of clinical symptoms, associated co-morbidities, echocardiographic, electrocardiographic, and angiographic features, some patients are better suited for myectomy while others are better suited for ASA. This chapter will review indications for septal reduction therapy and how to individualize the selection of the appropriate septal reduction procedure in clinical practice.

Keywords

Myectomy • Alcohol septal ablation • Septal reduction • Indication

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Key Points

- Septal reduction therapy is recommended for patients with severe LV outflow tract obstruction and drug-refractory symptoms, such as severe dyspnea or chest pain (usually NYHA or CCS functional classes III/IV) or other important exertional symptoms (syncope or near syncope).
- Selected patients who do not meet NYHA or CCS class III/IV criteria can be considered for septal reduction therapy, most typically when obstruction-related recurrent syncope is present despite optimal medical or device therapy.
- A detailed and comprehensive morphologic and physiologic evaluation of the HCM patient as a whole is of paramount importance to delineate the precise causation of symptomatology, and implicate outflow tract obstructive physiology in particular.
- Patients must qualify from symptomatic, hemodynamic and anatomic standpoints to be considered for septal reduction therapy.
- Transaortic septal myectomy is an effective treatment strategy for the majority of patients with LVOT gradient and severe drug-resistant symptoms given documented long-term results and safety data.
- ASA is a minimally invasive catheter-based approach that results in a lesser degree of patient discomfort and more rapid recovery when compared with an open-heart surgical procedure; however only patients with certain anatomic criteria, including coronary anatomy, are good candidates for ASA.
- For many patients, both ASA and myectomy procedures could provide reasonable treatment options; alternatively, some patients are better suited for myectomy while others are better suited for ASA.
- Evidence from non-randomized trials suggests that ASA and surgical myectomy result in similar short- and long-term outcomes with respect to hemodynamic and functional improvements, with greater propensity for pacemaker placement with ASA.

Introduction: The Importance of Outflow Tract Obstruction

It has been over 50 years since the first hemodynamic observations of hypertrophic cardiomyopathy (HCM) based on cardiac catheterization and surgical descriptions in 1957 by Brock [1]. Early reports of HCM focused on descriptions of intraventricular systolic pressure gradient, making dynamic obstruction within the left ventricular outflow tract (LVOT) the most recognized and integral feature of HCM [2]. The dynamic nature of LV outflow tract obstruction could be provoked by exercise, infusion of isoproterenol, premature ventricular beats, vasodilation with amyl nitrite inhalation or nitroglycerin, as well as by altering preload via the commonly performed Valsalva maneuver [2, 3]. Although dynamic obstruction of LV outflow has been widely reported, its prevalence and clinical implication in this disease state have been the subject of controversy for many years [4, 5].

The important role of obstruction in HCM, and therefore the potential value of surgical myectomy or alcohol septal ablation, has now been confirmed in the last several years by a substantial body of literature from both clinical and echocardiographic studies. Echocardiographic studies confirmed systolic anterior motion (SAM) of the mitral valve as the mechanism of LV outflow obstruction. Anterior mitral valve leaflet to septal contact (during systole) has been shown to cause LV outflow obstruction in the majority (~95 %) of obstructive cases [6]. Left ventricular outflow tract obstruction at rest is observed in approximately 25 % of patients with HCM [7]. However, a large proportion of HCM patients without a resting gradient have a provocable outflow gradient. Indeed, a multicenter study utilizing stress echocardiography to evaluate physiologically provocable outflow gradients demonstrated that ~70 % of HCM patients have an LV outflow gradient either at rest, or with Valsalva maneuver or exercise challenge [8]. Identification of LV outflow obstruction with exercise echocardiography or provoking it during cardiac catheterization may help to identify symptomatic HCM patients who may benefit from therapies to relieve the obstruction, including medications and invasive septal reduction.

A relationship between LV outflow tract gradient, symptoms of heart failure and long-term prognosis has been demonstrated in several multicenter cohort studies [7, 9–12]. For instance, Maron et al. showed in a large HCM cohort of >1,100 patients a strong relationship between having a (resting) peak instantaneous gradient of >30 mmHg and probability of death due to HCM (relative risk 2.0, $p=0.001$) or probability of progression to NYHA class III/IV heart failure or death from heart failure or stroke (relative risk 4.4, $p<0.001$) [7]. Elliott et al. demonstrated in a cohort of >900 HCM patients a strong relationship between LV outflow tract gradient and sudden death or ICD discharge [10]. The severity of LV outflow gradient was also found to be related to a higher occurrence of sudden death or ICD discharges. In addition, the risk of progression to NYHA class III/IV or death was particularly pronounced in patients older than 40 years of age, suggestive that presence of prolonged LVOT obstruction or an interaction with co-morbidities more frequent in the elderly, such as coronary artery disease, might be related to more adverse events in patients with HCM.

Autore et al. in a cohort of >500 HCM patients have also shown that those with obstruction were at a greater risk for cardiovascular death compared with those without an obstruction (relative risk 2.1, p=0.02) [9]. However, LV obstruction was only a significant predictor of cardiovascular mortality in NYHA class I or II patients, whereas in those with severe heart failure symptoms (NYHA III or IV patients) the NYHA functional class became the main prognostic indicator independent of the presence of LV outflow gradient. These epidemiological data raise the possibility that septal reduction early in the natural history of the disease, contrary to the manner in which it is oftentimes performed today, may be of benefit to modify its course. And, similarly, it may be possible that early and aggressive medical therapy to reduce outflow obstruction may impact the natural history of the disease.

Role of Surgical Myectomy

Surgical septal myectomy (known as the Morrow procedure) emerged as the primary strategy for relieving mechanical obstruction to LV outflow, even before it was widely accepted that SAM of the mitral valve was the primary mechanism of the obstruction [13]. The surgery is indicated in HCM patients with pronounced LV outflow obstruction and severe heart failure symptoms (New York Heart Association classes III and IV). Traditionally, the myectomy consisted of transaortic resection of a small amount of basal septal muscle with consequent enlargement of the LV outflow tract that resulted in permanent elimination of mechanical impedance to LV outflow, SAM-related mitral regurgitation, and eventual normalization of LV pressures and improvement in diastolic function [14]. Contemporary surgeries for HCM include extended septal resections and if necessary partial resection or mobilization of the papillary muscles. Suturing of the medial and lateral segments of the anterior leaflet of the mitral valve to the posterior annulus is a more recent and novel addition that may be associated with improvement in mitral regurgitation and prevention of residual and recurrent LVOT obstruction [15].

As a result, a majority of patients undergoing myectomy experience low post-procedural outflow gradients that lead to relief of heart failure symptoms and ability to return to normal exercise capacity and quality of life [16–19]. Long-term studies after myectomy report sustained clinical improvement with 85–90 % of patients becoming asymptomatic (or only mildly symptomatic) for up to 25 years after myectomy. In addition to improvements in quality of life, there is also observational evidence that myectomy may favorably alter the natural course and progression of HCM, and may improve long-term survival, with a normal or near-normal life expectancy in HCM patients after myectomy [20]. Importantly, however, these outcomes have been limited to a relatively small number of high-volume HCM centers, mostly in the United States, and relatively young patients with few comorbidities.

Advent of Alcohol Septal Ablation

In 1994, Sigwart introduced an unconventional percutaneous catheter approach that used absolute alcohol to induce a small, targeted myocardial infarction in the septum as an alternative to surgical myectomy [21]. When performed by skilled operators at high–volume centers, alcohol septal ablation (ASA) results in an increase in LV outflow diameter, a reduction in LVOT gradient in >80–90 % of patients, regression of LVH, and improved diastolic function [22, 23]. Long-term benefits result from the creation of a localized septal infarction and scarring, which lead to progressive increase in LVOT diameter as a result of septal thinning and LV remodeling [24–26]. After ASA, the severity of mitral regurgitation is reduced, LV end–diastolic pressure falls, and the size of the left atrium decreases, likely contributing to secondary effects including beneficial reduction in atrial fibrillation burden and severity of pulmonary hypertension [27–29]. Improvement in diastolic function may be explained by an improvement in LV load–dependent relaxation and a reduction in LV stiffness due to regression of LV hypertrophy and decrease in interstitial collagen content [26, 29–31].

Similar to surgery, ASA results in a significant improvement in functional class (NYHA and CCS class), peak oxygen consumption and exercise capacity for up to 8–10 years. In addition, recent studies have indicated that ASA results in improvements in LV synchrony, microvascular function of the subendocardium, and myocardial energetics parameters [24, 25]. Importantly, HCM patients after a successful ASA procedure also appear to have long-term survival rates that are comparable to the non-HCM population [32]. These data suggest that ASA, similar to surgical septal reduction, may positively alter the natural history of this disease.

Evaluation of the Patient for Septal Reduction Therapy

For invasive therapies to be indicated, the patient must qualify from symptomatic, hemodynamic and anatomic standpoints. Furthermore, symptoms and hemodynamic criteria must be present despite optimal medical therapy. Accordingly, oftentimes several weeks to months of uptitration and sequential addition of medications are necessary in order to determine response to therapy, and document persistent severe symptoms and obstructive physiology. When done correctly, many patients will respond to aggressive medical

therapy, obviating the need for invasive management. However, even in the subset of patients controlled with medications, the disease may progress or side effects may develop, and invasive therapy may become warranted at a later time.

Assessment of Symptom Parameters

A detailed and comprehensive evaluation of the HCM patient as a whole, even in the presence of significant LVOT gradient, is of paramount importance to delineate the precise causation of symptomatology. In particular, symptoms of dyspnea or angina must be clearly related to HCM physiology, and not due to other comorbid conditions. For example, concomitant presence of severe coronary artery disease or intrinsic lung disease can be the explanation for either incremental or sudden change in effort tolerance by the HCM patient. Patient selection for either form of septal reduction therapy, myectomy or ASA, is thus based on very careful individual assessment of symptoms to determine the extent to which they may be caused by HOCM physiology. Prior to embarking on invasive therapies, the physician must be convinced that relief of obstruction, and the cascade of LV unloading, reduction in LVH and improvement in diastolic dysfunction, will result in significant improvement in symptoms.

In patients with HCM, chest pain/discomfort and risk factors for coronary artery disease, invasive coronary angiography may be preferable to stress testing to exclude obstructive coronary artery disease, particularly if the patient is undergoing evaluation for septal reduction therapy. In HCM patients with chest pain/discomfort and low likelihood of CAD, particularly if not a candidate for septal reduction, assessment of ischemia or perfusion abnormalities suggestive of CAD with single photon emission computed tomography, positron emission tomography myocardial perfusion imaging, or computed tomographic imaging could be reasonable.

For patients with dyspnea, objective evaluation of functional capacity, NYHA class, or response to medical therapy may be needed. Treadmill exercise testing can be utilized, particularly if symptoms are vague and inconsistent with the results of non-invasive imaging. In patients with declining functional status, treadmill exercise testing in combination with exercise echocardiography may be helpful in correlating the degree of symptomatic progression of disease with the nature and severity of obstruction. In patients without LV outflow resting gradient, exercise echocardiography can be helpful to detect and quantify exercise-induced dynamic LVOT obstruction and exercise-induced blood pressure response [8, 33–35]. Cardiopulmonary testing parameters, such as peak oxygen consumption (VO2) and anaerobic threshold have been found to be reduced in the HCM population [36]. Cardiopulmonary testing may help to elucidate the mechanism of exercise limitation on an individual basis. Although clinical utility of such testing has not been well demonstrated in this population, it may be beneficial in those with mixed diseases, such as concomitant pulmonary disease or anemia [37].

It is important to note that the majority of symptomatic patients with HCM will respond to medical therapy with negative inotropic drugs (β-blockers, verapamil, and disopyramide); however, ~5–10 % of patients will remain with severe symptoms refractory to medications or intolerable side effects that limit medication use or dose escalation [38]. Septal reduction therapy is generally recommended for those patients with an LV outflow obstruction and severe drug-refractory symptoms, such as severe dyspnea or chest pain (usually NYHA functional classes III/IV or CCS classes III/IV) or other exertional symptoms (syncope or near syncope) that interfere with daily activities or quality of life despite optimal medical therapy [39, 40]. There is no established consensus regarding the definition of optimal medical therapy; however, most experts would agree that β-blockers and/or verapamil titrated to a resting heart rate of <60–65 beats per minute, and perhaps addition of disopyramide to β-blocking drugs or verapamil for those who do not respond to monotherapy, would constitute optimal medical therapy [41]. Septal reduction therapy may also be indicated in patients who are intolerant of optimal medical therapy, due to co-morbid conditions, such as bradycardia or asthma.

Selected patients who do not meet NYHA or CCS class III or IV criteria can be considered for septal reduction therapy as well. Those with symptoms refractory to optimal conservative therapy, that interfere substantially enough with their quality of life can be considered for invasive therapy, as long as they understand and accept the potential morbidity and mortality of an invasive management strategy. This may be more common in younger patients (e.g. <40 years of age) in whom marked limitations to cardiac output and reserve may occur while the patient can still maintain NYHA Class II activities. Furthermore, selected patients with advanced NYHA or CCS class II symptoms, such as post-prandial dyspnea, those with NYHA class II and acute exacerbation of CHF due to paroxysmal atrial fibrillation, and those with obstruction-related syncope or severe near syncope with chronic NYHA or CCS class II symptoms, may also be considered for these procedures. In patients with syncope or near syncope, the symptoms should be caused by LV outflow tract obstruction or combination of LVOT obstruction and autonomic dysfunction, rather than being arrhythmogenic in origin. Currently, there are no data to suggest that the indication for performing septal reduction should be extended to patients with HOCM and no or very mild symptoms, regardless of the severity or chronicity of obstruction.

Right heart catheterization should be considered in addition to left heart catheterization in HCM patients being

evaluated for septal reduction therapy, particularly in those with complaints of dyspnea, symptoms of heart failure or angina. It is imperative to differentiate other pulmonary or noncardiac causes of dyspnea, including COPD, as well as alternate cardiac etiologies, such as aortic stenosis, in the symptomatic patient with HCM. When present, the degree of pulmonary hypertension should be quantified, including calculation of the pulmonary vascular resistance. For patients with symptoms of heart failure and low/normal filling pressures, either fluid or exercise challenge can be performed to further investigate the etiology of symptoms. For those patients who have high pulmonary arterial pressures and low/normal filling pressures, nitric oxide inhalation or other vasodilators can help to establish pulmonary hypertension as a primary determinant of symptoms, and assess for reversibility and need for treatment.

Assessment of Hemodynamic Parameters

Candidates for septal reduction therapy must have an LV outflow tract gradient of ≥50 mmHg at rest, with physiologic provocation, or with exertion. While echocardiography is the gold standard, permitting evaluation of obstruction provoked by Valsalva maneuver or treadmill exercise, cardiac catheterization is frequently complementary and often necessary in patients with poor echocardiographic "windows" to evaluate or confirm the severity of LVOT gradient at rest and with provocative maneuvers. This can be particularly important in patients with labile LVOT gradients [42]. Cardiac catheterization in HCM patients requires meticulous attention to detail, due to a number of potential errors that can occur as a result of measurements inside a small, hypertrophied, hyperdynamic ventricle, including catheter entrapment. Peripheral augmentation or discrepancies due to peripheral arterial disease must be taken into account. The dynamic outflow obstruction leads to a characteristic arterial pressure waveform, frequently described as a 'spike-and-dome' configuration, most apparent in the proximal aorta. It is important to measure the LV pressure at the apex, so as to include the entirety of the ventricle and all potential areas of obstruction. The characteristic arterial morphology becomes even more evident during maneuvers that increase the dynamic gradient, such as the Valsalva or presence of extrasystoles. The narrowing in pulse pressure of the spike-and-dome arterial waveform as a result of obstruction and reduced stroke volume is commonly known as the Brockenbrough-Braunwald sign, and confirms the dynamic, sub-valvular nature of the obstruction. Care must be taken to rule out concomitant supra- or sub-valvular membrances as well as vavlular stenosis.

Diagnostic catheters can get entrapped in a small ventricle, inducing ventricular ectopy that can make precise gradient measurements difficult during single-catheter pull-back. Dual pressure transducers, with simultaneous measurements of left ventricular pressure and aortic/arterial pressures, are therefore required. Although some operators have used transseptal catheterization for the measurement of left ventricular pressures, thereby avoiding catheter entrapment, this is rarely required today [43]. When a retrograde catheter approach is utilized to measure LVOT gradient, pigtail catheters with multiple sideholes should be utilized first in order to determine the maximal gradient across the entirety of the outflow tract; however, they should then be exchanged for an end-hole catheter (i.e. multi-purpose catheter). Slow pullback across the outflow tract and into the aorta then facilitates precise localization of the level of obstruction.

Given the dynamic nature of the gradient, resting gradient will not always be present during the catheterization procedure. Sedatives and intravenous fluids should generally be avoided during catheterization so as not to mask the presence of LVOT gradient. If a significant resting gradient (gradient of ≥50 mmHg) is not found during catheterization, provocative maneuvers such as the Valsalva or an induction of an extrasystolic beat to measure the Brockenbrough-Braunwald sign (or a combination of both maneuvers) should then be performed. If a significant gradient is still not provoked, either exercise (e.g. supine bicycle exercise) or pharmacologic challenge (amyl nitrite, nitroglycerine or isoproterenol) is helpful when the clinical picture strongly suggests obstructive physiology. Isoproterenol hydrochloride provides direct stimulation of the β1 and β2 receptors that simulates exercise and, therefore, may uncover a labile outflow tract gradient [44]. From a practical standpoint, if significant obstruction cannot be elicited with physiologic maneuvers, however, LVOT obstruction as the primary etiology of the symptoms is unlikely.

Diastolic dysfunction can be evident by elevated left ventricular diastolic pressure and abnormal contour of the diastolic pressure tracing. Left ventriculography will frequently demonstrate a hyperdynamic, hypertrophied ventricle, with a relatively small cavity. Dynamic outflow obstruction can sometimes be seen during ventriculography as a "swan neck" deformity in a "banana-shaped" ventricle [45]. Significant mitral regurgitation from systolic anterior motion of the mitral valve leaflet can frequently be expected and seen during ventriculography, especially when PVCs are elicited.

Assessment of Anatomic Parameters

Non-invasive testing, particularly echocardiography, is generally the initial step in the diagnosis and, importantly, patient selection for septal reduction therapy from both the anatomic and hemodynamic standpoint. Septal wall thickness <15–16 mm is considered a contraindication to either

myectomy or ASA due to the potential risk of septal perforation with creation of a ventricular septal defect. Although this complication has been reported more often with surgical myectomy than with ASA, septal thickness in this range remains a contraindication for both.

Left ventricular outflow tract anatomy with regards to basal septal thickness and distribution/extent of thickness can be quite variable from patient to patient. It is important to identify patients with severe septal hypertrophy (≥30 mm) as well as those with focal basal septal hypertrophy ("septal bulge") as those patients may preferentially benefit from surgical myectomy or ASA, respectively. Significant intrinsic mitral valve as well as aortic valve disease needs to be carefully evaluated as it will have an important impact on selection of septal reduction therapy. The echocardiographic characteristics, severity and direction of mitral regurgitation will provide important data regarding etiology of obstruction and mitral regurgitation, and potential benefit of septal reduction therapy. Mitral regurgitation caused by SAM is invariably associated with a late systolic, posterolaterally directed jet. If mitral regurgitation is not posterolaterally directed on color flow Doppler imaging, and especially when it is anteriorly-displaced, the mitral apparatus should be examined very carefully with either transthoracic or transesophageal echocardiography (TEE) to determine an alternate cause.

Transesophageal echocardiography becomes of particular importance when mitral regurgitation is suspected to be due to structural abnormalities of the mitral and submitral valve apparatus, including direct insertion of the anterolateral papillary muscle into anterior mitral leaflet, accessory papillary muscles producing mid-cavity muscular obstruction, mitral valve prolapse, severe calcification, or presence of elongated mitral valve leaflets or chords [46–48]. TEE can also be of importance if discrete or tubular fixed subaortic stenosis or supra- or subvalvular membranes are suspected [49].

Cardiac magnetic resonance can supplement echocardiographic data by providing high resolution images with excellent and uniform contrast at the endocardial borders, and permitting virtually complete reconstruction of the left ventricular cavity. When critical morphological data regarding magnitude or distribution of hypertrophy, anatomy of the mitral valve apparatus or papillary muscles cannot be obtained from conventional echocardiographic studies, magnetic resonance imaging can become essential [50, 51].

Selective coronary angiography should be performed to exclude concomitant coronary disease. Furthermore, in those undergoing workup for septal reduction treatment, the size and distribution of the septal perforator arteries need to be carefully evaluated. Not infrequently coronary angiography will demonstrate marked systolic compression of septal branches of the left anterior descending artery and a "sawfish" systolic narrowing of the LAD artery [52]. In addition, septal arteries may arise from the left main, diagonal branches and even from the right coronary artery, and thus meticulous angiography in multiple views is imperative.

Table 17.1 Primary indications for septal reduction therapy

Symptoms are clearly and primarily attributed to obstructive HCM physiology (including secondary phenomena such as diastolic dysfunction, mitral regurgitation, reduced cardiac output and pulmonary hypertension).
Symptoms interfere substantially with life despite optimal medical therapy.
NYHA functional classes III/IV or CCS classes III/IV or other exertional symptoms (syncope or near syncope) that interfere with daily activities or quality of life despite optimal medical therapy.
Patients who are intolerant of optimal medical therapy due to co-morbid conditions, such as bradycardia or asthma.
Selected patients with advanced NYHA or CCS class II symptoms may also be considered, such as acute exacerbation of CHF due to paroxysmal atrial fibrillation or those with obstruction-related syncope or severe near syncope.
Septal thickness ≥15–16 mm at point of septal – mitral contact.
Left ventricular outflow tract gradient ≥50 mmHg at rest or with provocation/exercise.
Basal asymmetric septal hypertrophy, systolic anterior mitral valve leaflet to septal contact causing dynamic LV outflow obstruction, with associated mitral regurgitation and posterolaterally directed jet.

In summary, patients ultimately will be deemed to be candidates for isolated septal reduction therapy when (a) symptoms are clearly and primarily attributed to obstructive HCM physiology despite optimal medical therapy, (b) symptoms are severe heart failure or angina (as measured by NYHA or CCS class, respectively), recurrent obstruction-related syncope, or recurrent clinical decompensation due to refractory paroxysmal atrial fibrillation, (c) a gradient ≥50 mmHg can be documented on optimal medical therapy, either at rest or with provocation, and (d) obstruction is clearly subvalvular and dynamic, from septum-to-anterior mitral leaflet contact, and not due to fixed obstructive valvular disease or membranes (Table 17.1).

Individualization of Septal Reduction Therapy

Transaortic septal myectomy has traditionally been considered the most effective and appropriate treatment strategy for the majority of patients with significant LVOT gradient and severe drug-resistant symptoms, given documented long-term results and safety data [39]. In the early years of septal myectomy, perioperative mortality was relatively high ≥5 % [53]. Over the last 20 years, however, surgical results have dramatically improved, with operative mortality <1 %. Such results remain limited to relatively few centers with extensive experience with this operation in dedicated HCM centers [46, 54].

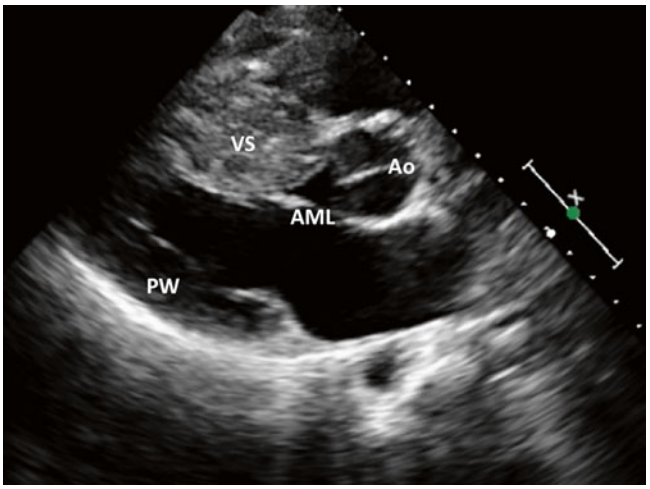

Fig. 17.1 Massive asymmetric hypertrophy of ventricular septum, favoring septal myectomy. *VS* ventricular septum, *AML* anterior mitral leaflet, *Ao* aorta, *PW* posterior free wall

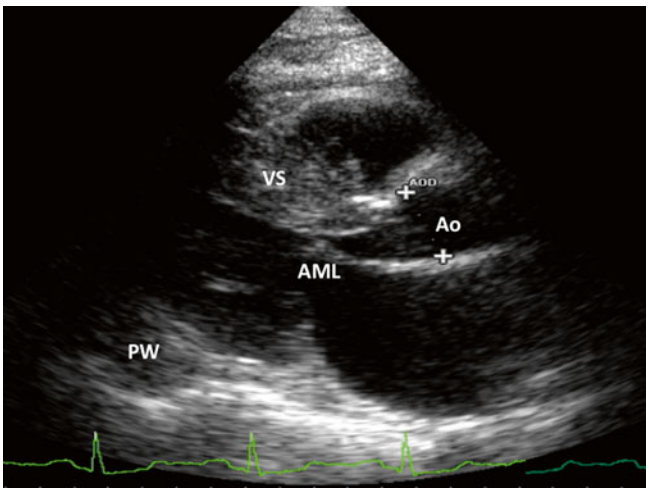

Fig. 17.2 Diffuse, concentric left ventricular hypertrophy that extends to the mid-ventricle, favoring septal myectomy. *VS* ventricular septum, *AML* anterior mitral leaflet, *Ao* aorta, *PW* posterior free wall

Besides septal thickness <15–16 mm, there are no other anatomical contraindications for surgical myectomy; indeed, most other abnormalities may be addressed during the same operation. The traditional myectomy (Morrow procedure) with ~3 cm septal resection or 'extended myectomy' with ~7 cm resection are currently being used [46, 54, 55]. Intrinsic disease of the mitral valve apparatus or papillary muscles may significantly contribute to the generation of LVOT gradient. Such patients are better served by surgical myectomy with additional surgical intervention as needed. In particular, surgical myectomy can be supplemented with mitral valve repair or leaflet plication, sometimes with the 'extended myectomy' to mid-ventricular level and with reconstruction of subvalvular apparatus [56, 57]. Enlarged or malpositioned papillary muscles contributing to obstruction can be 'shaved', incised off the ventricular wall and repositioned to the adjacent papillary muscle.

Surgery is often preferred in younger patients, those with massive septal hypertrophy (e.g. ≥30 mm) (Fig. 17.1), those with diffuse rather than focal left ventricular hypertrophy that extends to the mid-ventricle or even apex (Fig. 17.2), those with preexisting left bundle branch block (since ASA usually causes right bundle branch block, resulting in a high incidence of complete heart block), and those with concomitant cardiac disease requiring surgical intervention: intrinsic severe mitral valve disease, presence of membranes (Fig. 17.3), moderate/severe aortic stenosis (Fig. 17.4), coronary artery disease favoring coronary artery bypass grafting, and those with atrial fibrillation that might require a Maze procedure or left atrium appendage ligation.

The major advantage of ASA is its minimally invasive catheter-based approach that results in lesser degree of patient discomfort and morbidity when compared with an

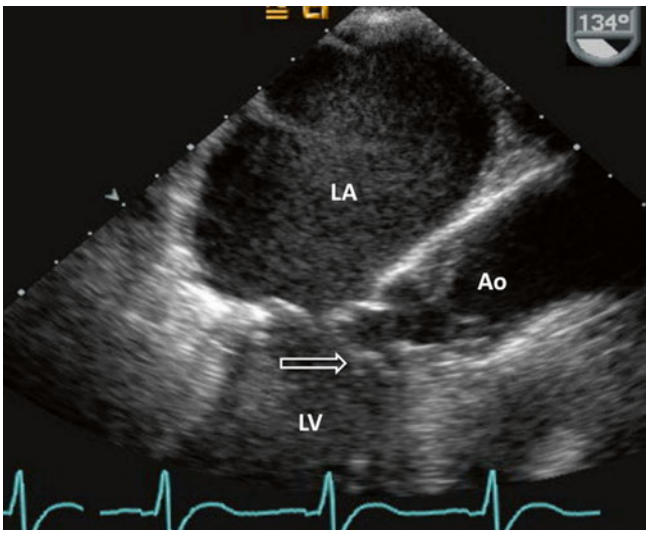

Fig. 17.3 Transesophageal echocardiographic (TEE) image of subvalvular membrane (*arrow*), favoring septal myectomy. *Ao* aorta, *LA* left atrium, *LV* left ventricle

open-heart surgical procedure, mainly by avoiding sternotomy, cardiopulmonary bypass, and ~4–6 weeks of postoperative recovery. On the other hand, only patients with certain anatomic criteria are good candidates for ASA as it requires favorable septal perforator anatomy (size, distribution, and accessibility) for delivery of alcohol to the target basal portion of the septum [58] (Fig. 17.5). Factors that favor ASA over myectomy include advanced age (>65 years), co-morbid conditions that would increase surgical risk (e.g. pulmonary hypertension or severe COPD causing significant concerns about lung or airway management), preexisting right bundle branch block (because myectomy usually causes left bundle branch block, and a high incidence of complete heart block), presence of pacemaker/ICD that would

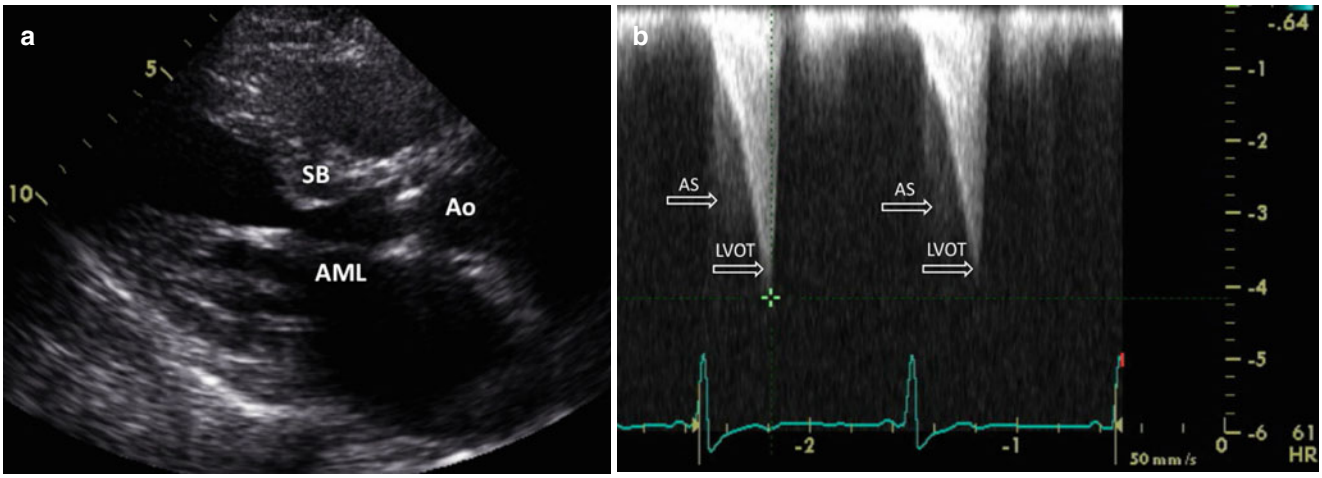

Fig. 17.4 Concomitant hypertrophy of the basal septum just below the aortic valve (dynamic obstruction) and valvular aortic stenosis (fixed obstruction) favoring combined septal myectomy and aortic valve replacement (**a**). Continuous wave Doppler spectra obtained from the apex demonstrating both aortic stenosis (faint spectrum) and left ventricular outflow tract obstruction with typical late-peaking configuration resembling a dagger or ski slope (**b**). *Ao* aorta, *AML* anterior mitral leaflet, *SB* septal bulge, *AS* aortic stenosis, *LVOT* left ventricular outflow tract

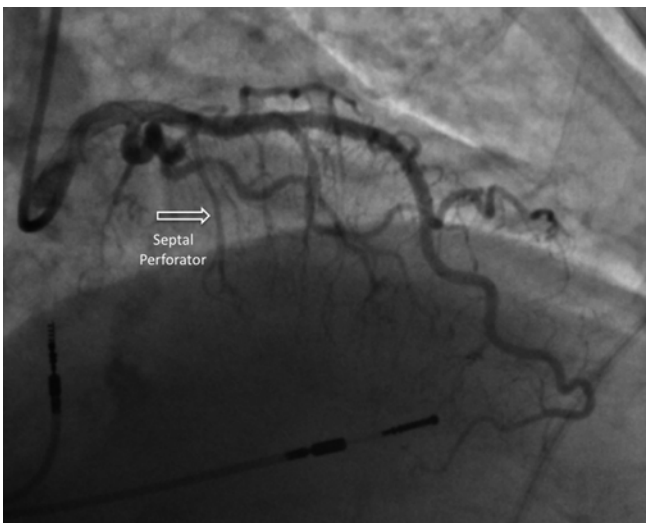

Fig. 17.5 Favorable septal perforator anatomy (adequately sized and accessible septal perforator) for delivery of alcohol to the target basal portion of the septum

substantially lower the procedural risk of ASA, prior cardiac or thoracic surgery (given the risks inherent to reoperation), and focal CAD that can be treated with stenting. ASA should generally be avoided in children.

Certain anatomical criteria make ASA more favorable, such as focal 'septal bulge' (Fig. 17.6), wide angle of papillary muscles and chords to ventricular septum, absence or minimal intrinsic disease of mitral valve apparatus and papillary muscles, and favorable coronary anatomy with a single septal perforator of appropriate size supplying the targeted asymmetric hypertrophied basal septum territory (Table 17.2).

For many patients, both procedures could provide reasonable treatment options. In such cases, the principle of patient autonomy suggests that patients can choose between myectomy and ASA after a thorough discussion of the risks and benefits related to each procedure. A heart team approach in dedicated HCM centers may offer patients an easier access to experienced interventional cardiologists and surgeons, skilled in patient selection for septal reduction therapy. ACCF/AHA 2011 Hypertrophic Cardiomyopathy Guidelines recommend that in those patients who are acceptable surgical candidates, surgical myectomy should generally be preferred (class IIa) over ASA (class IIb), whereas in those patients who are not acceptable candidates for surgical intervention, ASA would be the favored treatment option (class IIa) [39]. Patient preference for alcohol septal ablation over surgical myectomy was also reasonable after a balanced and thorough discussion (class IIb). However, as previously described, an individualized approach to selection of septal reduction therapy is commonly required, with comprehensive assessment of clinical symptoms, associated comorbidities, echocardiographic and angiographic features that might favor one approach over another.

Comparison of ASA and Septal Myectomy

No randomized controlled trials comparing ASA to surgical myectomy have been performed, and it is unlikely that a randomized trial comparing these two therapies in patients with anatomy favorable for both procedures will ever be performed [59]. In the absence of a randomized trial, we must rely on non-randomized, retrospective studies from relatively few centers with extensive experience in the

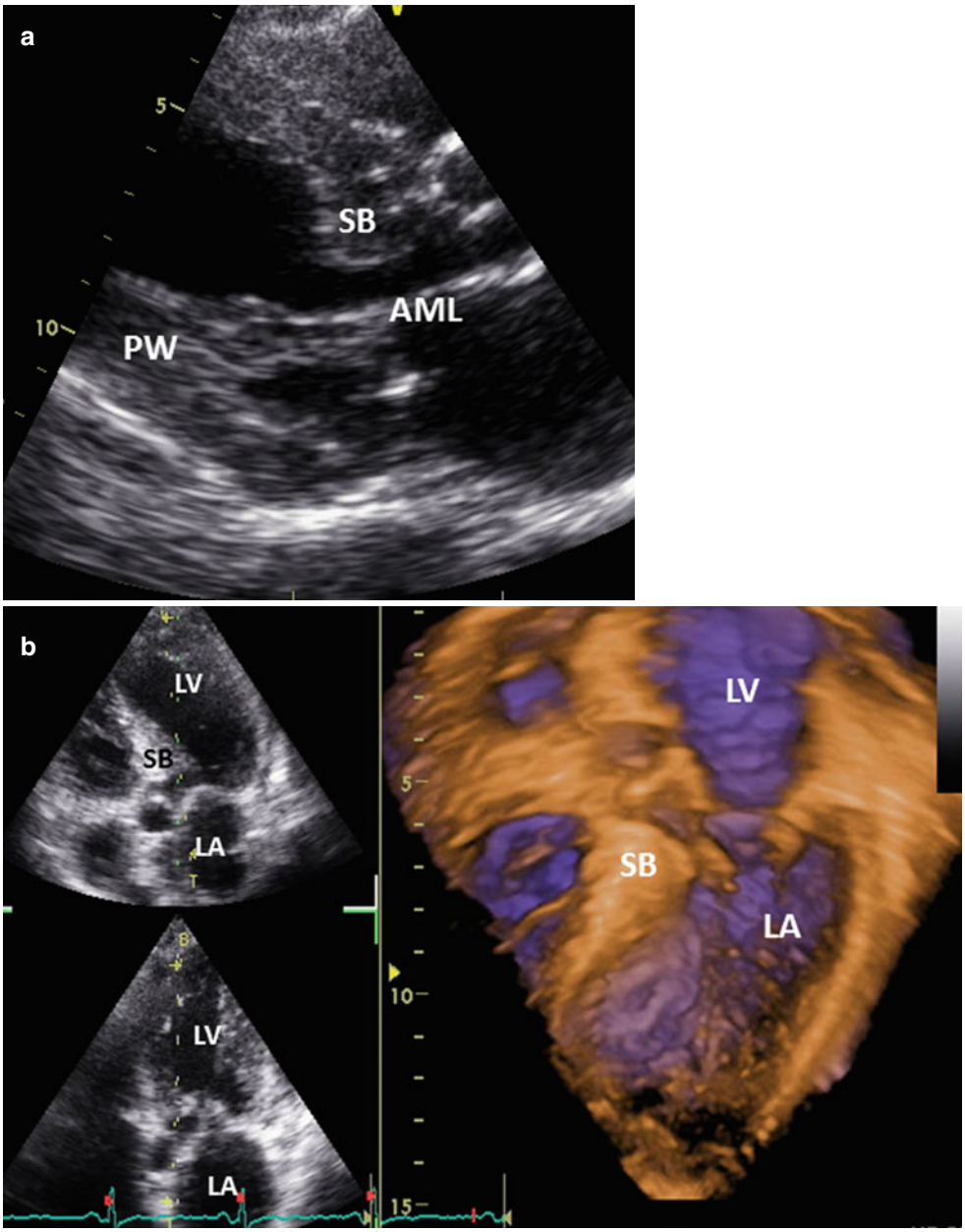

Fig. 17.6 Hypertrophy confined to the basal (proximal) septum just below the aortic valve ('septal bulge'), favoring ASA (**a**). Two and three-dimensional echocardiographic images of HCM with focal septal hypertrophy (**b**). *AML* anterior mitral leaflet, *SB* septal bulge, *LA* left atrium, *LV* left ventricle, *PW* posterior free wall

treatment of HCM. This evidence suggests that ASA and surgical myectomy result in similar outcomes with respect to hemodynamic and functional improvements [60–63]. One report from the Thoraxcenter (Erasmus Medical Center) suggested higher mortality rates for ASA, although in that study investigators used higher doses of ethanol (mean ~3.5 ml) than is currently being used in clinical practice [64]. In contrast, Sorajja et al. have reported the Mayo Clinic experience and demonstrated similar mortality rates after ASA and myectomy in age- and gender-matched cohorts [65]. In a large Multicenter North American Registry of 874 patients undergoing ASA, Nagueh et al. reported that ~95 % of patients were free from NYHA classes III and IV symptoms [66].

The overall 1-, 5-, and 10-year survival after surgical myectomy at the Mayo Clinic was 98, 96, and 83 %, respectively, and did not differ from that of the general age- and gender-matched U.S. population nor from patients with non-obstructive HCM [20]. Similarly, investigators from the Czech Republic reported that after ASA in 178 highly symptomatic patients, overall survival free of all-cause mortality at 1-, 5-, and 10-years was 97, 92, and 82 %, respectively [67]. This observed mortality was comparable to the expected survival for age- and gender-comparable general population. Furthermore, the Mayo Clinic investigators have reported that presence of ≥3 key patient and anatomic characteristics (age ≥65 years, gradient <100 mmHg, septal hypertrophy ≤18 mm, LAD diameter <4.0 mm) was associated with

Table 17.2 Features favoring septal myectomy versus alcohol septal ablation

Favor septal myectomy	Favor alcohol septal ablation
Symptoms that interfere substantially with lifestyle despite optimal medical therapy[a]	
Septal thickness ≥15–16 mm[a]	
Left ventricular outflow tract gradient ≥50 mmHg at rest or with provocation/exercise[a]	
Younger patients	Advanced age
Massive septal hypertrophy (e.g. ≥30 mm)	Co-morbid conditions that would increase surgical risk (e.g. pulmonary hypertension or severe COPD)
Diffuse left ventricular hypertrophy that extends to the mid-ventricle or even apex	Preexisting right bundle branch block
Preexisting left bundle branch block	Presence of pacemaker/ICD
Concomitant cardiac disease requiring surgical intervention (e.g. intrinsic mitral valve disease, presence of membranes, moderate/severe aortic stenosis, coronary artery disease favoring coronary artery bypass grafting)	Prior cardiac or thoracic surgery
Atrial fibrillation that requires a Maze procedure or left atrium appendage ligation	Concomitant focal CAD that can be treated with stenting Focal septal hypertrophy ('septal bulge') Wide angle of papillary muscles to septum Absence or minimal intrinsic disease of mitral valve apparatus and papillary muscles and of other conditions for which cardiac surgery is indicated Favorable coronary anatomy with an adequately sized, single septal perforator supplying the targeted myocardial segment Patient preference for septal ablation when both options are reasonable and patient has been fully informed regarding benefits and risk of both procedures

[a]Presence of features when both procedures could be performed

superior 4-year survival free of death and severe symptoms (90 %) in comparison to those with one or two such characteristics [68]. Their analysis also suggested that greater ASA case volume (>50 patients) was associated with superior outcomes [68].

Several meta-analyses of comparative studies of myectomy versus ASA have now been performed, demonstrating no difference in mortality and post-procedural NYHA class with these two approaches [69, 70]. Agarwal et al. have analyzed 12 studies and demonstrated in addition to no differences in short-term mortality (Fig. 17.7) and long-term mortality between ASA and myectomy, no differences in NYHA functional class, ventricular arrhythmia occurrence, re-interventions performed, and post-procedural mitral regurgitation between the two procedures [69]. Similar to prior analyses, there was a small yet significantly higher residual LVOT gradient amongst ASA as compared with myectomy, and a higher incidence of permanent pacemaker implantation after ASA. In another meta-analysis of 19 ASA studies and 8 surgical myectomy studies, Leonardi et al. have demonstrated similar unadjusted rates of all-cause mortality and sudden cardiac death [71]. However, ASA patients were older and had less septal hypertrophy when compared with myectomy patients. When adjusted for baseline characteristics, ASA was associated with lower all-cause mortality and sudden cardiac death rates, with no difference in NYHA class [71]. This may speak to inherent selection bias between two approaches, with older patients and those with more co-morbidities being preferentially referred and treated with ASA.

In addition to long-lasting reduction in symptoms of heart failure after ASA and surgical myectomy, septal reduction therapy may result in a long-term survival benefit as has been demonstrated in a number of retrospective studies [11, 20, 67, 72, 73]. In the large Mayo Clinic series of >1,300 HCM patients, 1-, 5-, and 10-year overall survival after surgical myectomy was 98, 96, and 83 %, respectively, and did not differ from that of the age- and gender-matched general U.S. population and was similar to patients with non-obstructive HCM [20]. Furthermore, when compared to nonoperated obstructive HCM patients, myectomy patients experienced superior survival free from all-cause mortality (98 %, 96 %, and 83 % vs. 90 %, 79 %, and 61 %, respectively; $p<0.001$) and sudden cardiac death (100 %, 99 %, and 99 % vs. 97 %, 93 %, and 89 %, respectively; $p=0.003$). Similarly, in a small cohort of ASA patients, overall survival at 1, 5, and 10 years (97, 92, and 82 %) was comparable to the expected survival for age- and gender-comparable general population [67]. These data suggest that invasive normalization of LVOT gradient and LV pressure, prevention of further LV remodeling, and possibly reduced arrhythmogenicity of the myocardial tissue may alter the course of this disease and improve long-term survival [13].

Given similar survival rates when comparing ASA and surgical myectomy in multiple retrospective cohort studies and meta-analyses, with follow-up out to 8 years, one would expect similar longer term (>10 years) survival rates as well [65, 66, 69–71]. And indeed, a similar analysis by Mayo Clinic reported that age- and gender-adjusted survival rates for surgical myectomy and alcohol septal ablation were tracking together out to 8 years, suggesting that both septal reduction therapies may positively and similarly impact the natural history of disease [32].

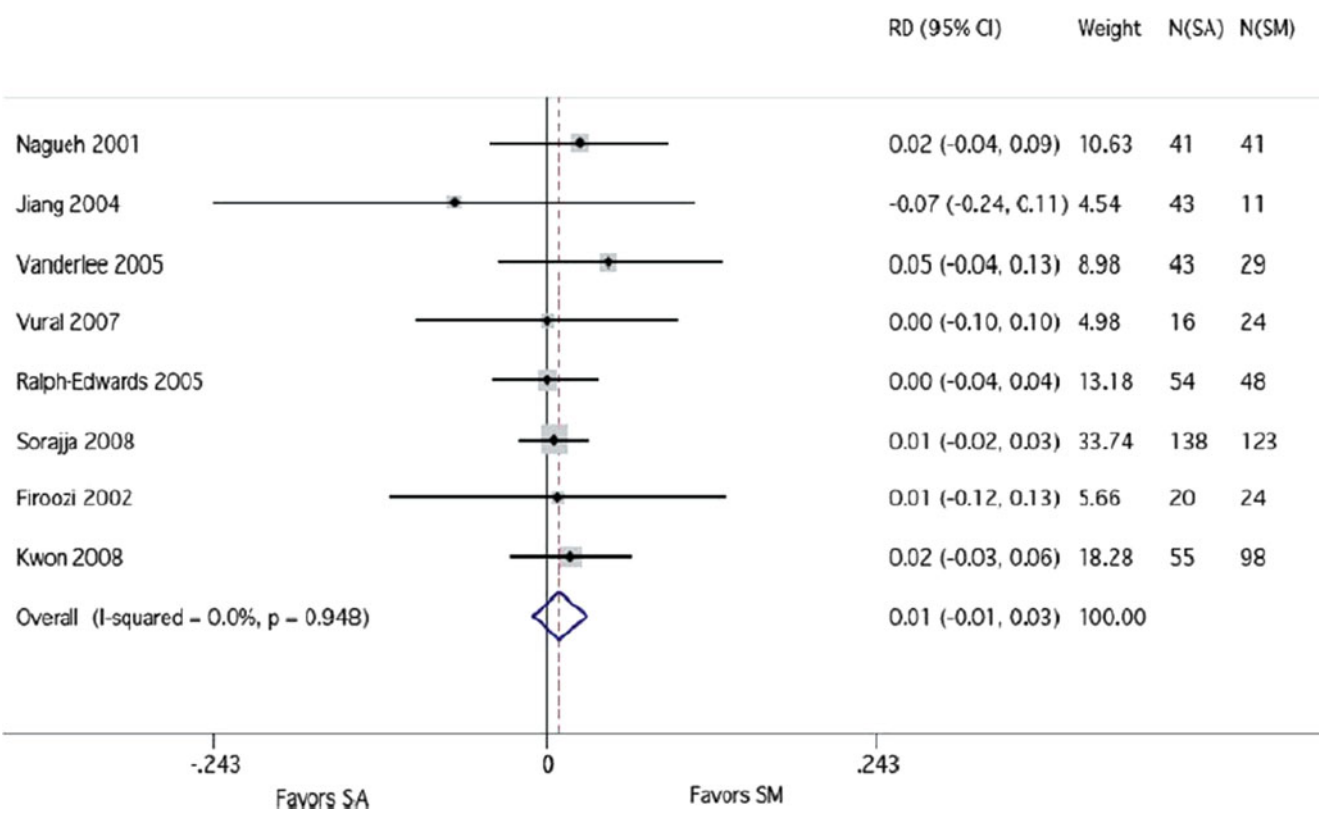

Fig. 17.7 A pooled meta-analysis comparison of short-term mortality between ASA and septal myectomy. The risk difference in short-term mortality between ASA and septal myectomy was insignificant (risk difference: 0.01; 95 % CI 0.01–0.03, p=0.35) (Adapted from Agarwal et al. [69]. Copyright 2010 by Elsevier Inc. Adapted with permission)

RD risk difference, *SA* septal ablation, *SM* septal myectomy, *CI* confidence interval. *Ao* aorta, *AML* anterior mitral leaflet, *LA* left atrium, *LV* left ventricle, *VS* ventricular septum, *PW* posterior free wall, *SB* septal bulge, *AS* aortic stenosis, *LVOT* left ventricular outflow tract

The debate of whether myectomy and ASA are truly equivalent options in terms of efficacy and outcomes has persisted since the introduction of the ASA technique over 20 years ago [74]. Given the above studies, it is clear that the debate regarding early symptomatic improvements in NYHA heart failure class, syncope, angina, and LV outflow tract gradient has been largely settled. There are sufficient data from retrospective cohort studies regarding rates of acute complications, LVOT gradient reduction, and short-term symptomatic improvement; both procedures are similarly efficacious in the modern era. In most reports, more complete gradient reduction is still achieved with surgery, but the magnitude does not translate into clinically meaningful differences in outcomes [69–71].

The second debate revolved around the early, periprocedural risks including the incidence of complete heart block and need for permanent pacemaker placement. Indeed, early experience with ASA encompassed the operator learning curve, which was associated with relatively good clinical efficacy, but more complications, including complete heart block, early ventricular arrhythmias, and even death or distant myocardial infarction from coronary dissection or inadvertent spillage of ethanol [75]. The next era of ASA, between years 2001–2010, was characteristic of improvements in technical aspects of the procedure, leading to less peri-procedural complications. Myocardial contrast echocardiography was used more commonly to select the target septal perforator, ethanol volume and rate of injection were reduced, and more judicious case selection was being practiced with a goal of improving the benefit-to-risk ratio. This transformation of ASA has now resulted in peri-procedural mortality rates of <1 % that closely track those seen with surgical myectomy [76].

During initial experience with ASA, the rates of conduction abnormalities with ASA were high, with up to 20–25 % of patients receiving permanent pacemakers for complete heart block or prophylactic implantable defibrillators for the risk of sudden death [65, 77]. With refinement of ASA technique, the rates of permanent pacemaker placement in more contemporary studies are now in the 8–17 % range [68, 76]. Despite significant reductions in the incidence of permanent pacemaker requirement, ASA still lags behind the ~2–3 % rates of pacemaker placement seen with surgery. However, it remains unclear whether this is solely due to the procedure itself or exacerbated by the older age at which patients are preferentially offered alcohol septal ablation.

The third debate, and the only one that has not been completely settled, revolves around the issue of long-term survival. Proponents of surgical myectomy have argued that ASA, by introducing transmural infarction and scar to the septum, may predispose this population to life-threatening sustained ventricular tachyarrhythmias and arrhythmia-related sudden death [78]. However, multiple meta-analyses of large observational series with up to 8 years of follow-up have failed to demonstrate even a signal of increase in death when comparing ASA with surgery [69, 71]. Furthermore, patients who have successfully undergone either procedure appear to have survival rates that track each other as well as a comparable non-HCM population [20, 65, 67], as mentioned above.

Noseworthy et al. however have reported that among patients with an ICD or pacemaker, ASA was associated with an annual rate of VT/VF, cardiac arrest, or appropriate ICD therapy of ~4.9 %/year [79]. The data from Mayo Clinic have also suggested a higher annualized rate of appropriate ICD discharges after undergoing ASA (4.3 %/year) compared with 0.24 %/year rate following myectomy [72]. This higher than expected rate of ICD discharges may be explained partly by intrinsic selection bias, where older patients with more co-morbidities (and therefore at higher VT/VF risk in general) tend to undergo ASA. In addition, many have called into question the appropriateness of surrogate markers, such as appropriate ICD discharge, since many of these arrhythmias are not truly life-threatening, and the higher prevalence of ICD implantation among ASA patients adds to a surveillance bias. And, of course, this has not translated into reduced survival. Nonetheless, this higher rate of monitored arrhythmias is concerning and requires further investigation.

All considered, only a prospective randomized trial could eliminate the selection bias of current clinical practice and provide the cardiovascular community with definitive comparative long-term data. Unfortunately, several obstacles make the design and performance of an appropriately powered randomized trial impossible [59]. Given relatively low event rates after either procedure, ~1,200 patients with obstructive HCM and severe drug-refractory symptoms would need to be randomized, which would require screening of ~34,000 consecutive HCM patients. Such an enormous number of HCM patients could not realistically be screened even with combination of major North American and European HCM centers. Therefore, an adequately powered randomized trial comparing long-term survival of ASA and myectomy would not be feasible.

The debate regarding optimal septal reduction therapy for symptomatic medically-refractory HCM patients is also evident in the dichotomy of practice between the United States and European HCM centers. In the United States ASA is reserved for those patients who are older or with significant co-morbidities, in whom surgery is either contraindicated or considered high risk. The American College of Cardiology Foundation/American Heart Association Guidelines on the diagnosis and management of HCM support this algorithm, which is largely followed at HCM treatment centers throughout the United States [39]. In contrast, in most European centers ASA is the preferred treatment of choice, for a number of reasons, including physician and patient preference, minimally invasive nature of the procedure, an increasing sense of equipoise, local availability of experienced ASA operators, and lack of regional surgical expertise [74, 78]. The extinction of surgical myectomy in many European countries, even from countries formerly with rich surgical traditions and experience such as Germany and Switzerland, has prompted a call to 'bring septal myectomy back for European patients' [78]. And, given the frequency with which additional anatomic problems are present in patients with HCM, it would seem appropriate that both procedures be available so as to optimally treat the largest number of patients with this disease.

Future Directions

As further evidence mounts regarding improved long-term survival after ASA, that appears identical to that seen with surgery, an argument could be made to change the recommendation for ASA to class IIa, making it an equivalent option to surgery in those who qualify anatomically for both procedures. In experienced HCM centers, the only meaningful difference between the two procedures might be the higher risk of permanent pacemaker in ASA patients versus the known risk of sternotomy and longer post-surgical recovery in those undergoing surgery. Recent modifications to ASA (the use of myocardial contrast echocardiography and reduction in the dosage of alcohol) as well as better patient selection have led to improvements in results and decrease in peri-procedural complications.

The current challenge is to inform practitioners in the US about the full capabilities of ASA and myectomy, to educate clinicians that experienced operators at HCM centers of excellence can perform these procedure today with similar short- and long-term outcomes, and to disseminate both techniques to larger areas of the country. In the United States there is currently a shortage of experienced operators, both surgical and interventional, that would need to be trained in case selection, optimal technique, and longitudinal care of HCM patients. In European countries, an important goal for the future may be to train more young surgeons to perform myectomy and, therefore, to provide HCM patients with

access not only to ASA, but also to centers with extensive experience in surgical myectomy.

As the ASA and myectomy procedures become safer in terms of peri-procedural complications, the threshold for invasive intervention may need to be lowered in the future. Patients with NYHA class II symptoms, particularly those with syncope, near syncope, and presence of intermittent or chronic atrial fibrillation, may derive significant symptomatic improvement after septal reduction. Given that septal reduction therapy may improve not only quality of life, but possibly even longevity, septal reduction therapy may need to be considered earlier in life [9].

Furthermore, should ASA be considered in patients without a confirmed diagnosis of HCM, but who instead have the favorable constellation of anatomic and physiologic features, including hypertrophy and LVOT gradient? Kovacic et al. have recently demonstrated that ASA can be beneficial in terms of post-procedural gradient reduction, end-diastolic pressure improvement, and symptomatic NYHA class improvement in a wide cohort of patients with symptomatic concentric LVH and LVOT obstruction [80]. In reality, a firm diagnosis of HCM is not always possible, and a small proportion of patients without HCM have likely inadvertently been undergoing both surgical myectomy and ASA for the relief of LVOT obstruction symptoms. Therefore, it may be reasonable to offer septal reduction therapy (ASA or surgical myectomy) to patients with the pathophysiology of dynamic outflow tract obstruction, whether or not due to HCM. In addition to genetically-mediated HCM, these could include hypertensive heart disease of the elderly, severe concentric hypertrophy (e.g. in patients with uncontrolled hypertension or end-stage renal disease), those with Takotsubo cardiomyopathy and outflow obstruction unresponsive to medical therapy, or those with prior mitral valve repair and iatrogenic LVOT obstruction, among other cohorts. In addition, ASA may become the first treatment option for elderly HCM patients refractory to medications, who frequently have favorable ASA anatomy with a focal 'septal bulge', that may not be suited for surgery due to advanced age and concomitant co-morbidities [81].

Future investigations regarding ASA therapy may need to focus on techniques to reduce the incidence of complete heart block, as well as longer term follow-up to assure safety and survival outcomes. Such novel technologies may include the use of polyvinyl alcohol foam particles, microspheres, absorbable gelatin sponges, or septal coils as alternatives to alcohol, with a goal of reducing the incidence of complete heart block and pacemaker requirement [82–85]. Finally, reduction in septal mass by radiofrequency catheter ablation and cryoablation are under further investigation as well and may become complementary procedures to either surgery or alcohol septal ablation [86, 87].

Clinical Pearls

- Identification of LV outflow tract obstruction with exercise echocardiography or provoking it during cardiac catheterization may help to identify symptomatic HCM patients who might benefit from therapies to relieve the obstruction, including medications and invasive septal reduction treatment.
- Cardiac catheterization may aid in assessing alternate yet treatable etiologies of the symptoms, such as obstructive coronary disease, important volume overload or depletion amenable to diuretics or volume expansion, respectively.
- Patients should be considered for septal reduction therapy only when (a) symptoms are clearly and primarily attributed to obstructive HCM despite optimal medical therapy, (b) symptoms are severe heart failure or angina (NYHA or CCS class III/IV), recurrent obstruction-related syncope, or recurrent clinical decompensation due to refractory paroxysmal atrial fibrillation, (c) a gradient ≥50 mmHg can be documented on optimal medical therapy, and (d) obstruction is clearly dynamic and subvalvular, typically from septum-to-anterior mitral leaflet contact. Echocardiography and cardiac catheterization must confirm the anatomic and hemodynamic findings.
- An individualized approach to selection of septal reduction therapy is required, with comprehensive assessment of clinical symptoms, associated co-morbidities, and echocardiographic, electrocardiographic, and angiographic features that might favor one approach over another.
- There are no randomized controlled trials comparing ASA to surgical myectomy. Evidence from non-randomized studies suggests that ASA and surgical myectomy result in similar short- and long-term outcomes with respect to hemodynamic and functional improvements, with greater propensity for pacemaker placement with ASA. For some patients, both procedures could provide reasonable treatment options. In such cases, the principle of patient autonomy suggests that patients can choose between myectomy and ASA after a thorough discussion of the risks and benefits related to each procedure.

References

1. Brock RC. Functional obstruction of the left ventricle (acquired aortic subvalvar stenosis). Guys Hosp Rep. 1957;106:221.
2. Braunwald E, Lambrew CT, Rockoff SD, Ross Jr J, Morrow AG. Idiopathic hypertrophic subaortic stenosis. I. A description of the

disease based upon an analysis of 64 patients. Circulation. 1964;29 Suppl 4:3–119.
3. Wigle ED, Lenkei SC, Chrysohou A, Wilson DR. Muscular subaortic stenosis: the effect of peripheral vasodilatation. Can Med Assoc J. 1963;89:896–9.
4. Criley JM, Lewis KB, White RI, Ross RS. Pressure gradients without obstruction: a new concept of "hypertrophic subaortic stenosis.". Circulation. 1964;32:881–7.
5. Maron BJ, Epstein SE. Clinical significance and therapeutic implications of the left ventricular outflow tract pressure gradient in hypertrophic cardiomyopathy. Am J Cardiol. 1986;58:1093–6.
6. Spirito P, Maron BJ. Patterns of systolic anterior motion of the mitral valve in hypertrophic cardiomyopathy: assessment of two-dimensional echocardiography. Am J Cardiol. 1984;54:1039–46.
7. Maron MS, Olivotto I, Betocchi S, et al. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. N Engl J Med. 2003;348:295–303.
8. Maron MS, Olivotto I, Zenovich AG, et al. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. Circulation. 2006;114:2232–9.
9. Autore C, Bernabò P, Barillà CS, Bruzzi P, Spirito P. The prognostic importance of left ventricular outflow obstruction in hypertrophic cardiomyopathy varies in relation to the severity of symptoms. J Am Coll Cardiol. 2005;45:1076–80.
10. Elliott PM, Gimeno JR, Tomé MT, et al. Left ventricular outflow tract obstruction and sudden death risk in patients with hypertrophic cardiomyopathy. Eur Heart J. 2006;27:1933–41.
11. Woo A, Williams WG, Choi R, et al. Clinical and echocardiographic determinants of long-term survival after surgical myectomy in obstructive hypertrophic cardiomyopathy. Circulation. 2005;111: 2033–41.
12. Maron BJ, Dearani JA, Ommen SR, et al. The case for surgery in obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol. 2004; 44:2044–53.
13. Maron BJ, Maron MS, Wigle ED, Braunwald E. The 50-year history, controversy, and clinical implications of left ventricular outflow tract obstruction in hypertrophic cardiomyopathy: From idiopathic hypertrophic subaortic stenosis to hypertrophic cardiomyopathy. J Am Coll Cardiol. 2009;54:191–200.
14. Spirito P, Maron BJ, Rosing DR. Morphologic determinants of hemodynamic state after ventricular septal myectomy-myectomy in patients with obstructive hypertrophic cardiomyopathy: M-mode and two-dimensional echocardiographic assessment. Circulation. 1984;70:984–95.
15. Nasseri BA, Stamm C, Siniawski H, Kukucka M, Komoda T, Delmo Walter EM, et al. Combined anterior mitral valve leaflet retention plasty and septal myectomy in patients with hypertrophic obstructive cardiomyopathy. Eur J Cardiothorac Surg. 2011;40:1515–20.
16. Schulte HD, Bircks WH, Loesse B, Godehardt EA, Schwartzkopff B. Prognosis of patients with hypertrophic obstructive cardiomyopathy after transaortic myectomy. Late results up to 25 years. J Thorac Cardiovasc Surg. 1993;106:709–17.
17. Robbins RC, Stinson EB. Long-term results of left ventricular myotomy and myectomy for obstructive hypertrophic cardiomyopathy. J Thorac Cardiovasc Surg. 1996;11:586–94.
18. Smedira NG, Lytle BM, Lever HM, Rajeswaran J, Krishnaswamy G, Kaple RK, Dolney DO, Blackstone EH. Current effectiveness and risks of isolated septal myectomy for hypertrophic obstructive cardiomyopathy. Ann Thorac Surg. 2008;85:127–33.
19. Dearani JA, Ommen SR, Gersh BJ, Schaff HV, Danielson GK. Surgery insight: septal myectomy for obstructive hypertrophic cardiomyopathy—the Mayo Clinic experience. Nat Clin Pract Cardiovasc Med. 2007;4:503–12.
20. Ommen SR, Maron BJ, Olivotto I, Maron MS, Cecchi F, Betocchi S, Gersh BJ, Ackerman MJ, McCully RB, Dearani JA, Schaff HV, Danielson GK, Tajik AJ, Nishimura RA. Long-term effects of surgical septal myectomy on survival in patients with obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol. 2005;46:470–6.
21. Sigwart U. Non-surgical myocardial reduction for hypertrophic obstructive cardiomyopathy. Lancet. 1995;346:211–14.
22. Lakkis NM, Nagueh SF, Dunn JK, Killip D, Spencer 3rd WH. Nonsurgical septal reduction therapy for hypertrophic obstructive cardiomyopathy: one-year follow-up. J Am Coll Cardiol. 2000;36:852–5.
23. Kim JJ, Lee CW, Park SW, Hong MK, Lim HY, Song JK, Jin YS, Park SJ. Improvement in exercise capacity and exercise blood pressure response after transcoronary alcohol ablation therapy of septal hypertrophy in hypertrophic cardiomyopathy. Am J Cardiol. 1999;83: 1220–3.
24. Chen J, Nagaraj H, Bhambhani P, Kliner DE, Soman P, Garcia EV, et al. Effect of alcohol septal ablation in patients with hypertrophic cardiomyopathy on left-ventricular mechanical dyssynchrony as assessed by phase analysis of gated SPECT myocardial perfusion imaging. Int J Cardiovasc Imaging. 2011. doi:10.1007/s10554-011-9942-y.
25. Timmer SA, Knaapen P, Germans T, Dijkmans PA, Lubberink M, Ten Berg JM, et al. Effects of alcohol septal ablation on coronary microvascular function and myocardial energetics in hypertrophic obstructive cardiomyopathy. Am J Physiol Heart Circ Physiol. 2011;301:H129–37.
26. Mazur W, Nagueh SF, Lakkis NM, Middleton KJ, Killip D, Roberts R, Spencer 3rd WH. Regression of left ventricular hypertrophy after nonsurgical septal reduction therapy for hypertrophic obstructive cardiomyopathy. Circulation. 2001;103:1492–6.
27. Faber L, Seggewiss H, Gleichmann U. Percutaneous transluminal septal myocardial ablation in hypertrophic obstructive cardiomyopathy: results with respect to intraprocedural myocardial contrast echocardiography. Circulation. 1998;98:2415–21.
28. Gietzen FH, Leuner CJ, Raute-Kreinsen U, Dellmann A, Hegselmann J, Strunk-Mueller C, Kuhn HJ. Acute and long-term results after transcoronary ablation of septal hypertrophy (TASH). Catheter interventional treatment for hypertrophic obstructive cardiomyopathy. Eur Heart J. 1999;20:1342–54.
29. Nagueh SF, Lakkis NM, Middleton KJ, Killip D, Zoghbi WA, Quinones MA, Spencer 3rd WH. Changes in left ventricular filling and left atrial function six months after nonsurgical septal reduction therapy for hypertrophic obstructive cardiomyopathy. J Am Coll Cardiol. 1999;34:1123–8.
30. Sitges M, Shiota T, Lever HM, Qin JX, Bauer F, Drinko JK, Agler DA, Martin MG, Greenberg NL, Smedira NG, Lytle BW, Tuzcu EM, Garcia MJ, Thomas JD. Comparison of left ventricular diastolic function in obstructive hypertrophic cardiomyopathy in patients undergoing percutaneous septal alcohol ablation versus surgical myotomy/myectomy. Am J Cardiol. 2003;91:817–21.
31. Boekstegers P, Steinbigler P, Molnar A, Schwaiblmair M, Becker A, Knez A, Haberl R, Steinbeck G. Pressure-guided nonsurgical myocardial reduction induced by small septal infarctions in hypertrophic obstructive cardiomyopathy. J Am Coll Cardiol. 2001;38:846–53.
32. Sorajja P, Ommen SR, Holmes Jr DR, Dearani JA, Rihal CS, Gersh BJ, Lennon RJ, Nishimura RA. Survival after alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Circulation. 2012;126:2374–80.
33. Olivotto I, Maron BJ, Montereggi A, et al. Prognostic value of systemic blood pressure response during exercise in a community-based patient population with hypertrophic cardiomyopathy. J Am Coll Cardiol. 1999;33:2044–51.
34. Sadoul N, Prasad K, Elliott PM, et al. Prospective prognostic assessment of blood pressure response during exercise in patients with hypertrophic cardiomyopathy. Circulation. 1997;96: 2987–91.
35. Frenneaux MP, Counihan PJ, Caforio AL, et al. Abnormal blood pressure response during exercise in hypertrophic cardiomyopathy. Circulation. 1990;82:1995–2002.

36. Jones S, Elliott PM, Sharma S, McKenna WJ, Whipp BJ. Cardiopulmonary responses to exercise in patients with hypertrophic cardiomyopathy. Heart. 1998;80:60–7.
37. Chikamori T, Counihan PJ, Doi YL, Takata J, Stewart JT, Frenneaux MP, McKenna WJ. Mechanisms of exercise limitation in hypertrophic cardiomyopathy. J Am Coll Cardiol. 1992;19:507–12.
38. Maron BJ, Bonow RO, Cannon 3rd RO, Leon MB, Epstein SE. Hypertrophic cardiomyopathy. Interrelations of clinical manifestations, pathophysiology, and therapy (2). N Engl J Med. 1987;316:844–52.
39. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naidu SS, Nishimura RA, Ommen SR, Rakowski H, Seidman CE, Towbin JA, Udelson JE, Yancy CW. American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines; American Association for Thoracic Surgery; American Society of Echocardiography; American Society of Nuclear Cardiology; Heart Failure Society of America; Heart Rhythm Society; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011;124:2761–96.
40. van der Lee C, Scholzel B, ten Berg JM, et al. Usefulness of clinical, echocardiographic, and procedural characteristics to predict outcome after percutaneous transluminal septal myocardial ablation. Am J Cardiol. 2008;101:1315–20.
41. Sherrid MV, Shetty A, Winson G, Kim B, Musat D, Alviar CL, Homel P, Balaram SK, Swistel DG. Treatment of obstructive hypertrophic cardiomyopathy symptoms and gradient resistant to first-line therapy with β-blockade or verapamil. Circ Heart Fail. 2013;6:694–702.
42. Nishimura RA, Ommen SR. Hypertrophic cardiomyopathy: the search for obstruction. Circulation. 2006;114:2200–2.
43. Wigle ED, Sasson Z, Henderson MA, Ruddy TD, Fulop J, Rakowski H, Williams WG. Hypertrophic cardiomyopathy: the importance of the site and the extent of hypertrophy: a review. Prog Cardiovasc Dis. 1985;28:1–83.
44. Elesber A, Nishimura RA, Rihal CS, Ommen SR, Schaff HV, Holmes Jr DR. Utility of isoproterenol to provoke outflow tract gradients in patients with hypertrophic cardiomyopathy. Am J Cardiol. 2008;101:516–20.
45. Baim DS. Grossman's cardiac catheterization, angiography, and intervention. Philadelphia: Lippincott Williams & Wilkins; 2006.
46. Minakata K, Dearani JA, Nishimura RA, Maron BJ, Danielson GK. Extended septal myectomy for hypertrophic obstructive cardiomyopathy with anomalous mitral papillary muscles or chordae. J Thorac Cardiovasc Surg. 2004;127:481–9.
47. Klues HG, Roberts WC, Maron BJ. Anomalous insertion of papillary muscle directly into anterior mitral leaflet in hypertrophic cardiomyopathy: significance in producing left ventricular outflow obstruction. Circulation. 1991;84:1188–97.
48. Klues HG, Maron BJ, Dollar AL, Roberts WC. Diversity of structural mitral valve alterations in hypertrophic cardiomyopathy. Circulation. 1992;85:1651–60.
49. Grigg LE, Wigle ED, Williams WG, et al. Transesophageal Doppler echocardiography in obstructive hypertrophic cardiomyopathy: clarification of pathophysiology and importance in intraoperative decision making. J Am Coll Cardiol. 1992;20:42–52.
50. Maron MS, Lesser JR, Maron BJ. Management implications of massive left ventricular hypertrophy in hypertrophic cardiomyopathy significantly underestimated by echocardiography but identified by cardiovascular magnetic resonance. Am J Cardiol. 2010;105:1842–3.
51. Rickers C, Wilke NM, Jerosch-Herold M, et al. Utility of cardiac magnetic resonance imaging in the diagnosis of hypertrophic cardiomyopathy. Circulation. 2005;112:855–61.
52. Brugada P, Bär FW, de Zwaan C, Roy D, Green M, Wellens HJ. "Sawfish" systolic narrowing of the left anterior descending coronary artery: an angiographic sign of hypertrophic cardiomyopathy. Circulation. 1982;66:800–3.
53. Maron BJ. Controversies in cardiovascular medicine. Surgical myectomy remains the primary treatment option for severely symptomatic patients with obstructive hypertrophic cardiomyopathy. Circulation. 2007;116:196–206.
54. Schoendube FA, Klues HG, Reith S, et al. Long-term clinical and echocardiographic follow-up after surgical correction of hypertrophic obstructive cardiomyopathy with extended myectomy and reconstruction of the subvalvular mitral apparatus. Circulation. 1995;92 suppl 9:II122–7.
55. Morrow AG, Brockenbrough EC. Surgical treatment of idiopathic hypertrophic subaortic stenosis: technic and hemodynamic results of subaortic ventriculomyotomy. Ann Surg. 1961;154:181–9.
56. McIntosh CL, Maron BJ, Cannon RO, Klues HG. Initial results of combined anterior mitral leaflet plication and ventricular septal myotomy-myectomy for relief of left ventricular outflow tract obstruction in patients with hypertrophic cardiomyopathy. Circulation. 1992;86:II60–7.
57. Kofflard MJ, van Herwerden LA, Waldstein DJ, Ruygrok P, Boersma E, Taams MA, ten Cate FJ. Initial results of combined anterior mitral leaflet extension and myectomy in patients with obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol. 1996;28:197–202.
58. Singh M, Edwards WD, Holmes Jr DR, Tajik AJ, Nishimura RA. Anatomy of the first septal perforating artery: a study with implications for ablation therapy for hypertrophic cardiomyopathy. Mayo Clin Proc. 2001;76:799–802.
59. Olivotto I, Ommen SR, Maron MS, Cecchi F, Maron BJ. Surgical myectomy versus alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Will there ever be a randomized trial? J Am Coll Cardiol. 2007;50:831–4.
60. Nagueh SF, Ommen SR, Lakkis NM, Killip D, Zoghbi WA, Schaff HV, Danielson GK, Quinones MA, Tajik AJ, Spencer WH. Comparison of ethanol septal reduction therapy with surgical myectomy for the treatment of hypertrophic obstructive cardiomyopathy. J Am Coll Cardiol. 2001;38:1701–6.
61. Qin JX, Shiota T, Lever HM, Kapadia SR, Sitges M, Rubin DN, Bauer F, Greenberg NL, Agler DA, Drinko JK, Martin M, Tuzcu EM, Smedira NG, Lytle B, Thomas JD. Outcome of patients with hypertrophic obstructive cardiomyopathy after percutaneous transluminal septal myocardial ablation and septal myectomy surgery. J Am Coll Cardiol. 2001;38:1994–2000.
62. Firoozi S, Elliott PM, Sharma S, Murday A, Brecker SJ, Hamid MS, Sachdev B, Thaman R, McKenna WJ. Septal myotomy-myectomy and transcoronary septal alcohol ablation in hypertrophic obstructive cardiomyopathy. A comparison of clinical, haemodynamic and exercise outcomes. Eur Heart J. 2002;23:1617–24.
63. Ralph-Edwards A, Woo A, McCrindle BW, Shapero JL, Schwartz L, Rakowski H, Wigle ED, Williams WG. Hypertrophic obstructive cardiomyopathy: comparison of outcomes after myectomy or alcohol ablation adjusted by propensity score. J Thorac Cardiovasc Surg. 2005;129:351–8.
64. Ten Cate FJ, Soliman OII, Michels M, Theuns DAMJ, de Jong PL, Geleijnse ML, Serruys PW. Long-term outcome of alcohol septal ablation in patients with obstructive hypertrophic cardiomyopathy. A word of caution. Circ Heart Fail. 2010;3:362–9.
65. Sorajja P, Valeti U, Nishimura RA, Ommen SR, Rihal CS, Gersh BJ, Hodge DO, Schaff HV, Holmes Jr DR. Outcome of alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Circulation. 2008;118:131–9.
66. Nagueh SF, Groves BM, Schwartz L, Smith KM, Wang A, Bach RG, Nielsen C, Leya F, Buergler JM, Rowe SK, Woo A, Maldonado YM, Spencer 3rd WH. Alcohol septal ablation for the treatment of

hypertrophic obstructive cardiomyopathy. A multicenter North American registry. J Am Coll Cardiol. 2011;58:2322–8.
67. Veselka J, Krejci J, Tomasov P, Zemanek D. Long-term survival after alcohol septal ablation for hypertrophic obstructive cardiomyopathy: a comparison with general population. Eur Heart J 2014; Jan 24. [Epub ahead of print].
68. Sorajja P, Binder J, Nishimura RA, Holmes Jr DR, Rihal CS, Gersh BJ, Bresnahan JF, Ommen SR. Predictors of an optimal clinical outcome with alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Catheter Cardiovasc Interv. 2013; 81:E58–67.
69. Agarwal S, Tuzcu EM, Desai MY, Smedira N, Lever HM, Lytle BW, Kapadia SR. Updated meta-analysis of septal alcohol ablation versus myectomy for hypertrophic cardiomyopathy. J Am Coll Cardiol. 2010;55:823–34.
70. Alam M, Dokainish H, Lakkis NM. Hypertrophic obstructive cardiomyopathy-alcohol septal ablation vs. myectomy: a meta-analysis. Eur Heart J. 2009;30:1080–7.
71. Leonardi RA, Kransdorf EP, Simel DL, Wang A. Meta-analyses of septal reduction therapies for obstructive hypertrophic cardiomyopathy: comparative rates of overall mortality and sudden cardiac death after treatment. Circ Cardiovasc Interv. 2010;3:97–104.
72. McLeod CJ, Ommen SR, Ackerman MJ, et al. Surgical septal myectomy decreases the risk for appropriate implantable cardioverter defibrillator discharge in obstructive hypertrophic cardiomyopathy. Eur Heart J. 2007;28:2583–8.
73. Ball W, Ivanov J, Rakowski H, et al. Long-term survival in patients with resting obstructive hypertrophic cardiomyopathy comparison of conser- vative versus invasive treatment. J Am Coll Cardiol. 2011;58:2313–21.
74. Naidu SS. Survival and Pacemaker Risk After Alcohol Septal Ablation: Informing the Choice of Invasive Therapy for Hypertrophic Cardiomyopathy. Can J Cardiol. 2013 Jul 23. doi:pii: S0828-282X(13)00301-2.
75. Fernandes VL, Nagueh SF, Wang W, Roberts R, Spencer 3rd WH. A prospective follow-up of alcohol septal ablation for symptomatic hypertrophic obstructive cardiomyopathy — the Baylor experience (1996–2002). Clin Cardiol. 2005;28(3):124–30.
76. Veselka J, Lawrenz T, Stellbrink C, Zemanek D, Branny M, Januska J, Groch L, Dimitrow P, Krejci J, Dabrowski M, Mizera S, Kuhn H. Low Incidence of Procedure-Related Major Adverse Cardiac Events After Alcohol Septal Ablation for Symptomatic Hypertrophic Obstructive Cardiomyopathy. Can J Cardiol. 2013 Aug 6. pii: S0828-282X(13)00263-8.
77. Maron BJ, Spirito P, Shen WK, Haas TS, Formisano F, Link MS, Epstein AE, Almquist AK, Daubert JP, Lawrenz T, Boriani G, Estes III NAM, Favale S, Piccininno M, Winters SL, Santini M, Betocchi S, Arribas F, Sherrid MV, Buja G, Semsarian C, Bruzzi P. Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy. JAMA. 2007;298: 405–12.
78. Maron BJ, Yacoub M, Dearani JA. Benefits of surgery in obstructive hypertrophic cardiomyopathy: bring septal myectomy back for European patients. Eur Heart J. 2011;32:1055–8.
79. Noseworthy PA, Rosenberg MA, Fifer MA, Palacios IF, Lowry PA, Ruskin JN, Sanborn DM, Picard MH, Vlahakes GJ, Mela T, Das S. Ventricular arrhythmia following alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Am J Cardiol. 2009;104: 128–32.
80. Kovacic JC, Khanna D, Kaplish D, et al. Safety and efficacy of alcohol septal ablation in patients with symptomatic concentric left ventricular hypertrophy and outflow tract obstruction. J Invasive Cardiol. 2010;22:586–91.
81. Naidu SS. Invasive thoughts: honoring two decades of alcohol septal ablation for hypertrophic cardiomyopathy. J Invasive Cardiol. 2013;25:369–70.
82. Gross CM, Schulz-Menger J, Kramer J, Siegel I, Pilz B, Waigand J, Friedrich MG, Uhlich F, Dietz R. Percutaneous transluminal septal artery ablation using polyvinyl alcohol foam particles for septal hypertrophy in patients with hypertrophic obstructive cardiomyopathy: acute and 3-year outcomes. J Endovasc Ther. 2004;11: 705–11.
83. Llamas-Esperon GA, Sandoval-Navarrete S. Percutaneous septal ablation with absorbable gelatin sponge in hypertrophic obstructive cardiomyopathy. Catheter Cardiovasc Interv. 2007;69:231–5.
84. Lafont A, Durand E, Brasselet C, Mousseaux E, Hagege A, Desnos M. Percutaneous transluminal septal coil embolisation as an alternative to alcohol septal ablation for hypertrophic obstructive cardiomyopathy. Heart. 2005;91:92.
85. Durand E, Mousseaux E, Coste P, Pilliere R, Dubourg O, Trinquart L, Chatellier G, Hagege A, Desnos M, Lafont A. Non-surgical septal myocardial reduction by coil embolization for hypertrophic obstructive.
86. Lawrenz T, Kuhn H. Endocardial radiofrequency ablation of septal hypertrophy. A new catheter-based modality of gradient reduction in hypertrophic obstructive cardiomyopathy. Z Kardiol. 2004;93: 493–9.
87. Keane D, Hynes B, King G, Shiels P, Brown A. Feasibility study of percutaneous transvalvular endomyocardial cryoablation for the treatment of hypertrophic obstructive cardiomyopathy. J Invasive Cardiol. 2007;19:247–51.

Surgical Myectomy and Associated Procedures: Techniques and Outcomes

18

Sandhya K. Balaram and Daniel G. Swistel

Abstract

Septal myectomy is currently the gold standard for treatment of symptomatic obstructive hypertrophic cardiomyopathy that is not responsive to medical management. The heterogeneity of this disease process requires a broad knowledge of anatomic and functional abnormalities found in these patients. Specific operative techniques have been developed that have shown excellent short and long term outcomes with rare complications. Concomitant cardiac surgery, if required, may be performed safely along with myectomy.

Keywords

Hypertrophic cardiomyopathy • Septal myectomy • Extended septal myectomy • Intraoperative trans-esophageal echocardiography • Systolic anterior motion • Mitral regurgitation • Mitral valve surgery

Abbreviations

AF	Atrial fibrillation
ASA	Alcohol septal ablation
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
HCM	Hypertrophic cardiomyopathy
ICD	Internal cardiac defibrillator
LV	Left ventricle
LVOTO	Left ventricular outflow tract obstruction
MVR	Mitral valve replacement
NYHA	New York Heart Association
PPM	Pacemaker
RPR	Resection-Plication-Release
SAM	Systolic anterior motion
SCD	Sudden cardiac death

Key Points

- Isolated septal myectomy results in a low operative mortality of <1 % and excellent long term survival when performed at experienced centers. It is the gold standard for relief of symptomatic left ventricular outflow tract obstruction in hypertrophic cardiomyopathy.
- The heterogeneity, complexity, and incidence of obstructive hypertrophic cardiomyopathy (HCM) require a unique procedure that has been most successful when performed in centers with a dedicated HCM program and experienced surgeons.
- Intraoperative transesophageal echocardiography is critical in understanding the pathophysiology of HCM by demonstrating the septal size, the point of mitral-septal contact, and associated mitral valve and papillary muscle abnormalities.
- The benefits of septal myectomy include improvement in quality of life, heart failure symptoms, and long-term survival.
- Survival after myectomy is equal to age and sex-matched non-HCM controls.

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- Complications are seen in <2 % of patients after undergoing septal myectomy. Concomitant surgery such as coronary revascularization, atrial fibrillation ablation procedures, and mitral valve repair, may be done safely with little additional risk.
- As long-term data is collected and analyzed, indications for septal myectomy may continue to evolve.

Introduction

Over the past 50 years, improvements in surgical techniques and expanded understanding of hypertrophic cardiomyopathy (HCM) and its pathophysiology have led to the current era in which septal myectomy has excellent, reproducible results. Based on formal guidelines, those patients with symptomatic obstructive HCM who have failed medical management and demonstrate left ventricular outflow gradients of >50 mmHg should be considered for surgical intervention. Better understanding of septal myectomy in regards to echocardiographic evaluation, operative techniques, and reported outcomes, is critical in treating this heterogeneous and complex disease.

Surgery for HCM

Background and History

The description of an area of muscular hypertrophy causing obstruction to left-ventricular outflow below the aortic valve is commonly credited to Sir Russel Brock and the pathologist, Dr. Donald Teare in Guy's Hospital Reports from 1957 [1, 2]. Although the first to elucidate the nature of the obstruction, they offered no possibility of therapy. In the ensuing years, the complex of cardiac structural abnormalities has been given many names, but is now termed obstructive Hypertrophic Cardiomyopathy (HCM). Descriptions of the malady exist as early as the beginning of the nineteenth century from France and England, and in a report from Germany at the beginning of the twentieth century [3–5].

With the advent of cardio-pulmonary bypass and open-heart surgery, a variety of surgical techniques were promulgated as possible therapies for this disorder. Cleland accomplished the first successful surgery in 1958 [6]. Early procedures were associated with an extremely high mortality risk, most probably associated with problems of myocardial protection, air embolism, and the need for left ventriculotomy. In a study group gathering sponsored by the Ciba Foundation in 1970, debate centered on the therapeutic success and complications of a simple myotomy versus limited myectomy and the role of the mitral valve in obstruction. Well-known surgeons of the time, including John Kirklin, Brian Barratt-Boyes, Douglas Wigle, Hugh Bentall and physician Eugene Braunwald all proposed different approaches to surgical management. These included resection of the right side of the ventricular septum through a limited right ventricular myotomy [7]. Results were mixed and fraught with complications. Dr. Andrew Morrow, working with the group at the National Institute of Health (NIH), subsequently described a trans-aortic approach to a left-ventricular myectomy that significantly relieved the bulk of the obstruction with a reasonable operative risk. His approach, the "Morrow Procedure", was popularly adopted after his presentation of results from 83 patients and their follow-up in 1975 [8].

Table 18.1 Evolution of surgical techniques for treatment of obstructive hypertrophic cardiomyopathy

Year	Surgeon	Procedure
1958	Cleland	Transaortic resection of muscle bar
1960	Morrow	Transaortic septal myectomy
1961	Kirklin	Transaortic/transventricular access
1964	Johnson	Myectomy combined with mitral valve replacement
1970	Cooley	Mitral valve replacement alone
1990	McIntosh	Myectomy combined with vertical plication of the anterior mitral leaflet
1990	Messmer	Extended septal myectomy
2000	Swistel	Septal resection, horizontal plication of mitral valve, and release of lateral attachments

Evolution of Procedure

Since the mid-1980's, given the failure of the Morrow procedure in a number of patients, progress in surgical therapy has been directed at those cases where simple myectomy does not adequately relieve the obstruction to flow. Improvements in operative technique related directly to better understanding of the disease process, first by pathologic studies and later through the use of echocardiography (Table 18.1). Recognizing the role of the anterior leaflet of the mitral valve in obstruction, Cooley first proposed mitral valve replacement (MVR) for cases with severe mitral insufficiency in 1976 [9]. This was particularly valuable in cases where the septum was relatively thin and the morphology of the anterior leaflet was especially long or broad [9]. MVR was used for treatment of HCM and data was published supporting this treatment [10, 11]. However, the associated risks of mitral valve replacement in a relatively young group of patients was not preferred therapy, and McIntosh and Maron subsequently promoted a vertical mitral valve plication to stiffen the leaflet and limit its excursion into the outflow tract [12]. The abnormal morphology of the mitral valve in HCM patients was

described in detail by Klues et al. and added significantly to the expanding knowledge of this disease process [13, 14].

In 1994, Messmer and his group described a more extensive myectomy, which included thinning or remodeling of the papillary muscle and division of abnormal lateral attachments to allow the anterior leaflet to fall into a more posterior position within the ventricular chamber [15, 16]. This "extended myectomy" is generally accepted and performed at all major HCM surgical centers. However, with the advent of higher resolution echocardiography showing a wider range of morphologic variations that promote obstruction, as well as the development of HCM centers of excellence where these variations have been better understood, it has become recognized that therapy often requires individualization.

As a result, other groups have offered alternative variations to surgical management to accommodate the various complex phenotypes that represent HCM [17–23]. In some circumstances, the hypertrophied muscle may be localized and dominant: basal, mid-ventricular or apical. In others, a more diffuse hypertrophy may be present. The anterior leaflet of the mitral valve may be grossly elongated and the septum minimally thickened, limiting the amount of resection that can be accomplished. Many of the variations of technique involve the mitral valve and highlight its prominent role in this disease process. These techniques include plication, retention plasty, leaflet extension, and edge-to-edge repairs [19–21, 23]. Additional morphologic variations have included abnormal or accessory papillary muscles and subvalvular structures. As demonstrated by the Mayo Clinic group, these papillary muscles are often redundant and must be either resected or thinned to obliterate the outflow tract gradients [22]. More recently, the Cleveland Clinic group described suturing the antero-lateral papillary muscle posteriorly to either the posterior papillary muscle or the myocardial wall [24]. This serves to draw the anterior mitral leaflet out of the way of the dominant direction of flow towards the outflow tract and minimize the opportunity for systolic anterior motion (SAM) [24].

Analysis of the pathophysiology of the anterior leaflet of the mitral valve has led our group to conclude that a simple, reproducibly excellent result can be obtained by shortening the leaflet in an antero-posterior dimension with a horizontal plication [25–28]. As opposed to a vertical plication, this preserves the coaptation zone of both leaflets and leaves their relationship intact. We termed this the *RPR* procedure: Resection/Plication/Release: *r*esection of the hypertrophied muscle, *p*lication of the anterior leaflet of the mitral valve, and *r*elease of lateral attachments and/or the resection of the subvalvular mechanism to allow a more posterior displacement of the valve and control of any accessory structures contributing to obstruction [25]. By placing a row of plication sutures high on the anterior curtain area of the valve, the leaflet is stiffened in exactly the correct dimension to limit the possibility of bowing out into the outflow tract and meeting the contact point on the septum.

Table 18.2 Morphologic variants of hypertrophic cardiomyopathy determined by preoperative transesophageal echocardiography

Site	Characteristics
Septum	Width measurement
	Location of hypertrophy: basal, midventricular, or apical
	Point of mitral-septal contact
Mitral valve	Degree of mitral regurgitation
	Length of anterior mitral leaflet
	Abnormal morphology/intrinsic disease of mitral leaflets
Papillary muscles	Location and size
	Presence of lateral attachments
Subvalvular apparatus	Thickened chords contributing to obstruction

As surgical experience has grown, the many variations of structure and pathophysiology that cause obstruction have become better appreciated. A variety of surgical strategies is available and must be tailored in each case to match the particular morphology causing obstruction. In fact, variations in morphology are so common that in 1988 McIntosh and Maron noted "it is relatively uncommon to encounter a patient with obstructive HCM at operation in whom septal hypertrophy is both particularly marked and homogeneously distributed so that the standard myotomy-myectomy can be undertaken with no preoperative deliberation regarding the pattern and magnitude of septal thickness" [29].

Operative Technique

A systematic technique is necessary to analyze the pathophysiology of obstruction in a particular patient and tailor a procedure using a variety of possible techniques to limit systolic anterior motion of the mitral leaflet (SAM), relieve obstruction, and restore mitral valve competency. Key elements of the procedure are partially determined before incision using echocardiography (Table 18.2). Echocardiographic findings are reviewed pre-operatively to clarify the thickness of the septum and characterize its morphology and location. The length of the anterior leaflet is measured and the point of mitral-septal contact is determined. It is important to note whether the mid portion of the leaflet contacts the septum or whether the leading edge is primarily involved. Although at times somewhat harder to identify, accessory papillary structures may be seen. In the operating room, all patients have a 2D/3D transesophageal echo (TEE) transducer placed and the analysis is repeated under anesthesia. Not all patients have a resting gradient, although general anesthesia vasodilates the patient and may provoke a gradient in itself.

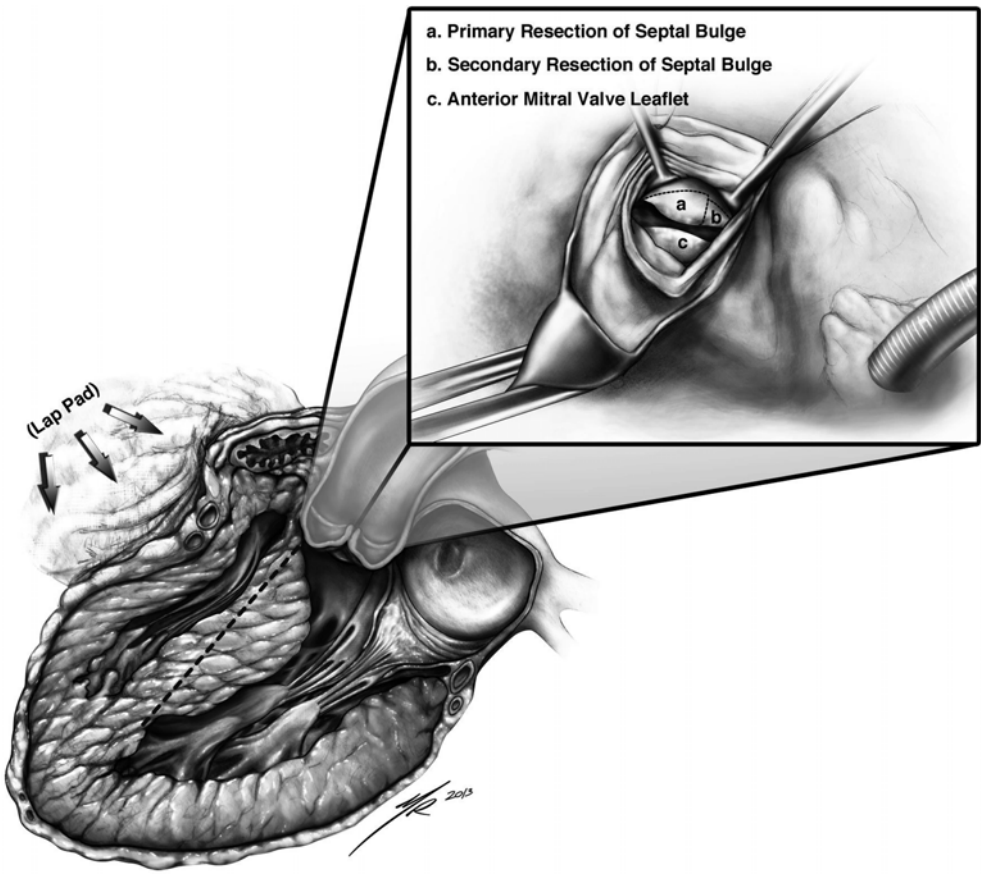

Fig. 18.1 Surgeon's view of the heart as visualized through a transverse aortotomy. Myectomy is performed to include sections "a" and "b" and begins below the annulus of the aortic valve. An icy laparotomy pad placed between the right ventricle and chest wall may assist in bringing the septum further into view. The incision is begun 3–5 mm below the aortic annulus, depending on the site of mitral-septal contact as determined by echocardiography

Occasionally, inotropic agents are necessary to provoke obstruction.

A full or partial sternotomy incision is carried out to perform the procedure. Arterial cannulation is performed through the upper ascending aorta, a single dual-staged atrial venous cannulation is utilized, and the left-ventricle is vented through the right superior pulmonary vein. Antegrade and retrograde cardioplegia are administered. Once the heart is arrested with cardioplegia, a generous transverse aortotomy is performed. Leaflet retractors are placed to protect the aortic valve leaflets and the left ventricle is examined. Thickened, fibrotic scar tissue is almost always present at the area of mitral-septal contact. It is often helpful to place an icy laparotomy pad over the left ventricle to provide posterior pressure on the anterior septum (Fig. 18.1). A three-pronged hook is placed between the right coronary ostia and the commissure of the left and right aortic leaflets and engaged into the septal muscle beyond the area of mitral-septal contact as calculated from the preoperative transesopheageal echo. The myectomy is performed with a long-handled, 45°, #15 knife blade (Fig. 18.2). The incision is started at least 3–5 mm below the aortic annulus. This area is not involved in the pathogenesis of SAM, preserves the AV node to limit the incidence of post-operative complete heart block, and lessens the possibility of an iatrogenic ventricular septal defect. Depending on the predetermined thickness of the septum, anywhere from 1.0 to 1.5 cm of muscle thickness is resected. Once the first few millimeters of muscle are cut, the hook is released and the myectomy segment is grasped with a very long forceps and the resection is continued. The medial border of the resection is usually just lateral to the right coronary ostia, and extends laterally almost to the lateral commissure of the mitral valve. This yields a segment about 3 or 4 cm in width. In typical cases of basal hypertrophy, the resection extends into the ventricle just beyond the mid-portion of the anterolateral papillary muscle. The segment is then an approximate square: 3.0–4.0 cm on each side and 1.0–1.5 cm thick. This is the so-called "extended myectomy". In cases where the obstruction is more mid-ventricular, additional muscle can be removed up to the junction of the papillary muscles and medially deeper within the chamber avoiding the area where the conduction system is known to reside. In general, the best portion of muscle is resected in the first attempt. Thereafter, the muscle tends to shred and it is more difficult to get a purchase on additional segments. Irregular areas are smoothed out with an angled pituitary rongeur.

With sufficient experience in this procedure, one may extend this resection to the apex of the ventricle for patients with apical obstruction without a formal apical myotomy. An

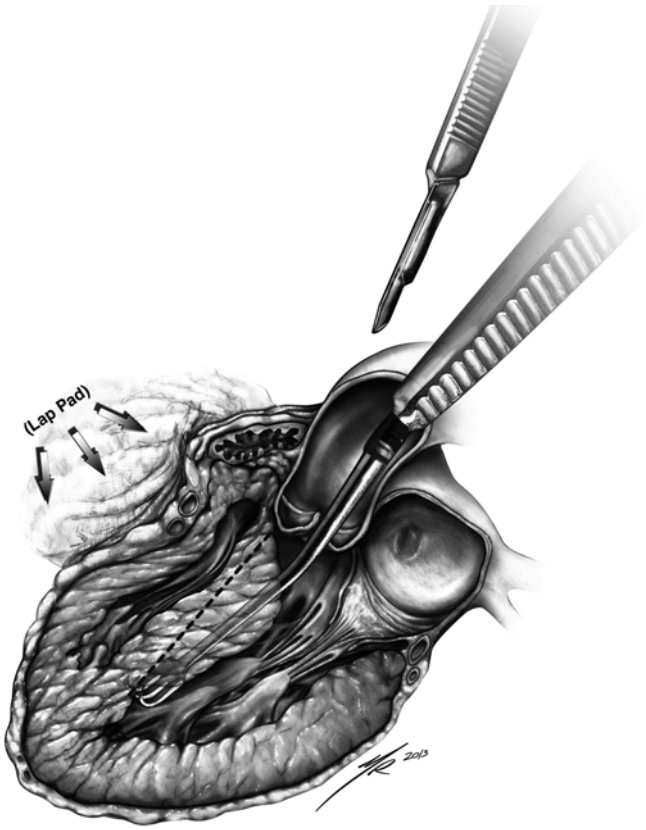

Fig. 18.2 Characteristic outflow tract morphology with basal septal hypertrophy. Insertion of the hook allows the surgeon to stabilize the septum while using the knife to excise a wide portion of muscle that begins just past the bundle and continues across to the far side, often extending to both trigones. Depending on the predetermined thickness of the septum, anywhere from 1.0 to 1.5 cm. of muscle thickness is resected

apical myotomy is most useful when the patient already suffers from an apical aneurysm. In apical obstruction without aneurysmal formation, it is very difficult to identify the papillary muscles and differentiate them from hypertrophied resectable muscle. Treatment for apical HCM and midventricular obstruction has recently been described via a transapical approach [30–33]. These procedures are performed in very few specialized centers with limited data. In this technique, both the mitral valve apparatus and the papillary muscles must be carefully avoided with the opening and enlarging of the left ventricular (LV) cavity [30–33].

Once the myectomy is complete, it is much simpler to visualize the interior of the left-ventricle and examine the mitral subvalvular structures and identify any lateral attachments of the antero-lateral papillary muscle and the LV free wall. Often, these lateral attachments are already resected with the myectomy segment, but additional thinning of the junction of the antero-lateral papillary muscle with the LV free wall can be easily accomplished with a medium sized pituitary rongeur (Fig. 18.3). This muscle will then fall more posteriorly into the LV chamber and draw the anterior leaflet of the mitral valve with it. Overly aggressive resection here, however, can lead to antero-apical free wall rupture.

Attention is then directed to the anterior leaflet of the mitral valve itself. If there are abnormal papillary muscles attached directly, careful analysis of other underlying chords is necessary to decide whether the muscle here can be completely resected or whether only some degree of thinning can be accomplished. If there are no other supporting structures, resection may lead to a flail segment and post-operative central insufficiency. In many instances where accessory attachments exist, it is possible to resect a portion of the muscle or chords involved in obstruction and leave a more apical portion intact that retains additional attachments to the leading edge of the leaflet. The anatomy here can be extremely variable and it is difficult to generalize any approach to systematic resection.

It is relatively simple, however, to deal with an extremely long anterior leaflet. Pre-operative echo analysis yields information on the total length of the anterior leaflet and directs the amount of plication, which can be from as little as 2 or 3 mm to as much as five or six in cases where the total leaflet length may exceed 4.0 cm [25]. From the left side of the patient, the surgeon can easily place four or five vertical mattress sutures of 5.0 prolene in a horizontal line to shorten the leaflet from anywhere between 3 and 6 mm depending on the previously calculated overall length of the leaflet. This leaves the coaptation zone of the leaflets intact and limits the capacity for mitral-septal contact by stiffening and shortening the leaflet to minimize bowing (Fig. 18.4). Redundancy in the length of the anterior mitral leaflet is usually found in those greater than 25 mm in length and a shortening plication should be considered [28].

Next, the LV cavity is copiously irrigated and suctioned to remove any residual debris and examined for any loose sections of partially resected muscle. The heart is allowed to fill passively as the aortotomy is closed and standard deairing maneuvers are performed before the cross-clamp is removed. After separation from heart-lung bypass, the initial TEE view examines for adequacy of the procedure. Subsequently, an inotropic agent, usually at least 10 μg/kg of dobutamine, is administered to stimulate the myocardium. The outflow tract area is examined for any mitral-septal contact, color flow turbulence, and residual gradient. A gradient above 20 mmHg under provocation, turbulent flow, or more than 1+ mitral insufficiency generally requires a reassessment of the procedure. A decision is required whether additional muscle should be resected, the condition could be rectified with post-operative β-blockade and/or disopyramide, or further mitral valve repair is necessary. Mitral valve replacement is rarely necessary unless there are severe valvular pathology or leaflet changes associated with chronic rheumatic disease [28, 34, 35].

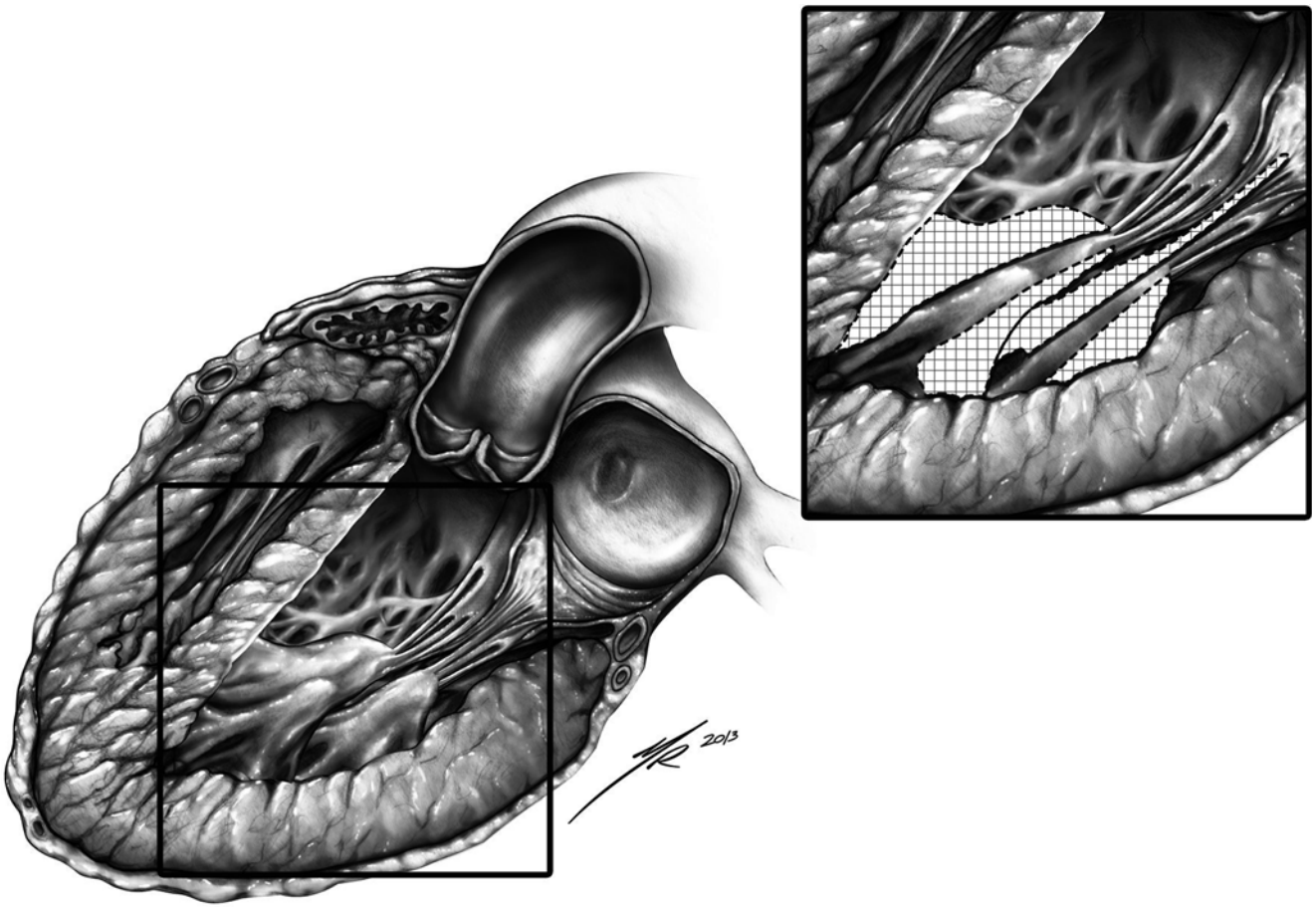

Fig. 18.3 Diagram showing the operative approach for resection and thinning of the papillary muscles as well as release of abnormal lateral attachments between papillary muscles and ventricular free wall that allow the anterior leaflet to fall more posteriorly

Postoperative Management

Postoperative critical care management after septal myectomy is similar to other open cardiac surgical procedures. The first step begins with transfer of the patient to the intensive care unit during which a systems-based evaluation is performed assessing respiratory status and hemodynamics. Next, standard postoperative laboratory studies, chest x-ray, and electrocardiogram are obtained. Many patients have a new left bundle branch block and some patients are temporarily dependent on epicardial pacing from the operating room.

The cardiovascular system is closely monitored, particularly in terms of intravascular fluid status. Patients initially often have a period of further rewarming that results in vasodilation and may require additional colloid or crystalloid to maintain filling. Optimization of preload is obtained using information from pulmonary artery monitoring and continuous mixed venous saturations. Occasionally, alpha-adrenergic agents are used. The use of inotropes is discouraged in these patients postoperatively and is rarely necessary given normal left ventricular function.

Patients are monitored for coagulopathy and postoperative bleeding. Rarely, blood transfusion is necessary, and usually required only in older patients with multiple concomitant procedures and/or co-morbidities. Atrial fibrillation may occur and is treated with amiodarone, β-blockade, and cardioversion if necessary. These patients are typically extubated within 6 h of surgery and remain in the hospital an average of 5 days. Increased length of stay correlates directly with age, co-morbidities, and associated procedures. Preoperative medications including β-blockers, calcium–channel blockers, and/or disopyramide, are started postoperatively. Standard nursing, physical therapy, and respiratory therapy continue during the recovery period. During the acute hospitalization, repeat echocardiography is done only for symptoms or clinical concerns.

Once patients are discharged from the hospital, they follow up with both their surgeon and cardiologist. All patients are followed within a formal hypertrophic cardiomyopathy program and receive echocardiograms every 3–6 months initially and yearly thereafter.

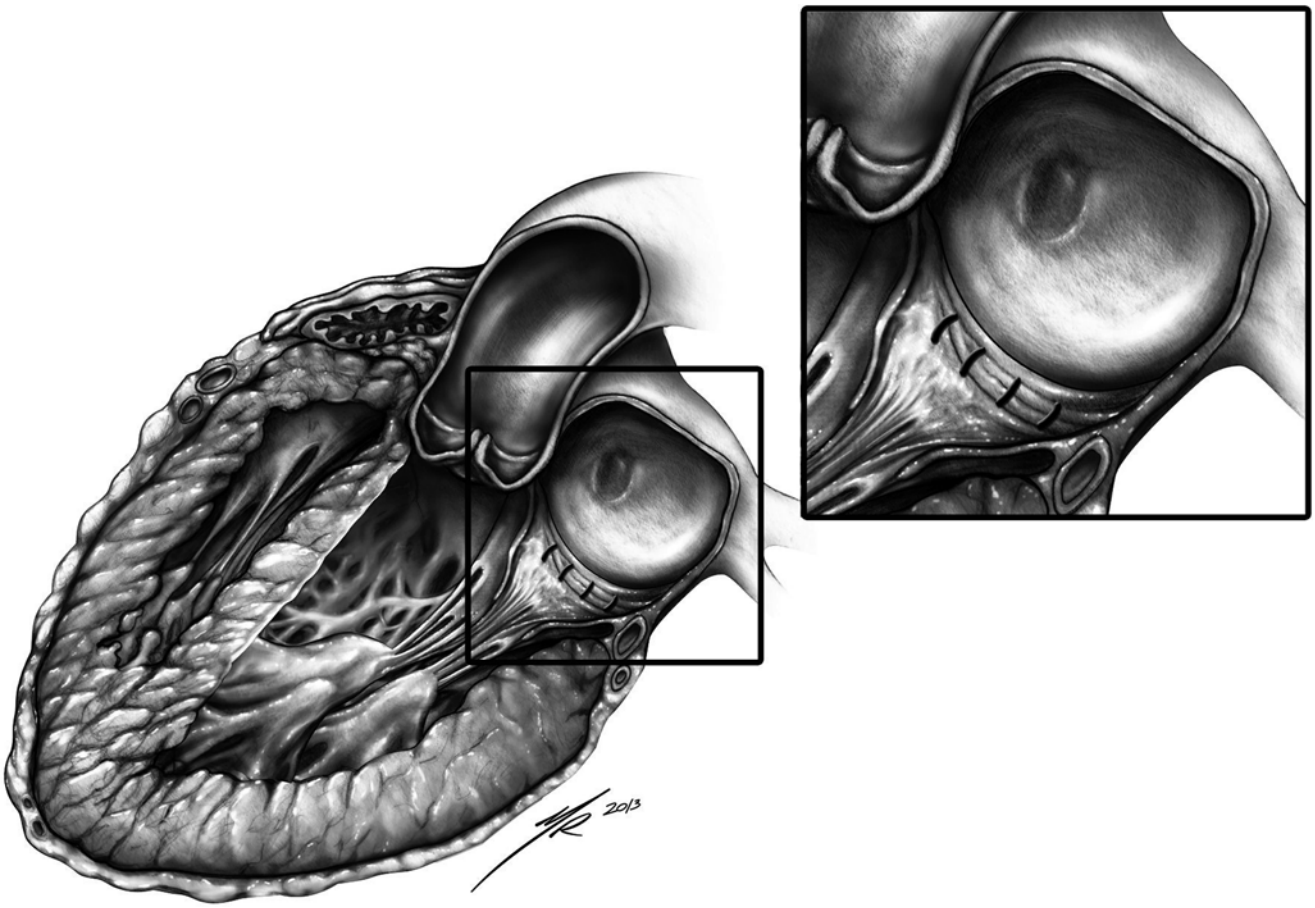

Fig. 18.4 Diagram of the horizontal mitral valve plication technique: placing sutures on the aortic side of the anterior mitral leaflet in order to shorten and stiffen the leaflet, thereby preventing systolic anterior motion in the setting of an elongated, redundant anterior mitral leaflet

Outcomes

Improvements in technique and better understanding of HCM pathophysiology have resulted in surgical treatments that have become refined over the past 50 years. In 2003, a specialized consensus panel published guidelines formally recommending septal myectomy as the gold standard therapy for those patients with symptomatic obstructive HCM refractory to medical management [36]. This was restudied more recently in 2011 by the ACCF/AHA Consensus panel report, which further reinforced the importance of surgical therapy [37].

It is important to remember that the majority of patients with HCM are treated medically, which may include the use of β-blockers, verapamil, or disopyramide [38–41]. Despite this treatment, approximately 5 % of patients with obstructive HCM will continue to have symptoms, which may include chest pain, dyspnea, syncope, or exercise intolerance. Patients with obstructive HCM and persistent symptoms despite medical management with a resting or provoked gradient of >50 mmHg should be considered for septal myectomy [36, 37].

Multiple large retrospective studies have reported long-term data and demonstrated excellent outcomes after septal myectomy [28, 42–51] (Table 18.3). Yet overly cautious concerns about surgical myectomy such as high surgical risk, the potential for ventricular septal defect (VSD), and the need for postoperative pacemaker implantation, still exist [52]. Regional referral patterns are highly influenced by knowledge and biases regarding therapy. The absence of formal randomized trials for surgical myectomy due to practical and ethical issues complicates definitive answers regarding survival benefits [53].

Operative Mortality

Operative mortality and the risk of serious complications influences referral for treatment and are required knowledge when counseling patients. During the early years of septal myectomy, operative mortality of 2.9–6.0 % was reported [42–46]. As techniques have advanced, the risk of surgery in the current era has decreased significantly. This marked

Table 18.3 Mortality and long-term survival after septal myectomy

Year	Series	Patients (n)	Operative mortality (%)	5-year survival (%)	10-year survival (%)
1993	Schulte et al. [43]	364	2.9	92	88
1995	Heric et al. [44]	178	6	86	70
1996	Robbins and Stinson [45]	158	3.2	5.4	71.5
1998	Schoenbeck et al. [46]	110	3.6	93	80
2005	Ommen et al. [47]	289	0.8	96	83
2005	Woo et al. [48]	388	1.5	95	83
2007	Dearani et al. [49]	1,134	0.8	N/A	N/A
2012	Balaram et al. [28]	132	0.0	99	92
2013	Desai et al. [51]	699	0.0	N/A	N/A

Table 18.4 Risk factors for septal myectomy [48]

Age >50
Female gender
Preoperative atrial fibrillation
Left atrial enlargement >46 mm
Concomitant coronary artery bypass grafting

improvement is a result of many factors: better understanding of the disease, focused use of intraoperative echocardiographic guidance, improved myocardial protection, and advances in postoperative care. Recent data from experienced centers, as summarized in Table 18.3, demonstrates an overall mortality for isolated myectomy of 0.0–0.8 % [28, 32, 47–51].

Significant mortality predictors reported by the Toronto group include: age >50, female gender, preoperative atrial fibrillation, concomitant coronary bypass grafting (CABG), and preoperative left atrial size of 46 mm or greater [48] (Table 18.4). Female gender has specific correlations in HCM surgery including under-representation, diagnosis at an older age, and delays in diagnosis that may make the risk greater for women [54]. After surgery, they have lower functioning status and a higher risk of cardiovascular events and death [48]. It has been suggested that women may have a more aggressive form of the disease or be more prone to disease progression [48, 54, 55]. A more recent study of 699 patients at the Cleveland Clinic looked specifically at predictors of long term survival and found that age >50 and postoperative atrial fibrillation were independent predictors of lower long-term survival by multivariate analysis [51].

Conflicting literature exists regarding the addition of concomitant surgery that initially was found to increase the mortality of myectomy by up to threefold [46]. Although these additional procedures have been identified as univariate risk factors for surgery, they do not portend a significantly shorter survival than those with myectomy alone and are not considered a significant risk factor after multivariate analysis [51, 56]. Recent studies have shown no significant difference between short and long-term survival in the two cohorts (Fig. 18.5). While recent mortality for isolated myectomy ranges from 0.0 to 1.5 % [28, 47–51], in some studies the addition of concomitant procedures can increase this risk to 2.1–3.4 % [48, 49]. In the current era, many patients are older with complex pathology, and it is accepted that there will be a slight difference in risk between isolated myectomy and the addition of concomitant procedures.

Short and Long Term Outcomes

Septal myectomy results in both immediate and long-term gradient reduction in obstructive HCM. Immediately after myectomy, postoperative gradients of 0–10 mmHg are expected in the operating room and remain low over time [36]. At many centers, resting and dobutamine-stimulation gradients are checked intraoperatively to assess for the presence of hemodynamic significance. Patients may require additional myectomy for significant gradients with stimulation, persistent systolic anterior motion (SAM) and/or mitral regurgitation (MR). Gradients can be expected to fall in the first 3 months after myectomy and may continue to decline [50]. Long-term follow up confirms gradients of <30 mmHg in up to 98 % of patients [28, 48–51].

Improvement in heart failure symptoms post-myectomy is of critical importance. Left ventricular outflow tract obstruction (LVOTO) has been shown to be a strong predictor of heart failure progression and death, and an independent risk factor for HCM-related mortality [57, 58]. Surgically managed patients undergo immediate relief of obstruction and show a reversal of heart failure progression and significantly better HCM-related survival [47] including those having no or mild symptoms [57].

From a physiologic perspective, the relief of obstruction results in a clear decrease in wall stress, left ventricular end systolic and diastolic pressures, and ischemia [18, 36, 47, 48, 59–61]. After myectomy, improvements of left ventricular end-systolic and end-diastolic pressures occur in >90 % of patients [9]. A decrease in the risk of atrial fibrillation and in the size of left atrium has also been reported, and is likely secondary to the improvement in chronic

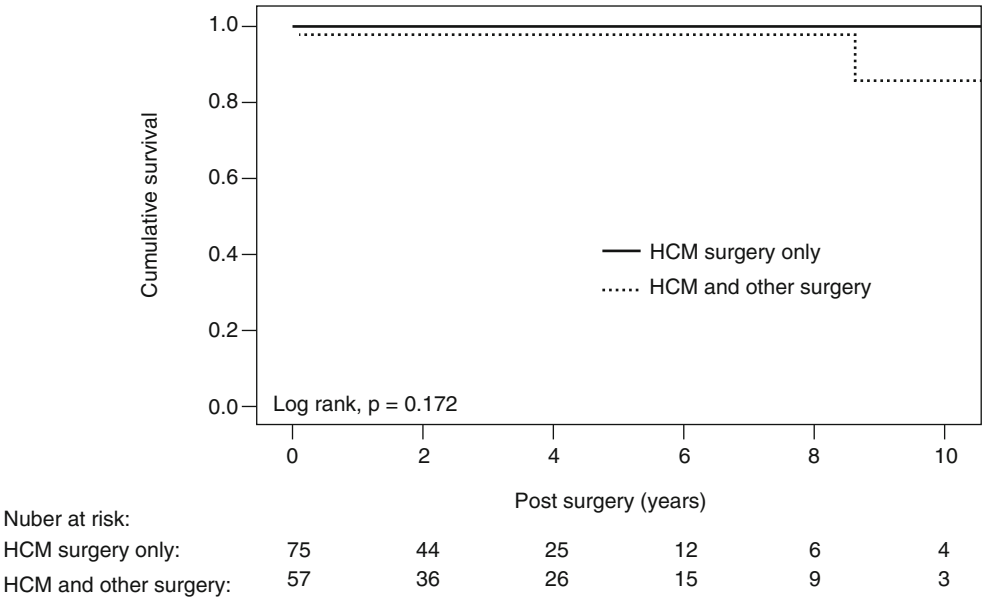

Fig. 18.5 Survival free from all-cause mortality for patients who underwent operations for hypertrophic cardiomyopathy (HCM) only (n = 75) and those who underwent operations for HCM and a concomitant cardiac procedure (n = 57). No statistically significant difference is seen for short and long-term survival (Permission obtained from Elsevier Ltd. Balaram et al. [28])

mitral regurgitation and diastolic function after relief of obstruction [48, 59, 61, 62].

Mitral regurgitation, as associated with obstructive HCM and SAM, improves after septal myectomy. The change from the Morrow procedure to Messmer's extended myectomy reduced the appearance of residual mitral regurgitation first described in the literature [63]. Some have argued that extended myectomy alone is adequate for the resolution of SAM [64]. However, the heterogeneity of HCM presents multiple variables in terms of mitral valve pathology. Mitral abnormalities may be secondary to Venturi forces with obstruction alone [18, 65, 66] or be related to mitral leaflets with or without papillary muscle abnormalities [13, 14, 67]. It is imperative to understand that both intrinsic and functional mitral valve abnormalities may be present and contributing to obstruction. The addition of required mitral valve surgery has been shown in multiple studies with excellent results [12, 28, 34, 51].

Marked clinical improvements of heart failure symptoms are seen with relief of obstruction that correlate with physiologic changes. After myectomy, patients report improvements in quality of life in all large series [28, 46–51]. More than 90 % of patients will improve at least two functional classes after surgery [32]. In multiple studies, advanced NYHA classes comprise <10 % of patients in the post-myectomy population [32, 47, 51].

Prognosis and Survival Benefit

The variability of HCM in terms of genetic penetration and clinical presentation can complicate the issue of prognosis. In early publications, the referral bias of symptomatic patients relegated to experienced tertiary care centers translated into a reported annual HCM-related mortality rate as high as 3–5 % [68, 69]. With time, variability in clinical presentation has made clear that up to two-thirds of individuals with HCM have either minimal or no disability [41]. With these cohorts included, the annual mortality rate of HCM is now estimated to be approximately 1 %, similar to that of the general adult population [38, 70, 71]. Without prospective randomized trials, the question of whether myectomy improves long term prognosis has been referred to large retrospective reviews.

What is known is that significant obstruction affects both morbidity and mortality due to the supply-demand mismatch that occurs in the face of increased ventricular wall tension, hypertrophied myocardium, and myocardial ischemia [58, 72, 73]. High gradients decrease left ventricular ejection velocity and flow in obstructive disease [65, 74]. A resting LVOT gradient >30 mmHg, in particular, results in a fourfold higher risk of heart failure, stroke, or death [58].

Septal myectomy, with relief of obstruction, appears now to be an independent predictor of survival. Multiple observational studies have now shown that surgical relief of obstruction improves long term survival [47, 49, 51, 75] Data shows that those patients who undergo myectomy have a significantly lower risk for all cause mortality and HCM-related death compared to those patients with obstruction who did not undergo surgery [58] (Fig. 18.6). Follow up data up to 15 years after surgery shows excellent survival that has been shown to be age and gender-matched to be equivalent to the general population without HCM [47].

Data also suggests a decrease in the incidence of sudden cardiac death after myectomy although the risk is not completely abolished [47]. The need for placement of an ICD

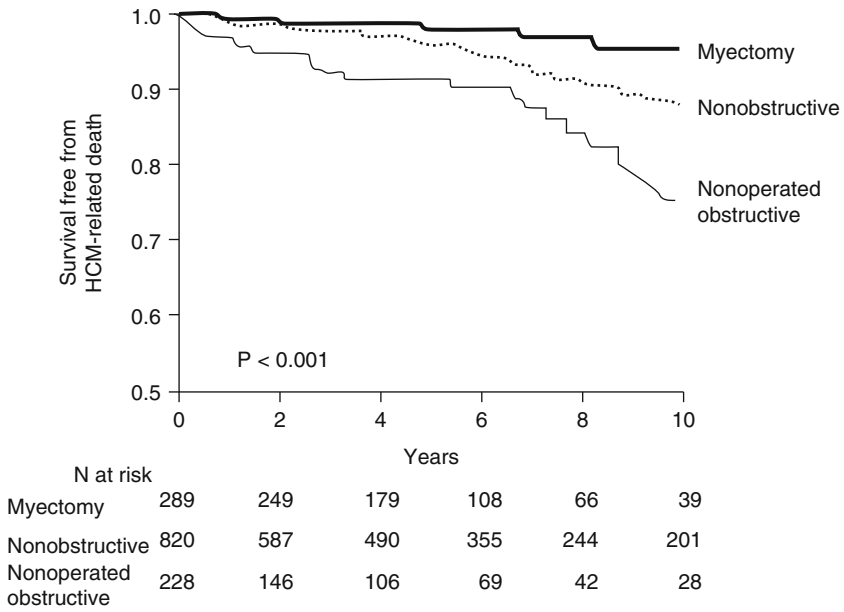

Fig. 18.6 Survival free from hypertrophic cardiomyopathy-related death among patients in three hypertrophic cardiomyopathy (HCM) subgroups: surgical myectomy (n = 289), nonoperated with obstruction (n = 228), and nonobstructive (n = 820). Overall log-rank, p = 0.001; myectomy versus nonoperated obstructive hypertrophic cardiomyopathy, p = 0.001; myectomy versus nonobstructive hypertrophic cardiomyopathy, p = 0.01 (Permission obtained from Elsevier Ltd. Ommen et al. [47])

needs to be considered separately from the need for myectomy, and based on accepted high risk markers of SCD such as the individual family history, previous arrhythmias, and the presence of massive LVH [72, 76]. Myectomy has been shown to be particularly beneficial for patients of younger age who do not have significant comorbidities that could affect their survival, and who tend to have more massive hypertrophy extending to the mid-ventricle [47]. Referral, patient selection, and bias can make these data hard to interpret, particularly when comparing to nonsurgically treated patients who have co morbidities that may contribute to a worse prognosis regardless of treatment. One study did demonstrate the incidence of appropriate ICD firing occurred at a rate of only 0.24 % per year after myectomy as opposed to 4.5 % per year in a non-surgical group (p = 0.004) [77]. This strong presumptive evidence is encouraging but must be tempered with the knowledge that HCM is a disease of the myocardium itself and relief of obstruction alone may not change the underlying substrate and risk for sudden death.

Complications

The morbidity of septal myectomy has, along with mortality, decreased over recent years. Overall, significant complications can be expected in <2 % of all patients undergoing septal myectomy [32]. A common complication is postoperative atrial fibrillation with an incidence of up to 30 %, similar to other cardiac surgeries [28, 48, 50]. Myectomy or postoperative edema that occurs near the location of the conduction tissue within the septum may result in heart block requiring permanent transvenous pacing. The septal area of concern is at the base of the ventricular septum to the right of the nadir of the right coronary cusp. The requirement for a postoperative pacemaker ranges from 1 to 7 % and is most common in patients with preexisting conduction abnormalities such as complete right bundle branch block [28, 32, 47–50].

A potentially devastating complication of myectomy is the creation of a postoperative ventricular septal defect (VSD). The area of critical concern is the lateral septum inferior to the right coronary cusp and close to the annulus of the aortic valve. Injury may occur if too much septum is removed close to the annulus of the aortic valve; it may be more common in those patients with a relatively thin septum (<2.0 cm). The reported incidence of VSD ranges from 0.7 to 2.0 %. This has been treated with patch repair of the septum with good results [28, 48, 56].

Other complications include cerebrovascular accidents (0.6–1.9 %) that are typically the result of embolic events [50, 51]. Pericardial effusion or late pericardial tamponade can occur in the postoperative period. This may be seen particularly in those patients who require anticoagulation such as for chronic atrial fibrillation or concomitant MAZE procedures (1.0–2.3 %) [28, 50].

Rarely, patients may present with recurrent LVOT obstruction after myectomy. The incidence of this based on data from large centers is approximately 2.0–3.4 % [50, 51, 78]. The most common mechanisms for recurrent symptoms are incomplete myectomy, mid-ventricular obstruction, or anomalous mitral valve anatomy [78]. Re-growth of myocardium, particularly in the young, is also a possibility.

The specific circumstance of septal myectomy that occurs after unsuccessful alcohol septal ablation (ASA) has been associated with higher complication rates including operative mortality (13 %), postoperative arrhythmias, and postopera-

tive PPM/ICD implantation (36 %) [79]. However, this group has also demonstrated good relief of symptoms and gradient reduction after myectomy and may benefit greatly from surgical intervention. Although this data is from a small series, it is important to note that these patients are unique and worthy of increased vigilance in the postoperative period.

Concomitant Surgery

CABG

Among concomitant surgical procedures, coronary artery bypass grafting (CABG) surgery is most commonly required in these patients. Coronary revascularization is required in 10–15 % of patients undergoing septal myectomy [28, 47–51]. As older patients are now referred for surgery, the need for CABG may increase in the future. HCM patients with coronary artery disease have other sources of myocardial ischemia added to the supply and demand from increased wall stress that may adversely affect outcomes. As a result, concomitant CABG has been found to be a risk factor for mortality [48].

The Cleveland Clinic group showed that obstructive CAD and concomitant surgery are both risk factors by univariate analysis but have not been shown to increase risk for myectomy by multivariate statistics [51]. Minami et al. studied concomitant procedures compared to isolated myectomy and found a slight increase in early mortality that was not statistically significant (2.0 % vs. 1.3 %) [56]. This was accompanied by divergent Kaplan Meier curves for long term survival that also did not reach statistical significance (80 % vs. 87 %) [56]. Overall, good long term results can be expected with septal myectomy in terms of gradient reduction, clinical improvement, and long term results, even if concomitant CABG is performed.

Arrhythmia Surgery

The association between obstructive HCM and atrial fibrillation is well-described [3, 80–84] Increases in left ventricular end-diastolic pressures in the setting of diastolic dysfunction result in increased left atrial size and places patients with HCM at risk of atrial fibrillation. Chronic mitral regurgitation, systolic motion, and disease severity also play a role. Surgical myectomy alone has not definitively been shown to decrease atrial fibrillation and left atrial size [36]. Most experienced centers therefore add concomitant arrhythmia surgery to myectomy for patients with preoperative atrial fibrillation. Although the lesion set for HCM patients in particular is not well described, many groups perform standard pulmonary vein isolation with radiofrequency ablation while others use the biatrial Cox-Maze II or IV [32, 85]. Left atrial appendage ligation is typically always performed with intraoperative ablation procedures. These procedures can be performed with no significant increase in operative risk [85].

With myectomy alone, the Toronto group showed that nearly half [46 %] of patients who were in preoperative AF remained in normal sinus rhythm (NSR) in the postoperative period, with age and left atrial size playing no significant role in these patients. Of those patients who were in NSR preoperatively, up to 21 % developed late AF [48]. After myectomy, patients who remained in sinus rhythm showed a decrease in left atrial diameter versus those that developed new postoperative AF who had no significant change in LA size [48, 62]. Although atrial fibrillation may present several years after surgery, it may perhaps be considered as one of the contributing indications for myectomy in the future, especially when paroxysmal atrial fibrillation may result in recurrent clinical decompensations of heart failure in an otherwise stable patient.

Mitral Valve Surgery

As previously stated, mitral valve abnormalities and hypertrophic cardiomyopathy have a strong correlation [13, 14, 18, 67, 86]. Mitral valve repair or replacement may be required along with septal myectomy. Historically, MVR was considered an alternative treatment to myectomy. Mitral valve repair is currently much preferred to avoid problems of chronic anticoagulation such as embolization or bleeding, increased morbidity, and the potential need for reoperation in young patients. Anterior mitral leaflet plication techniques have been used with good success but intrinsic mitral valve disease may require more complex repairs such as chordal transposition, synthetic chord placement, annuloplasty rings, or other techniques [28, 32, 34, 35]. Intrinsic calcified disease of the mitral valve, such as rheumatic disease, is the most common reason for mitral valve replacement [6, 34]. Other indications include previous attempted myectomy, congenital mitral valve abnormalities, and septal measurement of less than 2 cm [34, 51]. A recent study found that up to 23 % of patients may require dedicated mitral valve surgery at the time of septal resection [51]. The addition of separate mitral valve surgery as a concomitant procedure does increase the risk of surgery to approximately 4.6 % [34].

Future Directions

The predominant goals for HCM surgery over the next several years are to continue to gain understanding and spread knowledge regarding the complex genetics and pathophysiology involved in this disease process. It is important that the outcomes in both low and high volume centers remain good, and that more surgeons are educated on this specialized technique in order to increase patient access to care. Data regarding late survival and the risk of sudden death after surgery

will continue to be evaluated and weighed against data from less invasive treatments. Evaluation of information from large multicenter databases may expand indications for surgery to those who are asymptomatic with obstructive gradients or others with complications such as atrial fibrillation. Technical advances for difficult problems such as midventricular and apical obstruction will continue to evolve.

Clinical Pearls

- Surgical strategies must be uniquely tailored to match the particular morphology causing obstruction.
- Although extended septal myectomy may be adequate in many patients for relief of mitral regurgitation, intrinsic abnormalities of the mitral valve must be addressed at the time of initial surgery.
- The use of dobutamine in the operating room to stimulate gradients is helpful to determine adequacy of septal resection.
- Mitral valve replacement should be considered mainly for severe primary mitral valve pathology such as rheumatic disease that is not amenable to repair.
- Septal thickness of <1.8 cm needs to be approached carefully with a complete evaluation and precise plans for resection, so as to minimize the risk of ventricular septal defect. Mitral valve plication may be particularly beneficial for these patients.
- A transapical approach may be considered for the difficult problem of midventricular or apical obstruction
- The need for placement of an ICD in the postoperative period should be individualized based on patient risk.

References

1. Brock R. Functional obstruction of the left ventricle (acquired aortic subvalvular stenosis). Guys Hosp Rep. 1957;106:221–38.
2. Teare D. Asymmetrical hypertrophy of the heart in young adults. Br Heart J. 1958;20:1–8.
3. Bertin RJ. Hypertrophy of the left ventricle, with contraction of its cavity. Traite des Maladies du Coeur et des Gros Vaisseaux. Paris: J.B. Baillière; 1839.
4. Schmincke A. Narrowing of left ventricular outflow (Ueber linkseitige muskulose Conus-stenosen). Dtsch Med Wochenschr. 1907;33: 2082–3.
5. Chevers N. Observations on the diseases of the orifice and valves of the aorta, Guy's Hospital reports. London: Guy's Hospital; 1842. p. 387.
6. Cleland WP. The surgical management of obstructive cardiomyopathy. J Cardiovasc Surg. 1963;4:489–91.
7. Van de Wall E, van der Heide JN H. Treatment of hypertrophic obstructive cardiomyopathy by septectomy. In: Wolstenholme GEW, Ciba Foundation Study Group, editors. Hypertrophic obstructive cardiomyopathy, vol. 37. London: J. & A. Churchill; 1971. p. 160–82.
8. Morrow AG, Reitz BA, Epstein SE, Henry WL, Conkle DM, et al. Operative treatment in hypertrophic subaortic stenosis. Techniques, and the results of pre and postoperative assessments in 83 patients. Circulation. 1975;52(1):88–102.
9. Cooley DA, Leachman RD, Wukasch DC. Mitral valve replacement for idiopathic hypertrophic cardiomyopathy. J Cardiovasc Surg. 1976;17:380–7.
10. Kracjer Z, Leachman RD, Cooley DA, Coronado R. Septal myotomy-myomectomy versus mitral valve replacement in hypertrophic cardiomyopathy: 10-year follow-up in 185 patients. Circulation. 1989;80(Suppl II):II-57. 57.
11. McIntosh CL, Greenberg GJ, Maron BJ, Leon MB, Cannon 3rd RO, Clark RE. Clinical and hemodynamic results after mitral valve replacement in patients with obstructive hypertrophic cardiomyopathy. Ann Thorac Surg. 1989;47(2):236–46.
12. McIntosh CL, Maron BJ, Cannon III RO, Klues HG. Initial results of combined anterior mitral leaflet plication and ventricular septal myotomy-myectomy for relief of left ventricular outflow tract obstruction in patients with hypertrophic cardiomyopathy. Circulation. 1992; 86(suppl II):1160–7.
13. Klues HG, Maron BJ, Dollar AL, Roberts WC. Diversity of structural mitral valve alterations in hypertrophic cardiomyopathy. Circulation. 1992;85(5):1651–60.
14. Klues HG, Roberts WC, Maron BJ. Morphological determinants of echocardiographic patterns of mitral valve systolic anterior motion in obstructive hypertrophic cardiomyopathy. Circulation. 1993;87: 1570–9.
15. Messmer B. Extended myectomy for hypertrophic obstructive cardiomyopathy. Ann Thorac Surg. 1994;58:575–7.
16. Schoendube FA, Klues HG, Reith S, Flachskampf FA, Hanrath P, Messmer BJ. Long-term clinical and echocardiographic follow-up after surgical correction of hypertrophic obstructive cardiomyopathy with extended myectomy and reconstruction of the subvalvular mitral apparatus. Circulation. 1995;92(suppl II):112–27.
17. Joyce FS, Lever HM, Cosgrove DM. Treatment of hypertrophic cardiomyopathy by mitral valve repair and septal myectomy. Ann Thorac Surg. 1994;57:1025–7.
18. Sherrid MV, Chaudhry FA, Swistel DG. Obstructive hypertrophic cardiomyopathy: echocardiography, pathophysiology, and the continuing evolution of surgery for obstruction. Ann Thorac Surg. 2003;75:620–32.
19. Swistel DG, DeRose Jr JJ, Sherrid MV. Management of patients with complex hypertrophic cardiomyopathy: resection/plication/ release. Oper Tech Thorac Cardiovasc Surg. 2004;9:261–7.
20. Bhudia SK, McCarthy PM, Smedira NG, Lam BK, Rajeswaran J, Blackstone EH. Edge-to-edge (Alfieri) mitral repair: results in diverse clinical settings. Ann Thorac Surg. 2004;77(5):1598–606.
21. Van der Lee C, Kofflard MJM, van Herwerden LA, Vletter WB, ten Cate FJ. Sustained improvement after combined mitral leaflet extension and myectomy in hypertrophic obstructive cardiomyopathy. Circulation. 2003;108:2088–92.
22. Dearani JA, Danielson GK. Septal myectomy for obstructive hypertrophic cardiomyopathy. Oper Tech Thorac Cardiovasc Surg. 2004; 9:278–92.
23. Delmo Walter EM, Siniawski H, Hetzer R. Sustained improvement after combined anterior mitral valve leaflet retention plasty and septal myectomy in preventing systolic anterior motion in hypertrophic obstructive cardiomyopathy in children. Eur J Cardiothorac Surg. 2009;36:546–52.
24. Kwon DH, Smedira NG, Thamilarasan M, Lytle BW, Lever H, Desai MY. Characteristics and surgical outcomes of symptomatic patients with hypertrophic cardiomyopathy with abnormal papillary muscle morphology undergoing papillary muscle reorientation. J Thorac Cardiovasc Surg. 2010;140(2):317–24.
25. Swistel DG, Balaram SK. Surgical myectomy for hypertrophic cardiomyopathy in the 21st century, the evolution of the "RPR" repair:

resection, plication, and release. Prog Cardiovasc Dis. 2012;54: 498–502.
26. Balaram SK, Sherrid MV, Derose Jr JJ, Hillel Z, Winson G, Swistel DG. Beyond extended myectomy for hypertrophic cardiomyopathy: the resection-plication-release (RPR) repair. Ann Thorac Surg. 2005;80(1):217–23.
27. Balaram SK, Tyrie L, Sherrid MV, Afthinos J, Hillel Z, et al. Resection-plication-release for hypertrophic cardiomyopathy: clinical and echocardiographic follow-up. Ann Thorac Surg. 2008;86(5): 1539–44.
28. Balaram SK, Ross RE, Sherrid MV, Schwartz GS, Hillel Z, Winson G, Swistel DG. Role of mitral valve plication in the surgical management of hypertrophic cardiomyopathy. Ann Thorac Surg. 2012;94(6):1990–7; discussion 1997–8.
29. McIntosh CL, Maron BJ. Current operative treatment of obstructive hypertrophic cardiomyopathy. Circulation. 1988;78(3):487–95.
30. Schaff HV, Brown ML, Dearani JA, Abel MD, Ommen SR, et al. Apical myectomy: a new surgical technique for management of severely symptomatic patients with apical hypertrophic cardiomyopathy. J Thorac Cardiovasc Surg. 2010;139:634–40.
31. Said SM, Schaff HV, Able MD, Dearani JA. Transapical approach for apical myectomy and relief of midventricular obstruction in hypertrophic cardiomyopathy. J Card Surg. 2012;27(4):443–8.
32. Said SM, Dearani JA, Ommen SR, Schaff HV. Surgical treatment of hypertrophic cardiomyopathy. Expert Rev Cardiovasc Ther. 2013; 11(5):617–27.
33. Kunkala MR, Schaff HV, Nishiura RA, Abel MD, Sorajja P, Dearani JA, Ommen SR. Transapical approach to myectomy for midventricular obstruction in hypertrophic cardiomyopathy. Ann Thorac Surg. 2013;96(2):564–70.
34. Kaple RK, Murphy RT, DePaola LM, Houghtaling PL, Lever HM, et al. Mitral valve abnormalities in hypertrophic cardiomyopathy: echocardiographic features and surgical outcomes. Ann Thorac Surg. 2008;85:1527–36.
35. Wan CKN, Dearani JA, Sundt TM, Ommen SR, Schaff HV. What is the best surgical treatment for obstructive hypertrophic cardiomyopathy and degenerative mitral regurgitation? Ann Thorac Surg. 2009;88:727–32.
36. Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, et al. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for practice guidelines. J Am Coll Cardiol. 2003;42:1687–713.
37. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2011;124(24):e783–831.
38. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. JAMA. 2002;287(10):1308–20.
39. Sherrid MV. Dynamic left ventricular outflow obstruction in hypertrophic cardiomyopathy revisited: significance, pathogenesis, and treatment. Cardiol Rev. 1998;6(3):135–45.
40. Sherrid M, Barac I. Pharmacologic treatment of symptomatic hypertrophic cardiomyopathy. In: Maron FJ, editor. Diagnosis and management of hypertrophic cardiomyopathy. Boston: Blackwell-Futura; 2004. p. 200–19.
41. Maron BJ, Casey SA, Poliac LC, Gohman TE, Almquist AK, et al. Clinical course of hypertrophic cardiomyopathy in a regional United States cohort. JAMA. 1999;281(7):650–5.
42. Mohr R, Schaff HV, Danielson GK, Puga FJ, Pluth JR, et al. The outcome of surgical treatment of hypertrophic obstructive cardiomyopathy: experience over 15 years. J Thorac Cardiovasc Surg. 1989;97(5):666–74.
43. Schulte HD, Borisov K, Gams E, Gramsch-Zabel H, Losse B, Schwartzkopff B. Management of symptomatic hypertrophic obstructive cardiomyopathy-long-term results after surgical therapy. Thorac Cardiovasc Surg. 1999;47:213–8.
44. Heric B, Lytle BW, Miller DP, Rosenkranz ER, Lever HM, et al. Surgical management of hypertrophic obstructive cardiomyopathy. Early and late results. J Thorac Cardiovasc Surg. 1995;110(1):195–206; discussion 206–8.
45. Robbins RC, Stinson EB. Long-term results of left ventricular myotomy and myectomy for obstructive hypertrophic cardiomyopathy. J Thorac Cardiovasc Surg. 1996;111(3):586–94.
46. Schonbeck MH, Brunner-La Rocca HP, Vogt PR, Lachat ML, Jenni R, et al. Long-term follow-up in hypertrophic obstructive cardiomyopathy after septal myectomy. Ann Thorac Surg. 1998;65(5):1207–14.
47. Ommen SR, Maron BJ, Olivotto I, Maron MS, Cecchi F, et al. Long-term effects of surgical septal myectomy on survival in patients with obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol. 2005;46(3):470–6.
48. Woo A, Williams WG, Choi R, Wigle ED, Rozenblyum E, et al. Clinical and echocardiographic determinants of long-term survival after surgical myectomy in obstructive hypertrophic cardiomyopathy. Circulation. 2005;111(16):2033–41.
49. Dearani JA, Ommen SR, Gersh BJ, Schaff HV, Danielson GK. Surgery insight: septal myectomy for obstructive hypertrophic cardiomyopathy- the Mayo Clinic experience. Nat Clin Pract Cardiovasc Med. 2007;4(9):503–12.
50. Smedira NG, Lytle BW, Lever HM, Rajeswaran J, Krishnaswamy G, et al. Current effectiveness and risks of isolated septal myectomy for hypertrophic obstructive cardiomyopathy. Ann Thorac Surg. 2008;85(1):127–33.
51. Desai MY, Bhonsale A, Smedira NG, Naji P, Thamilarasan M, Lytle BW, Lever HM. Predictors of long-term outcomes in symptomatic hypertrophic obstructive cardiomyopathy patients undergoing surgical relief of left ventricular outflow tract obstruction. Circulation. 2013;128(3):209–16.
52. Maron BJ, Ommen SR, Nishimura RA, Dearani JA. Myths about surgical myectomy: rumors of its death have been greatly exaggerated. Am J Cardiol. 2008;101(6):887–9.
53. Maron BJ, Dearani JA, Ommen SR, Maron MS, Schaff HV, Gersh BJ, Nishimura RA. The case for surgery in obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol. 2004;44:2044–53.
54. Olivotto I, Maron MS, Adabag AS, Casey SA, Vargiu D, Link MS, Udelson JE, Cecchi F, Maron BJ. Gender-related differences in the clinical presentation and outcome of hypertrophic cardiomyopathy. J Am Coll Cardiol. 2005;46(3):480–7.
55. Sorajja P, Ommen SR, Nishimura RA, Gersh BJ, Berger PB, Tajik AJ. Adverse prognosis of patients with hypertrophic cardiomyopathy who have epicardial coronary artery disease. Circulation. 2003;108(19): 2342–8.
56. Minami K, Boethig D, Woltersdorf H, Seifert D, Körfer R. Long term follow-up of surgical treatment of hypertrophic obstructive cardiomyopathy (HOCM): the role of concomitant cardiac procedures. Eur J Cardiothorac Surg. 2002;22(2):206–10.
57. Autore C, Bernabò P, Barillà CS, Bruzzi P, Spirito P. The prognostic importance of left ventricular outflow obstruction in hypertrophic cardiomyopathy varies in relation to the severity of symptoms. J Am Coll Cardiol. 2005;45(7):1076–80.
58. Maron MS, Olivotto I, Betocchi S, Casey SA, Lesser JR, et al. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. N Engl J Med. 2003;348: 295–303.
59. Wigle ED, Rakowski H, Kimball BP, Williams WG. Hypertrophic cardiomyopathy: clinical spectrum and treatment. Circulation. 1995;92:1680–92.
60. Nishimura RA, Holmes DR. Hypertrophic obstructive cardiomyopathy. N Engl J Med. 2004;350:1320–7.

61. Wigle ED, Sasson Z, Henderson MA, Ruddy TD, Fulop J, et al. Hypertrophic cardiomyopathy: the importance of the site and the extent of hypertrophy: a review. Prog Cardiovasc Dis. 1985;28: 1–83.
62. Watson DC, Henry WL, Epstein SE, Morrow AG. Effects of operation on left atrial size and the occurrence of atrial fibrillation in patients with hypertrophic subaortic stenosis. Circulation. 1977;55(1): 178–81.
63. Roberts CS, Gertz SD, Klues HG, Cannon 3rd RO, Maron BJ, McIntosh CL, Roberts WC. Appearance of or persistence of severe mitral regurgitation without left ventricular outflow obstruction after partial ventricular septal myotomy-myectomy in hypertrophic cardiomyopathy. Am J Cardiol. 1991;68(17):1726–8.
64. Yu EH, Omran AS, Wigle ED, Williams WG, Siu SC, Rakowski H. Mitral regurgitation in hypertrophic obstructive cardiomyopathy: relationship to obstruction and relief with myectomy. J Am Coll Cardiol. 2000;36(7):2219–25.
65. Sherrid MV, Chu CK, Delia E, Mogtader A, Dwyer Jr EM. An echocardiographic study of the fluid mechanics of obstruction in hypertrophic cardiomyopathy. J Am Coll Cardiol. 1993;22(3): 816–25.
66. Shah PM, Gramiak R, Adelman AG, Wigle ED. Echocardiographic assessment of the effects of surgery and propranolol on the dynamics of outflow obstruction in hypertrophic subaortic stenosis. Circulation. 1972;45:516–21.
67. Klues HG, Roberts WC, Maron BJ. Anomalous insertion of papillary muscle directly into anterior mitral leaflet in hypertrophic cardiomyopathy: significance in producing left ventricular outflow obstruction. Circulation. 1991;84(3):1188–97.
68. McKenna W, Deanfield J, Faruqui A, England D, Oakley C, et al. Prognosis in hypertrophic cardiomyopathy: role of age and clinical, electrocardiographic and hemodynamic features. Am J Cardiol. 1981;47(3):532–8.
69. Shah PM, Adelman AG, Wigle ED, Gobel FL, Burchell HB, et al. The natural (and unnatural) history of hypertrophic obstructive cardiomyopathy. Circ Res. 1974;35(2):suppl II:179–95.
70. Arteaga E, Ianni BM, Fernandes F, Mady C. Benign outcome in a long-term follow-up of patients with hypertrophic cardiomyopathy in Brazil. Am Heart J. 2005;149(6):1099–105.
71. Spirito P, Chiarella F, Carratino L, Berisso MZ, Bellotti P, et al. Clinical course and prognosis of hypertrophic cardiomyopathy in an outpatient population. N Engl J Med. 1989;320(12):749–55.
72. Elliott PM, Gimeno JR, Tome MT, Shah J, Ward D, et al. Left ventricular outflow tract obstruction and sudden death risk in patients with hypertrophic cardiomyopathy. Eur Heart J. 2006;27(16):1933–41.
73. Maron MS, Olivotto I, Zenovich AG, Link MS, Pandian NG, et al. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. Circulation. 2006;114(21):2232–9.
74. Sherrid MV, Wever-Pinzon O, Shah A, Chaudhry FA. Reflections of inflections in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2009;54(3):212–9.
75. Woo A, Rakowski H. Does myectomy convey survival benefit in hypertrophic cardiomyopathy? Heart Fail Clin. 2007;3(3):275–88.
76. Elliott PM, Poloniecki J, Dickie S, Sharma S, Monserrat L, et al. Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. J Am Coll Cardiol. 2000;36(7):2212–8.
77. McLeod CJ, Ommen SR, Ackerman MJ, Weivoda PL, Shen WK, et al. Surgical septal myectomy decreases the risk for appropriate implantable cardioverter defibrillator discharge in obstructive hypertrophic cardiomyopathy. Eur Heart J. 2007;28(21):2583–8.
78. Minakata K, Dearani JA, Schaff HV, O'Leary PW, Ommen SR, Danielson GK. Mechanisms for recurrent left ventricular outflow tract obstruction after septal myectomy for obstructive hypertrophic cardiomyopathy. Ann Thorac Surg. 2005;80(3):851–6.
79. El Bardissi AW, Dearani JA, Nishimura RA, Ommen SR, Stulak JM, Schaff HV. Septal myectomy after previous septal artery ablation in hypertrophic cardiomyopathy. Mayo Clin Proc. 2007; 82(12):1516–22.
80. Robinson K, Frenneaux MP, Stockins B, Karatasakis G, Poloniecki JD, McKenna WJ. Atrial fibrillation in hypertrophic cardiomyopathy: a longitudinal study. J Am Coll Cardiol. 1990;15(6):1279–85.
81. Olivotto I, Cecchi F, Casey SA, Dolara A, Traverse JH, Maron BJ. Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. Circulation. 2001;104(21):2517–24.
82. Olivotto I, Maron BJ, Cecchi F. Clinical significance of atrial fibrillation in hypertrophic cardiomyopathy. Curr Cardiol Rep. 2001;3(2):141–6.
83. Maron BJ, Casey SA, Hauser RG, Aeppli DM. Clinical course of hypertrophic cardiomyopathy with survival to advanced age. J Am Coll Cardiol. 2003;42(5):882–8.
84. Nistri S, Olivotto I, Betocchi S, Losi MA, Valsecchi G, Pinamonti B, Conte MR, Casazza F, Galderisi M, Maron BJ, Cecchi F. Prognostic significance of left atrial size in patients with hypertrophic cardiomyopathy (from the Italian Registry for Hypertrophic Cardiomyopathy). Am J Cardiol. 2006;98(7):960–5.
85. Chen MS, McCarthy PM, Lever HM, Smedira NG, Lytle BL. Effectiveness of atrial fibrillation surgery in patients with hypertrophic cardiomyopathy. Am J Cardiol. 2004;93(3):373–5.
86. Cavalcante JL, Barboza JS, Lever HM. Diversity of mitral valve abnormalities in obstructive hypertrophic cardiomyopathy. Prog Cardiovasc Dis. 2012;54(6):517–22.

Alcohol Septal Ablation: Technique and Outcome

19

Paul Sorajja

Abstract

Dynamic left ventricular outflow tract obstruction is common in patients with hypertrophic cardiomyopathy, and can be associated with debilitating symptoms of heart failure. For those patients with drug-refractory symptoms, alcohol septal ablation is an effective therapy. The outcomes of alcohol septal ablation can approach the gold standard of surgical myectomy when performed in selected patients and in centers that are dedicated to the comprehensive, longitudinal care of patients with HCM.

Keywords

Ablation • Hypertrophic • Cardiomyopathy • Catheter • Hemodynamics • Obstruction

Key Points

- Alcohol septal ablation may be considered for patients with drug-refractory, severe symptoms due to obstructive hypertrophic cardiomyopathy who are at high-risk of complications from surgical myectomy.
- The outcome of alcohol septal ablation is heavily dependent on appropriate patient selection, longitudinal and multidisciplinary care, and operator expertise. The procedure should only be performed in specialized centers.
- Due to lack of long-term data, alcohol septal ablation is not recommended for patients aged <21 years, and generally should also be avoided in those aged <40 years.
- In selected patients who have undergone alcohol septal ablation at highly experienced centers, the outcome approaches that of surgery in terms of survival and symptom-relief. Patients who are younger (aged <65 years) had better symptom relief with surgical myectomy in one large series of patients.
- The major complication of alcohol septal ablation is pacemaker dependency, which is related to baseline conduction disease. Patients at greater risk of pacemaker dependency are those with left bundle-branch block (~50 %), while dependency still occurs in patients with a normal electrocardiogram (~10 %).

Dynamic left ventricular outflow tract (LVOT) obstruction in hypertrophic cardiomyopathy (HCM) is a complex phenomenon that arises from an interplay of ventricular septal hypertrophy, subaortic Venturi and drag effects, and anterior displacement of the mitral valve apparatus [1]. This phenomenon leads to left ventricular hypertension and mitral regurgitation, the latter resulting from systolic anterior motion of the mitral valve and decreased leaflet coaptation.

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Dynamic LVOT obstruction, detected either at rest or following provocative maneuvers, affects 70 % of patients with HCM [2]. Although many patients may have minimal or no symptoms, a subset can have debilitating symptoms of dyspnea, chest pain, or syncope. Negative inotropic agents, such as β-receptor blockers, disopyramide, and calcium-channel antagonists (verapamil or diltiazem), are the cornerstone of drug therapy for symptomatic LVOT obstruction. When severe symptoms persist despite drug therapy, definitive means of septal reduction therapy should be considered [3].

Percutaneous alcohol septal ablation, as an alternative to the gold standard of surgical myectomy, has emerged as an efficacious therapy for the relief of drug-refractory symptoms due to obstructive HCM. First described by Ulrich Sigwart in 1994, the procedure entails percutaneous injection of alcohol into one or more septal perforator arteries, leading to a controlled myocardial infarction of the ventricular septum and relief of the dynamic LVOT obstruction [4]. The success of alcohol septal ablation is dependent on appropriate patient selection, operator experience, and clinical expertise, with care delivered in the setting of a center dedicated to the comprehensive and longitudinal care of the HCM patient.

Patient Selection

In selecting appropriate patients, it should be noted that the therapeutic goal of alcohol septal ablation is to treat symptoms by reducing systolic thickening of the ventricular septum that is responsible for dynamic LVOT obstruction and associated mitral regurgitation. Patients who may be candidates for the procedure therefore are those with: (1) severe, drug-refractory cardiovascular symptoms, which is defined as New York Heart Association class III/IV dyspnea, Canadian Cardiac Society angina class III/IV, or disabling syncope; (2) dynamic LVOT obstruction due to systolic anterior motion of the mitral valve (gradient ≥30 mmHg at rest or ≥50 mmHg with provocation); (3) ventricular septal thickness ≥15 mm; (4) no significant intrinsic mitral valve disease; (5) absence of need for concomitant cardiac surgical procedure (e.g. valve replacement, bypass grafting); (6) suitable coronary anatomy; (7) and informed patient consent. Informed consent entails a shared-decision making process, in which there is a comprehensive discussion of all of the therapeutic options, including alcohol septal ablation, medical therapy, and surgical myectomy. In this discussion with the patient and family, it is important to note the gold standard of surgical myectomy, which is associated with relief of symptoms in >90 %, an operative mortality of <1 %, and life expectancy comparable to the general population when performed on acceptable surgical candidates in experienced centers [5].

Comprehensive imaging with two-dimensional and Doppler echocardiography is elementary to the ability to appropriately select patients for alcohol septal ablation. In order for the procedure to be effective, LVOT obstruction should be *dynamic*, arising due to systolic thickening of the ventricular septum, and accompanied by systolic anterior motion of the mitral valve at rest or with provocation. Mitral regurgitation associated with dynamic LVOT obstruction is posterior in direction; the presence of central or anterior mitral regurgitation should raise the suspicion of intrinsic mitral valve disease (e.g. myxomatous degeneration) (Fig. 19.1). Particular care should be undertaken to distinguish the Doppler envelope of dynamic LVOT obstruction from that of mitral regurgitation, which can be challenging. Angiography to determine suitability of coronary anatomy should include studies of not only the left but also the right coronary artery, from which proximal septal perforators occasionally can arise.

National guidelines have outlined specific recommendations for alcohol septal ablation in regards to patient selection, emphasizing the importance of expertise of the operator and institution, preference of the procedure for patients who are either at high-risk or inoperable with surgical myectomy, and avoidance in patients who either have massive hypertrophy or who are relatively young (Table 19.1) [3]. In these guidelines, an experienced operator is defined as a person with a cumulative case volume of ≥20 procedures or one who is working in a dedicated HCM program with a cumulative experience of ≥50 procedures.

Procedural Technique

Hemodynamics

While Doppler echocardiography is highly accurate for the calculation of the LVOT gradient in HCM, comprehensive invasive hemodynamic studies should be performed in all patients before and after alcohol septal ablation. These studies determine the acute efficacy, which is a strong predictor of long-term clinical outcome, and if additional septal reduction therapy is needed [6].

It is important to note that LVOT obstruction in HCM is dynamic and exquisitely sensitive to ventricular loading conditions and contractility. The operator should be cognizant of this sensitivity when examining hemodynamic data from both the echocardiogram and invasive catheterization. Special attention must be given not only to the initial LVOT gradient observed at rest, but all dynamic and provocable gradients (e.g., variation with respiration, post-PVC accentuation) observed during the procedure. Of note, even mild variation in intrathoracic pressure during quiet respiration can result in large changes in the LVOT gradient (Fig. 19.2).

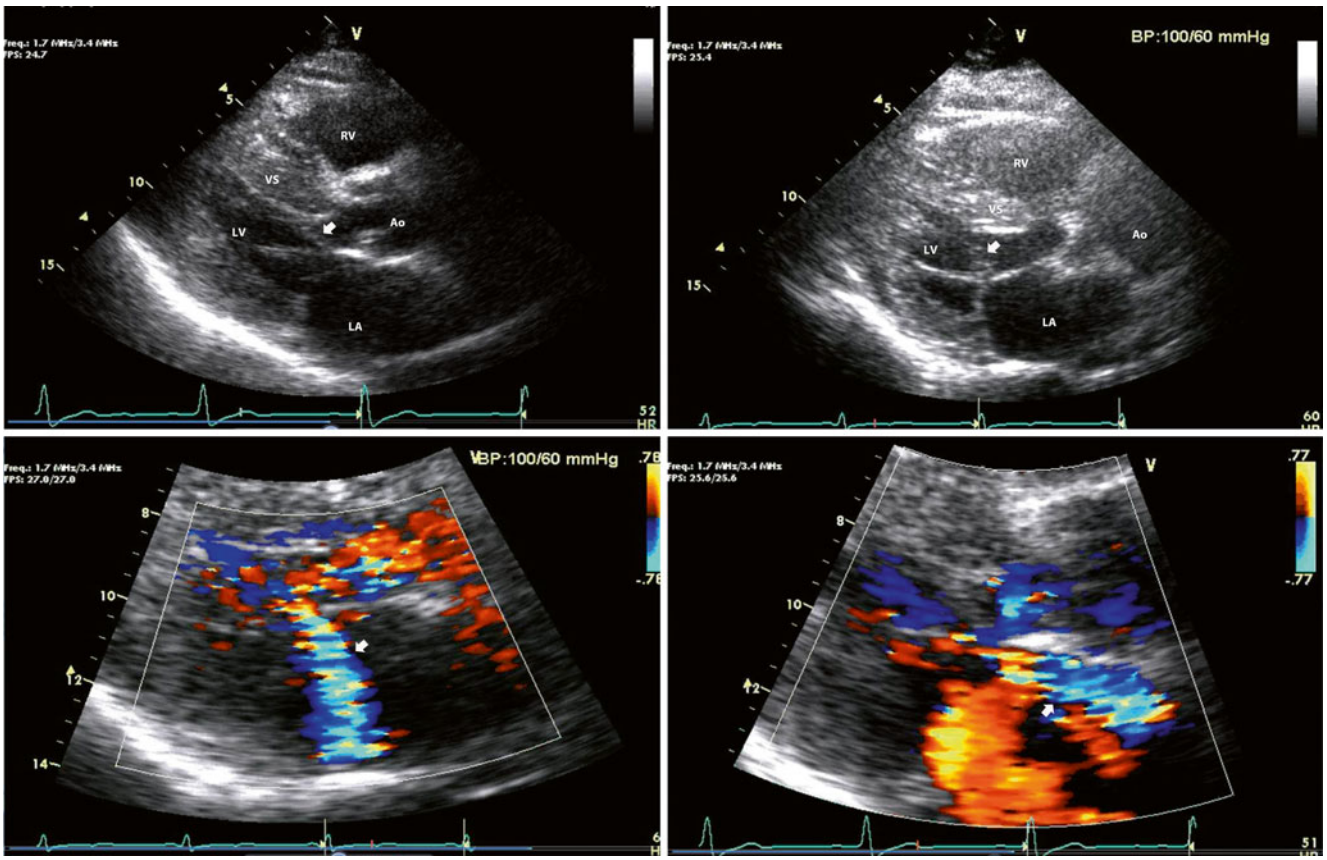


Fig. 19.1 Dynamic left ventricular outflow tract (LVOT) obstruction and associated mitral regurgitation in hypertrophic cardiomyopathy (HCM). *Left*, Parasternal long-axis view from transthoracic echocardiography showing dynamic LVOT obstruction with systolic anterior motion of the mitral valve (*top*, *arrow*) and mitral regurgitation, which is characteristically posterior in direction (*bottom*, *arrow*). *Right*, Parasternal long-axis view from transthoracic echocardiography in a patient with both HCM and degenerative mitral valve disease. In this patient, there also is septal hypertrophy and systolic anterior motion of the mitral valve (*top*, *arrow*). However, the direction of the mitral jet is anterior, demonstrating the presence of intrinsic mitral disease that would not benefit from alcohol septal ablation (*bottom*, *arrow*). *Ao* ascending aorta, *LA* left atrium, *LV* left ventricle, *RV* right ventricle, *VS* ventricular septum

Transseptal catheterization is the most accurate method for the invasive evaluation of LVOT obstruction in HCM. In this approach, a balloon-tipped catheter with side holes (e.g., 7 Fr Berman catheter, Arrow International Inc., Reading, PA) and filled with carbon dioxide can be positioned at the left ventricular inflow region. A pigtail catheter is placed retrograde in the ascending aorta for simultaneous measurement of the LVOT gradient. The transseptal approach helps to avoid catheter entrapment, which can be difficult to distinguish from changes in left ventricular pressure that occur due to the highly dynamic nature of LVOT obstruction. Use of a sheath with a sidearm port (e.g., 8 Fr Mullins) for the transseptal access also enables simultaneous recording of left atrial pressure for assessment for concomitant diastolic dysfunction and the impact of mitral regurgitation.

Alternatively, left ventricular pressure can be assessed with a 5 or 6 Fr catheter placed retrograde across the aortic valve. In this technique, a pigtail catheter with shaft side holes should not be used because some or all of the holes will be positioned above the level of subaortic obstruction, leading to erroneous measurements of left ventricular pressure and the LVOT gradient. Catheters that may be used for this purpose are a multipurpose with side holes at the catheter tip or a Halo pigtail. Single end-hole catheters (e.g., Judkins right) are not recommended due to the propensity for entrapment. In the retrograde approach, absence of catheter entrapment should be confirmed with hand contrast injections or demonstration of pulsatile flow from the catheter during disconnection from the tube extenders used for pressure transduction.

Temporary Pacemaker Placement

The incidence of pacemaker dependency from alcohol septal ablation varies according to the baseline conduction abnormalities. The area of infarction from septal ablation usually courses from the junction of the anterior and inferior septum,

Table 19.1 National guidelines for patient selection for alcohol septal ablation

Class I
Alcohol septal ablation should be performed only by experienced operators in the context of a comprehensive HCM clinical program, and only for the treatment of eligible patients with severe drug-refractory symptoms and LVOT obstruction.
Class IIa
Consultation with centers experienced in performing both surgical septal myectomy and alcohol septal ablation is reasonable when discussing treatment options for eligible patients with HCM with severe drug-refractory symptoms and LVOT obstruction.
When surgery is contraindicated or the risk is considered unacceptable because of serious co-morbidites or advanced age, alcohol septal ablation, when performed in experienced centers, can be beneficial in eligible adult patients with HCM with LVOT obstruction and severe drug-refractory symptoms.
Class IIb
Alcohol septal ablation, when performed in experienced centers, may be considered as an alternative to surgical myectomy for eligible adult patients with HCM with severe drug-refractory symptoms and LVOT obstruction when, after a balanced and thorough discussion, the patient expresses a preference for septal ablation.
The effectiveness of alcohol septal ablation is uncertain in patients with HCM with marked septal hypertrophy (i.e., >30 mm), and therefore the procedure is generally discouraged in such patients.
Class III: **HARM**
Alcohol septal ablation should not be done for patients who are asymptomatic with normal exercise tolerance or whose symptoms are controlled or minimized on optimal medical therapy.
Alcohol septal ablation should not be done unless performed as part of a program dedicated to the longitudinal and multi-disciplinary care of patients with HCM.
Alcohol septal ablation should not be done in patients with HCM with concomitant disease that independently warrants surgical correction (e.g., coronary artery bypass grafting for CAD, mitral valve repair for ruptured chordae) in whom surgery can be performed as part of the operation.
Alcohol septal ablation should not be done in patients with HCM who are less than 21 years of age, and is discouraged in adults less than 40 years of age if myectomy is a viable option.

Modified from Gersh et al. [3]

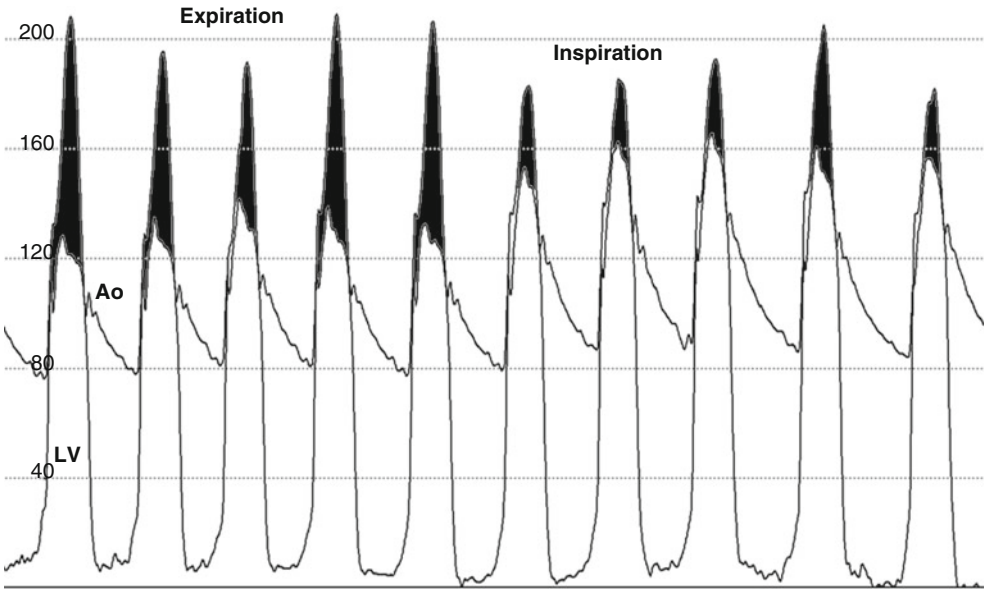


Fig. 19.2 Respiratory variation in left ventricular outflow tract obstruction in hypertrophic cardiomyopathy. These hemodynamic tracings were taken from a patient during quiet respiration. Note the marked variability in the LVOT gradient (*shaded*), which is greatest during expiration due to the respiratory decrease in ventricular afterload

proceeding inferiorly toward the right ventricular side of the ventricular septum [7]. This area frequently contains the right bundle branch, whose block occurs in ~50 % of cases of alcohol septal ablation [8]. Thus, for patients with baseline abnormalities of left bundle branch block, severe left axis deviation, or a very wide QRS interval, the rate of pacemaker dependency with septal ablation approaches 50 %. However, permanent pacemaker dependency from complete atrioventricular block still occurs in ~10 % of patients with a normal electrocardiogram. Thus, for patients without a previously placed permanent pacemaker, a temporary device is required prior to septal ablation.

Conventional 5 or 6 Fr temporary pacemakers can be utilized. These devices, however, have been associated with cardiac perforation due to their relative stiffness and long dwelling time in the post-procedural care of these patients.

Conversely, the use of a low profile, less traumatic temporary screw-in pacemaker (model 6416–140, Medtronic, Inc., Fridley, MN) has been associated with superior outcomes [9]. The temporary pacemaker should be placed distal or away from the target site of ablation to ensure continuous capture during septal infarction.

Coronary Angiography

The primary goal of coronary angiography is to determine the most appropriate septal artery for the procedure. As stated previously, both the left and right coronary arteries should be studied, as basal septal branches occasionally arise from the proximal right coronary artery. With right anterior oblique views, straight and caudal projections of the left coronary artery help to examine the angulation of the origin of the septal artery, while cranial projections can assist with the length of the vessel. The course of the artery in the ventricular septum should always be demonstrated using the left anterior oblique projections. It is important to note that the length of the septal artery may not be visible on angiography and appear short, but the vessel often can still be wired distally for support. Thus, the most important factors for choosing a candidate septal perforator artery are location (i.e., proximity to basal septum), width, and angulation, rather than length of the vessel.

Catheter Ablation

Conventional 6 or 7 Fr guide catheters are used to engage the left coronary artery with standard procedural anticoagulation (e.g., heparin 70–100 units/kg). A well-seated, coaxial guide is needed to facilitate contrast injections that definitively demonstrate no communication between the septal artery and epicardial vessel following balloon occlusion. Both a primary and a large secondary bend should be placed on the tip of a long 0.014″ guidewire to facilitate entry into the candidate septal artery. The wire should be carried considerably distal to ensure the stiff portion is at the occlusion site, helping to facilitate balloon delivery and minimize balloon movement during the procedure. A slightly oversized, (e.g., 2.0 mm balloon for a 1.5 mm vessel), short-length (e.g., 6–9 mm), over-the-wire balloon is placed entirely into the septal artery using standard catheter techniques. Oversizing of the balloon allows occlusion of the septal artery at low pressures (3–4 atm), which permit injection of material through the wire lumen of the catheter with minimal risk of septal artery dissection or trauma. Following inflation of the balloon catheter, the guidewire is withdrawn.

Coronary angiography then is performed to demonstrate no communication between the septal perforator and left anterior descending artery during balloon inflation in the right anterior oblique view, and then repeated to confirm the course of the balloon in the target vessel through the ventricular septum in the left anterior oblique view. Next, using undiluted contrast (approximately 1 ml), angiography of the septal artery through the balloon catheter confirms patency of the vessel for ablation and localization (i.e. no untoward collateralization). This injection should be done gently as a forceful one can result in vessel dissection and opening of distal collaterals, the significance of which can be difficult to determine. Angiographic contrast can be visible on echocardiography for identification of the perfusion bed, though many operators also prefer to additionally inject dedicated echocardiographic contrast (e.g., 0.5 ml Definity or Optison) (Fig. 19.3). Multiple echocardiographic views are used to confirm enhancement of the septal hypertrophy intimately related to LVOT obstruction and the absence of undesirable locations, such as the free walls, thinner areas of the septum more distal or proximal to the target region, right ventricle, or papillary muscles (Fig. 19.4). After delineation of the targeted myocardium, 1–3 ml of desiccated ethanol is infused slowly over a period of 3–5 min followed by ~0.5 cc of slow normal saline flush to eliminate any remaining alcohol in the balloon catheter lumen. The use of alcohol is preferred because this agent immediately results in a discrete myocardial infarction. In other percutaneous methods (e.g., vascular coiling, covered stent placement), septal infarction may not result due to extensive septal collateralization that is either pre-existing or develops during follow-up.

The balloon should be left inflated following saline flush for 5–10 min to reduce likelihood of alcohol extravasation into the epicardial vessel. For patient comfort, intravenous sedation or analgesia (e.g., fentanyl, 25–50 mg) frequently is given prophylactically or as needed. For patients without significant reduction of either the resting or provoked LVOT gradient, other septal perforator arteries can be targeted and treated in similar fashion. Of note, the residual LVOT gradient is a strong predictor of poor clinical outcome in patients who undergo alcohol septal ablation [6]. When assessing the acute result of the procedure, it is important to repeat hemodynamic evaluation with large lumen catheters devoid of the ablation equipment, as the balloon catheters will lead to pressure dampening, and to evaluate the LVOT gradient at rest and after provocative maneuvers (e.g., post-ectopic accentuation). In general, residual peak gradients <30 mmHg and preferably <10 mmHg are desired, prompting termination of the procedure.

Clinical Outcomes

Acute Procedural Success

Overall, alcohol septal ablation typically results in a 60–80 % reduction in the LVOT gradient. Results similar to

surgery for acute procedural success, when defined as a ≥80 % reduction in the peak resting or provoked LVOT gradient with a final residual resting gradient of ≤10 mmHg, occurs in 80–85 % of patients [6, 9]. Factors associated with higher likelihood of acute hemodynamic success include relatively less septal hypertrophy, lower LVOT gradients, and greater operator experience [10]. It is important to note that myocardial edema from the infarction can lead to recurrent LVOT obstruction in the subacute period and can be a source of confusion regarding the acute effect of the procedure, but that this edema subsides with ventricular remodeling. Ventricular remodeling and basal septal thinning leads to further reduction in the LVOT gradient over a period of 3–6 months after the procedure. Of note, regression of myocardial hypertrophy at the site of LVOT obstruction from the infarction and also remotely from the ventricular septum has been demonstrated in studies using cardiac magnetic resonance imaging, and may be responsible for improved diastolic function and further reductions in symptoms [11].

Procedural failure most frequently results from the lack of an appropriate septal artery, which may be absent in up to 20 % of patients [12]. The most common complication of alcohol septal ablation is temporary or complete atrioventricular block. Conduction abnormalities usually present during the procedure, but can occur subacutely due

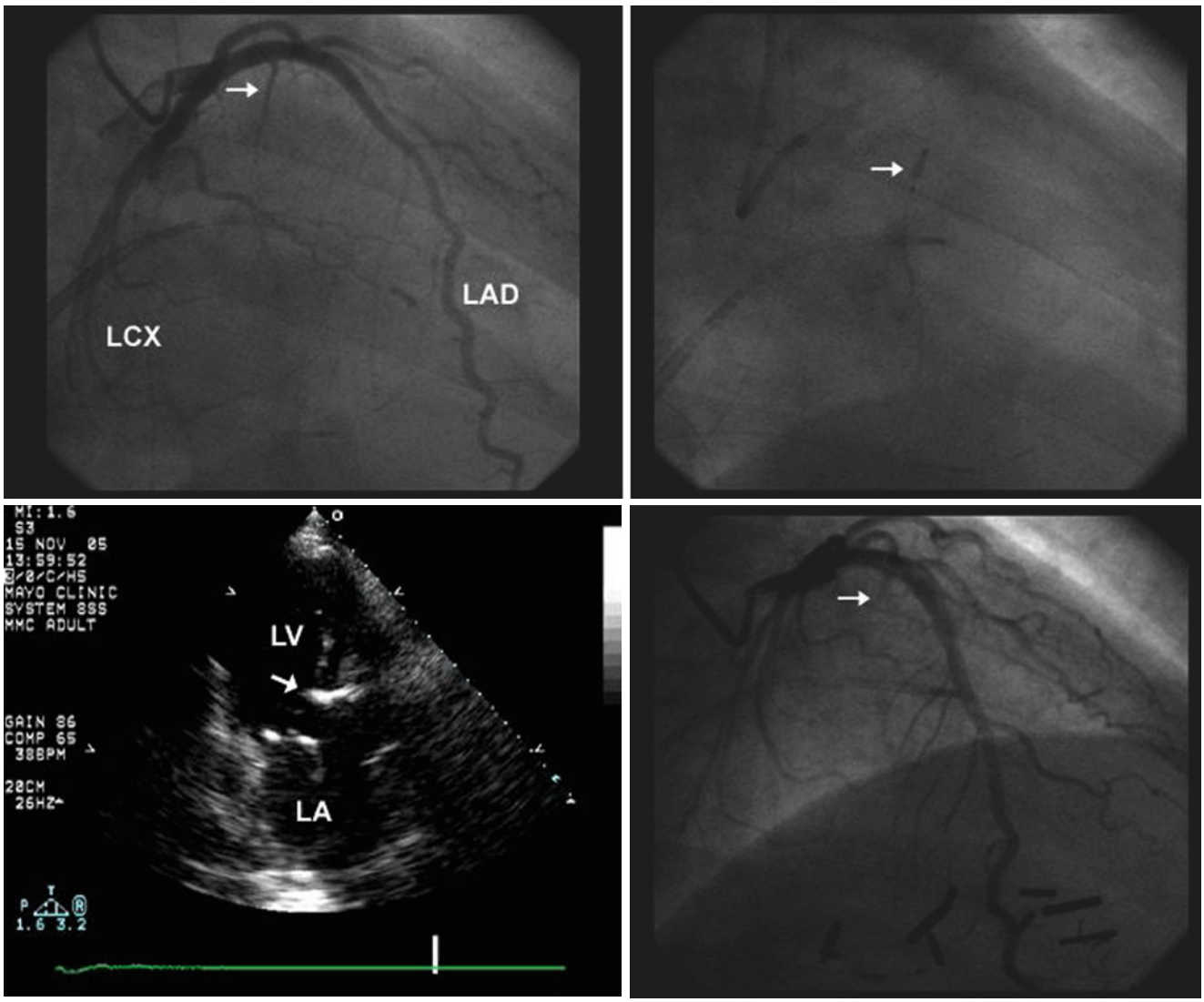
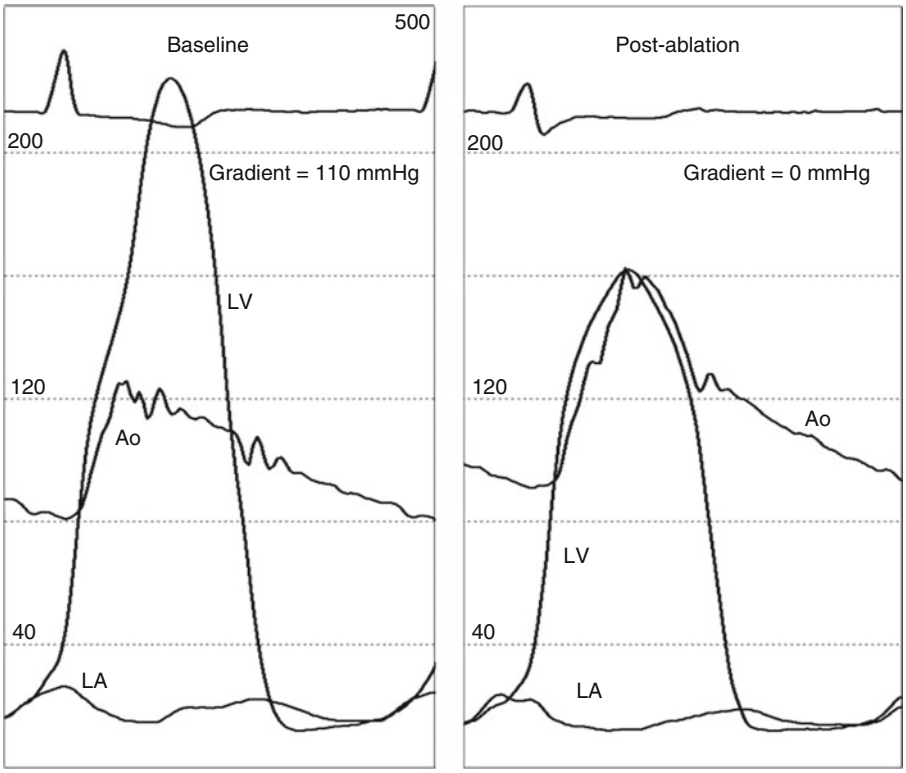


Fig. 19.3 Alcohol septal ablation procedure. *Top left*, Left coronary angiography demonstrates a large proximal septal perforator artery arising from the left anterior descending (*arrow*). *Top right*, Echocardiography demonstrates ventricular septal hypertrophy and outflow tract obstruction due to systolic anterior motion of the mitral valve (*arrow*). *Middle left*, With contrast injection through the septal artery, the myocardium intimately involved with obstruction is highlighted (*arrows*). *Middle right*, Following administration of alcohol, there is obliteration of the septal artery due to infarction. *Bottom left*, Baseline hemodynamic study demonstrates a gradient of 83 mmHg across the left ventricular outflow tract. *Bottom right*, Following septal ablation, the gradient is 0 mmHg. *Ao* ascending aorta, *LCX* left circumflex, *LAD* left anterior descending, *LV* left ventricle, *LA* left atrium, *RV* right ventricle

Fig. 19.3 (continued)



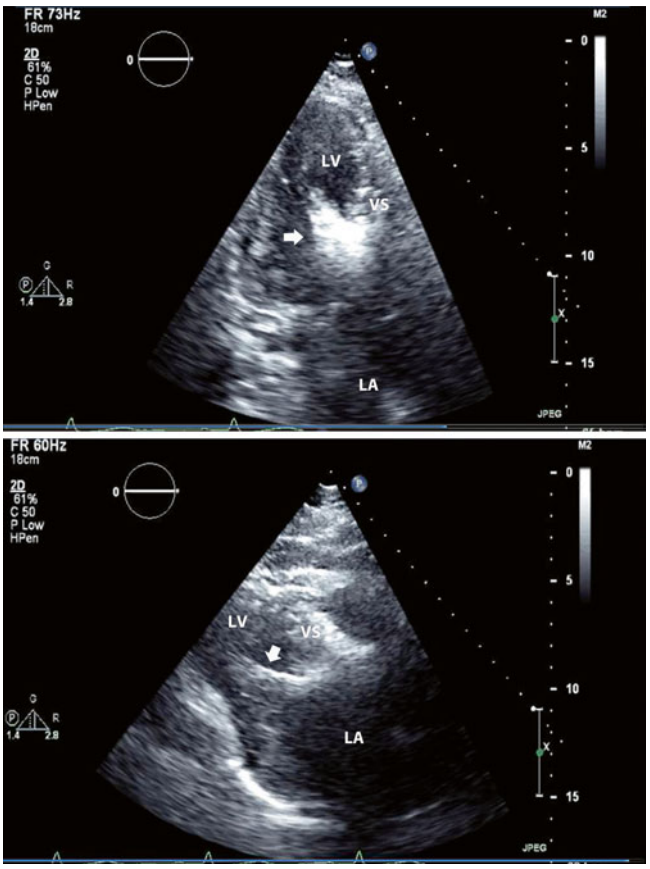


Fig. 19.4 Contrast enhancement of papillary muscles (*arrows*) in patient with hypertrophic cardiomyopathy during an attempt at alcohol septal ablation. *Top*, Apical long-axis view; *Bottom*, Parasternal long-axis view. *LA* left atrium, *LV* left ventricle, *VS* ventricular septum

to edema from the infarction with late heart block being rare. Other potential complications are cardiac tamponade, ventricular tachycardia or fibrillation, dissection of the left anterior descending artery, ventricular septal defect, and free wall myocardial infarction. For these reasons, patients should be observed in an intensive care setting for at least 3 days after the procedure. Overall, the published peri-procedural mortality rates for alcohol septal ablation are 1–2 %, with contemporary observational series in the United States and Europe reporting mortality rates <1 %.

Symptom Improvement

The clinical efficacy of alcohol septal ablation has been demonstrated with improvements in both subjective reporting of New York Heart Association functional class and objective testing, such as treadmill exercise time and peak exercise myocardial oxygen consumption. The clinical efficacy of alcohol septal ablation is related to the degree of reduction in severity of the LVOT gradient. Overall, alcohol septal ablation typically results in a ~25 % increase in objective measures of functional capacity.

Repeat procedures occasionally may be required (~5 % of cases). Shadowing of the basal septum from echocardiographic contrast can occur with imaging from the apical windows, leading to the false impression of successful ablation of the most proximal portion and resulting in residual obstructive hypertrophy. Stunning of the ventricular septum from balloon occlusion may occur without complete

infarction, leading to recovery of septal function and recurrent LVOT obstruction in follow-up. While several studies have shown clinical improvements comparable to that of myectomy, symptom relief is greater with surgery in younger patients. The reasons for this observation are not clear, but may be related to the residual gradients present after ablation (typically 10–20 mmHg) that are consequently higher than those after surgical myectomy (typically <10 mmHg). These relatively higher residual gradients may be less tolerated by younger, more active individuals.

Survival

Several single-center studies have compared the results of alcohol septal ablation to surgical myectomy with follow-up ranging from 3 months to 8 years [6, 9, 13–18]. Overall survival has been comparable to that of surgery, although the total number of ablation patients examined remains relatively small (n = 419 for all series combined).

In the Mayo Clinic study (n = 177), eight-year survival free of all-cause mortality (including appropriate defibrillator discharge) after alcohol septal ablation was 79 %, and similar to that of matched patients who had surgical myectomy (79 %) as well as the expected survival of a similar U.S. general population of individuals (79 %) [6]. For the combined endpoint of sudden death, appropriate defibrillator discharge, and unknown cause of death, the incidence was 1.41 % (95 % confidence interval, 0.67–2.52 %). In the Baylor-Medical University of South Carolina study (n = 629), overall survival was 89 % after 8 years of follow-up. While this study lacked a comparison group and follow-up was incomplete in 8 %, the reported incidence of sudden cardiac death was low (n = 7 or 1.1 %) [19]. In a separate study of 55 patients who underwent alcohol septal ablation at Cleveland Clinic, 76 % of patients survived at 10 years of follow-up [20].

In a study of 91 patients who underwent alcohol septal ablation at Erasmus MC Rotterdam, sudden cardiac death (or appropriate defibrillator discharge, n = 4) occurred in 19 patients (or 21 %) during a mean follow-up period of 5.7 years [21]. While these results raised concern regarding potential for arrhythmias after ablation, the study was noteworthy for a relatively higher average alcohol dose (3.5 ± 1.5 ml) among their patients, including a mean dose of 4.5 ± 1.2 ml in the first 25 patients. In the Mayo Clinic study, where long-term survival was not impaired, the mean alcohol dose was only 1.8 ml, and the septal wall thickness was similar to the patients in the Rotterdam study (23 ± 5 mm vs. 23 ± 5 mm). Of note, early studies of alcohol septal ablation, where contrast echocardiography was not routinely performed, were associated with larger infarct size, a greater risk of complications, and poorer clinical outcome [22].

In a multicenter registry of 874 alcohol ablation patients that included patients from aforementioned studies, there was significant improvement in functional status (~5 % with residual severe symptoms). Overall survival was 74 % at 9 years of follow-up with predictors of death being lower baseline ejection fraction, fewer number of arteries treated, larger number of ablation procedures, and higher septal thickness post-ablation [23]. Several meta-analyses have examined the outcome of patients undergoing alcohol septal ablation in comparison to surgery [24, 25]. Taken together, the aforementioned studies suggest that efficacious and comparable outcomes can be achieved with appropriate patient selection, use of lower doses of alcohol, and greater operator and institutional experience in the comprehensive care of patients with HCM.

Perspective

Although septal ablation has established itself as an efficacious therapy in selected HCM patients, its introduction has been met with controversy about its appropriate role in the management of these patients. These concerns have arisen primarily because of the established safety and durable efficacy of surgery, potential procedural morbidity of septal ablation (e.g., pacemaker dependency), and possible long-term deleterious effects of the therapeutic infarction.

The selection of alcohol septal ablation or surgical myectomy will continue to rely on carefully performed observational data and expert consensus, as randomized clinical trials in this field have been deemed to be not feasible [26]. For some patients, septal ablation may be the only option for definitive relief of LVOT obstruction due to poor candidacy for surgery. In others, septal ablation can be offered as an alternative treatment only after the risks of the procedure and the aforementioned concerns have been discussed fully with the patient. Without the need for general anesthesia and open surgery, the relatively less invasive aspects of septal ablation are its principal advantages. Hospital stay (typically 3–5 days) and physical rehabilitation is also relatively shorter. These issues are particularly relevant for elderly patients or those with morbidities that significantly increase the risk of open surgical repair. Of note, among patients who underwent septal ablation in one study, 20 % of these patients were believed to be at significantly increased operative risk for myectomy due to patient age (≥75 years) or presence of severe co-morbidities (e.g., end-stage renal disease, porcelain aorta, morbid obesity, cor pulmonale) [9].

Importantly, even though septal ablation uses conventional coronary angioplasty equipment, the procedure is complex with a steep learning curve and unique complications [10]. In addition, patients with HCM are uniquely

complex in terms of diagnosis and management, with many factors that should be taken into account when considering septal reduction therapy. Thus, national guidelines recommend that these management considerations be made in a tertiary center, where expertise in both percutaneous and surgical options can be offered [3].

Clinical Pearls

- Patient selection is key to the success of the procedure. Ensure that the procedure is performed only for *dynamic* LVOT obstruction and systolic anterior of the mitral valve, with predominantly *posterior* mitral regurgitation.
- Comprehensive cardiac imaging performed preprocedurally, and careful invasive hemodynamic studies during the procedure are needed to ensure success of the procedure.
- Basal septal shadowing occurs frequently with apical echocardiographic views. Thus, always start with the most proximal septal artery for interrogation of the perfusion bed. Injection of distal or apical arteries first will make it difficult to determine contrast enhancement proximally unless transesophageal echocardiography is used.
- Temporary screw-in pacemakers with small profile leads reduce the risk of cardiac perforation.
- Imaging with gadolinium and cardiac MRI helps determine the anatomic effect of the procedure and feasibility of repeat procedures.

References

1. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. JAMA. 2002;287:1308–20.
2. Maron MS, Olivotto I, Zenovich AG, et al. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. Circulation. 2006;114:2232–9.
3. Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Developed in collaboration with the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2011;58:e212–60.
4. Sigwart U. Non-surgical myocardial reduction for hypertrophic obstructive cardiomyopathy. Lancet. 1995;346:211–4.
5. Ommen SR, Maron BJ, Olivotto I, et al. Long-term effects of surgical myectomy on survival in patients with obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol. 2005;46:470–6.
6. Sorajja P, Ommen SR, Holmes Jr DR, et al. Survival after alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Circulation. 2012;126:2374–80.
7. Valeti US, Nishimura RA, Holmes DR, et al. Comparison of surgical septal myectomy and alcohol septal ablation with cardiac magnetic resonance imaging in patients with hypertrophic obstructive cardiomyopathy. J Am Coll Cardiol. 2007;49:350–7.
8. Talreja DR, Nishimura RA, Edwards WD, et al. Alcohol septal ablation versus surgical septal myectomy: comparison of effects on atrioventricular conduction tissue. J Am Coll Cardiol. 2004;44:2329–32.
9. Sorajja P, Valeti U, Nishimura RA, et al. Outcome of alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Circulation. 2008;118:131–9.
10. Sorajja P, Binder J, Nishimura RA, et al. Predictors of an optimal clinical outcome with alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Catheter Cardiovasc Interv. 2013;81:E58–67.
11. Van Dockum WG, Beek AM, ten Cate FJ, et al. Early onset and progression of left ventricular remodeling after alcohol septal ablation in hypertrophic obstructive cardiomyopathy. Circulation. 2005;111:2503–8.
12. Singh M, Edwards WD, Holmes Jr DR, Tajik AJ, Nishimura RA. Anatomy of the first septal perforating artery: a study with implications for ablation therapy for hypertrophic cardiomyopathy. Mayo Clin Proc. 2001;76:799–802.
13. Firoozi S, Elliott PM, Sharma S, Murday A, et al. Septal myotomy-myectomy and transcoronary septal alcohol ablation in hypertrophic obstructive cardiomyopathy: a comparison of clinical, hemodynamic and exercise outcomes. Eur Heart J. 2002;23:1617–24.
14. Nagueh S, Ommen SR, Lakkis NM, et al. Comparison of ethanol septal reduction therapy with surgical myectomy for the treatment of hypertrophic obstructive cardiomyopathy. J Am Coll Cardiol. 2001;38:1701–6.
15. Qin JX, Shiota T, Lever HM, et al. Outcome of patients with hypertrophic obstructive cardiomyopathy after percutaneous transluminal septal myocardial ablation and septal myectomy surgery. J Am Coll Cardiol. 2001;38:1994–2000.
16. Ralph-Edwards A, Woo A, McCrindle BW, et al. Hypertrophic obstructive cardiomyopathy: comparison of outcomes after myectomy or alcohol ablation adjusted by propensity score. J Thorac Cardiovasc Surg. 2005;129:351–8.
17. Jiang TY, Wu XS, Lu Q, et al. Transcoronary ablation of septal hypertrophy compared with surgery in the treatment of hypertrophic obstructive cardiomyopathy. Chin Med J. 2004;117:296–8.
18. Vural AH, Tiryakioglu O, Turk T, et al. Treatment modalities in hypertrophic obstructive cardiomyopathy: surgical myectomy versus percutaneous septal ablation. Heart Surg Forum. 2007;10:493–7.
19. Fernandes VL, Nielsen C, Nagueh SF, et al. Follow-up of alcohol septal ablation for symptomatic hypertrophic obstructive cardiomyopathy: the Baylor and Medical University of South Carolina experience 1996 to 2007. JACC Cardiovasc Interv. 2008;1:561–70.
20. Kwon DH, Kapadia SR, Tuzcu EM, et al. Long-term outcomes in high-risk symptomatic patients with hypertrophic cardiomyopathy undergoing alcohol septal ablation. JACC Cardiovasc Interv. 2008;1:432–8.
21. Ten Cate FJ, Solimon OI, Michels M, et al. Long-term outcome of alcohol septal ablation in patients with obstructive hypertrophic cardiomyopathy: a word of caution. Circ Heart Fail. 2010;3:362–9.
22. Faber L, Seggewiss H, Gleichman U. Percutaneous transluminal septal myocardial ablation in hypertrophic obstructive cardiomyopathy. Results with respect to intraprocedural myocardial contrast echocardiography. Circulation. 1998;98:2415–21.

23. Nagueh SF, Groves BM, Schwartz L, et al. Alcohol septal ablation for the treatment of hypertrophic obstructive cardiomyopathy. A multicenter North American registry. J Am Coll Cardiol. 2011;58: 2322–8.
24. Agarwal S, Tuzcu EM, Desai MY, et al. Updated meta-analysis of septal alcohol ablation versus myectomy for hypertrophic cardiomyopathy. J Am Coll Cardiol. 2010;55:823–34.
25. Alam M, Doakinsih H, Lakkis NM. Hypertrophic obstructive cardiomyopathy- alcohol septal ablation vs. myectomy: a meta-analysis. Eur Heart J. 2009;30:1080–7.
26. Olivotto I, Ommen SR, Maron MS, Cecchi F, Maron BJ. Surgical myectomy versus alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Will there ever be a randomized trial. J Am Coll Cardiol. 2007;50:831–4.

End-Stage Diastolic and Systolic Heart Failure: Evaluation and Timing of Heart Transplantation

20

Eric D. Popjes, Anjali Tiku Owens, and Mariell Jessup

Abstract

End stage hypertrophic cardiomyopathy occurs in an estimated 3–15 % of patients and can present as either systolic or diastolic dysfunction. Risk factors for developing end stage disease include a family history of end stage disease, younger age at initial diagnosis, increased wall thickness and persistent arrhythmia. The classic form of adverse remodeling includes left ventricular cavity dilation with regression of hypertrophy and decrease in ejection fraction. Standard medical therapy for systolic heart failure and consideration of prophylactic defibrillator is indicated when LVEF is less than 50 %. Heart transplant is a viable option for patients with end stage hypertrophic cardiomyopathy, including those with systolic heart failure, diastolic heart failure or refractory arrhythmia. Strategies used to bridge patients to transplant include continuous inotropic infusion, left ventricular assist device, intra-aortic balloon pump, and in rare cases extracorporeal membrane oxygenation. Survival after heart transplant for hypertrophic cardiomyopathy is equal to or better than survival for patients who have other types of cardiomyopathies.

Key Words

Congestive heart failure • End-stage HCM • LV systolic dysfunction • LV Diastolic dysfunction • Restrictive physiology • Left ventricular assist device (LVAD) • Heart transplantation

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Key Points

- End-stage HCM can present as systolic or diastolic heart failure.
- LV cavity enlargement with regression of wall thickness is the classic remodeling phenotype.
- Once heart failure symptoms are present with LVEF < 50 %, standard heart failure therapies should be instituted including ace-inhibitor, beta blocker, loop diuretics and aldosterone antagonists if indicated.
- End stage restrictive HCM presents a treatment dilemma.
- Patients with end-stage HCM are at risk for sudden cardiac death and should have an ICD placed for primary prevention.

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- Patients with end stage dilated HCM are potential candidates for mechanical circulatory support
- Heart transplant is a viable option for patients with advanced HCM and early referral should be made to a transplant center.
- Approximately 1–2 % of all transplants are done for HCM.

Progression of Disease

Hypertrophic cardiomyopathy (HCM) progresses to the "end-stage" in an estimated 3–15 % of patients [1–5]. End-stage (ES) HCM is classically characterized by a left ventricular ejection fraction (LVEF) of <50 % at rest, representing global systolic dysfunction. Recent studies have revealed several morphologically distinct patterns of remodeling in ES HCM. The most definitive remodeling includes dilation of the left ventricular (LV) cavity with regression of hypertrophy, at times progressing to distinct thinning of the walls with severe systolic dysfunction and some degree of mitral regurgitation. A second pattern includes dilated or progressively increasing LV cavity dimension with preserved hypertrophy. Yet another pattern includes a relatively normal or preserved LV cavity size with mild hypertrophy or slight regression of hypertrophy. Finally, some patients will present with continued marked hypertrophy and no dilation of LV cavity [2]. Atrial enlargement, pulmonary hypertension and a restrictive filling pattern are common features of advanced HCM. Importantly, patients who are truly at ES typically do not have evidence of LV outflow tract obstruction.

Disease progression is variable and often unpredictable, with a range of several years to many decades from diagnosis of HCM to transition to ES disease. Once ES HCM is identified, however, it is usually a rather precipitous decline to death or heart transplant, with some studies reporting an 11 % mortality rate per year [2]. A high index of suspicion is required, especially in cases where typical remodeling to a dilated phenotype is not apparent on standard transthoracic echocardiogram. High risk clinical characteristics for progression to ES disease include: younger age at diagnosis, family history of HCM and in particular family history of ES disease and/or sudden death, persistence of atrial fibrillation or ventricular tachycardia and greater wall thickness [1].

Cardiac MRI, cardiopulmonary exercise testing, and right heart catheterization can be helpful to identify high risk features heralding the onset of ES disease. In recent years, the use of MR imaging for the identification of large, confluent or transmural areas of delayed enhancement suggesting significant fibrosis of the LV has been associated with advanced cardiomyopathy and risk of sudden death and heart failure. Cardiac MRI may also have an emerging role in identifying the early transition to end stage disease, during which time the LVEF is in the 50–65 % range but significant late gadolinium enhancement can be discerned [6, 7].

Cardiopulmonary exercise testing (CPET) objectively quantifies exercise tolerance and is useful for tracking progressive functional limitation and a threshold for referral for advanced therapies such as heart transplant. Worrisome features on CPET include a peak oxygen consumption (VO_2 max) of ≤14 mL/kg/min or less than 50 % predicted for age [8]. In addition, the ratio of minute ventilation over minute carbon dioxide exhaled (VE/VCO_2) > 34 signals ventilatory insufficiency and portends a poor prognosis. Right heart catheterization is useful to define filling pressures and cardiac index in addition to the degree of pulmonary vascular disease in any patient who has symptoms of heart failure. Right heart catheterization is particularly helpful to define hemodynamics in cases where imaging has not shown typical remodeling but signs and symptoms of heart failure are present. In these situations, significant restrictive physiology with low cardiac output and severe pulmonary hypertension can be found.

Management of End-Stage HCM

Once symptoms progress to NYHA functional class III/IV in non-obstructive HCM, especially coupled with signs of adverse remodeling by cardiac imaging and/or recurrent atrial or ventricular arrhythmias despite standard therapies, it is appropriate to re-evaluate pharmacologic and device therapy and to refer the patient to a heart transplant center for further evaluation. Specifically, as outlined in both the ACC/AHA heart failure and hypertrophic cardiomyopathy guidelines, in patients with dilated ES HCM it is appropriate to initiate therapy with ace-inhibitors and beta blockers and to use loop diuretics as needed to relieve congestion. In some cases, aldosterone antagonists and digoxin may be beneficial. Consideration should be given to discontinuation of negative inotropic agents such as centrally acting calcium channel blockers and disopyramide [9, 10]. Other common cardiovascular conditions that may be contributing to the development of systolic dysfunction should be investigated, including coronary artery disease, valvular disease and metabolic disorders. After addressing reversible conditions, implantation of a defibrillator is reasonable for primary prevention of sudden cardiac death in patients with ES HCM who are not being referred for palliative care [10]. The role of cardiac resynchronization therapy (CRT) is less clear in this group of patients. Small single center studies suggest that some patients with ES HCM, left bundle branch block and dilated LV may derive symptomatic benefit from CRT in

terms of NYHA functional class and objective improvement in remodeling parameters [11, 12].

Optimal medical therapy is commonly limited in this population due to hypotension with vasodilators and pre-renal azotemia in response to diuretics given the steep left ventricular pressure-volume relationship present. Clinicians need to assess pulmonary hypertension including pulmonary vascular resistance and look for evidence of cardiac cirrhosis due to long standing elevation in right sided filling pressures as these conditions may preclude heart transplantation or necessitate dual organ transplant (heart/liver) in the case of cardiac cirrhosis.

Left Ventricular Assist Device Support in Patients with HCM

There is very limited data reported on the use of left ventricular assist device (LVAD) to support patients with end stage HCM. HCM patients were generally excluded from or not specifically mentioned in the clinical trials that have been performed to evaluate the efficacy of LVADs for destination therapy (DT) or as a bridge to transplant (BTT) [13–15]. Other than clinical experience most data on mechanical circulatory support for patients with HCM and severe heart failure are case reports or very small single center case series. Two case reports with the use of the HeartMate II LVAD as BTT both showed improved symptoms [16, 17]. One patient who had systolic dysfunction, pulmonary hypertension, and severe heart failure and was intolerant of medical therapy was successfully bridged to transplant. The other patient, who had had a previous myectomy and tricuspid valve repair but continued to have severe heart failure, frequent hospitalizations and high filling pressures, was successfully supported for 10 months and was still awaiting transplant at the time of publication of the report. A case series of 3 patients implanted with the Heartware left ventricular assist system (LVAS) showed similar successful support with improved hemodynamics and a similar degree of decrease in LV end-diastolic dimension when compared to those implanted with the Heartware LVAS who had dilated cardiomyopathy [18]. One patient was successfully bridged to transplant and one was still being supported at the time of the publication but one patient had died during support due to thrombus formation at the device's inflow cannula at the LV apex.

A case series from the Mayo Clinic reported on the support of 4 patients with HCM and 4 patients with restrictive CM using the Heartmate II LVAD [19]. Two of the HCM patients had concomitant myectomies. On average, the LV cavities were smaller, there was more LV hypertrophy, and there was a higher incidence of right ventricular dysfunction in these patients when compared to patients with DCM and LVAD support. All of the HCM patients had very low LVEF suggesting the dilated end stage form of HCM. After implant, pump flows were lower in the HCM patients which was thought to be related to more RV dysfunction but there was no difference in mortality, transfusion requirements, and overall length of stay when compared to the patients with DCM.

There are several concerns regarding the use of LVADs to support patients with severe heart failure and HCM. The smaller LV cavity size as compared to dilated cardiomyopathy may result in inadequate space for placement of the LVAD. In addition, apical hypertrophy may be present which may necessitate more extensive muscle resection at the time of implant, thereby making the procedure more complex and longer in duration. Malpositioned and hypertrophied papillary muscles may also pose a problem with LVAD cannula implantation and inflow obstruction. This may require relocation or resection of the papillary muscles in order to facilitate device implantation and allow for unobstructed flow into the inflow cannula. Lastly, once a LVAD is in place it may be particularly important for the HCM patient to be even more diligent than other patients about maintaining adequate hydration so that the LV does become underfilled and even smaller in size and LVAD inflow obstruction does not occur.

Bridging to Transplant

Supporting patients to a transplant can often prove to be a challenging task. Many strategies and therapies are used to bridge patients to transplantation, with the majority tailored to treating LV systolic dysfunction. Inotropic support in hospital or at home, LVADs, and intra-aortic balloon pumps (IABPs) are frequently used methods of support in the adult population. In pediatric patients extracorporeal membrane oxygenation (ECMO) plays a more frequent role than it does in adults. For the HCM patient with the end stage dilated form of the disease all of these treatment strategies can be and have been used with success, as the underlying anatomy in this situation is not dissimilar to patients with dilated cardiomyopathy (Fig. 20.1). However, patients with end stage restrictive HCM and smaller LV cavities are more challenging to support and bridge to transplantation. Inotropic agents are generally contraindicated and provide little or no clinical value as these patients already have normal or hyperdynamic systolic function. The small LV cavity seen in this form of HCM may not allow for LVAD (or biventricular VAD) placement or may limit the ability of the device to generate flow due to inlet obstruction. IABPs may do little to improve hemodynamics in these patients and are challenging to use long term and ECMO only has a role in supporting those who need total circulatory support over the short term rather than for an extended period of time.

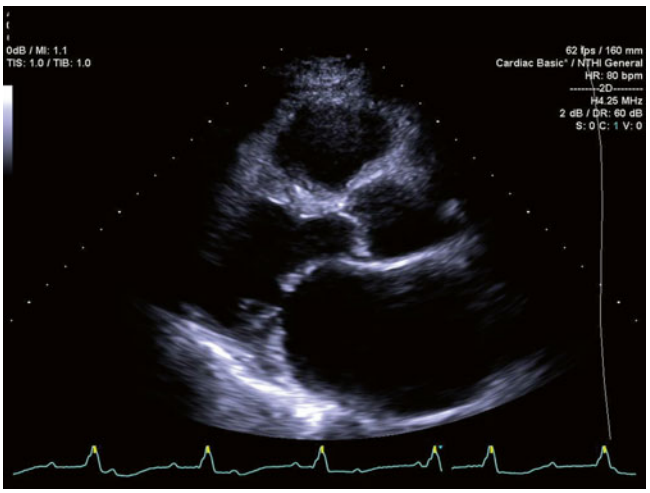

Fig. 20.1 Parasternal long axis echocardiographic view on a 55 year old man with long standing HCM who developed LV systolic dysfunction (LVEF 25 %), LV cavity enlargement and wall thinning, and progressive heart failure symptoms. Despite all medical therapies he progressed to class IV heart failure symptoms, underwent LVAD placement, and was successfully bridged to transplantation. LV size is mildly increased when adjusted for body surface area and larger than on previous echocardiograms. Septal thickness is at the upper limits of normal and the left atrium is severely enlarged

Unfortunately, the contraindication of various support strategies can place HCM patients with normal systolic function and restrictive physiology at a great disadvantage on the transplant waiting list since most listing prioritization systems throughout the world use these methods of treatment as means to justify a higher priority status. Moving HCM patients with end stage restrictive disease to a higher status becomes more difficult and waiting time on the list usually increases significantly. The same may also occur in those with life-threatening arrhythmias and less than severe heart failure symptoms. In some circumstances an exception to the usual listing rules may be requested and is frequently granted.

For those patients who may not be candidates for other forms of mechanical support or who need biventricular support, the use of a total artificial heart can be considered as a means to bridge to transplant. This device provides excellent mechanical support for severe heart failure and eliminates the concern over arrhythmias since the ventricles and most atrial tissue are removed and replaced by the device. Figure 20.2 demonstrates the case of a young man with severe HCM with massive LV hypertrophy, recurrent ventricular tachycardia and fibrillation, and moderate heart failure who underwent total artificial heart implantation as a bridge to transplantation. He was deemed to not be a candidate for other therapies or other forms of mechanical support due to the extreme nature of his disease. However, the total artificial heart has the disadvantages of not being as widely available as LVAD therapy, carrying considerable morbidity and requiring longer recovery times than LVADs, and being too large for implantation into patients who are smaller than average in size or did

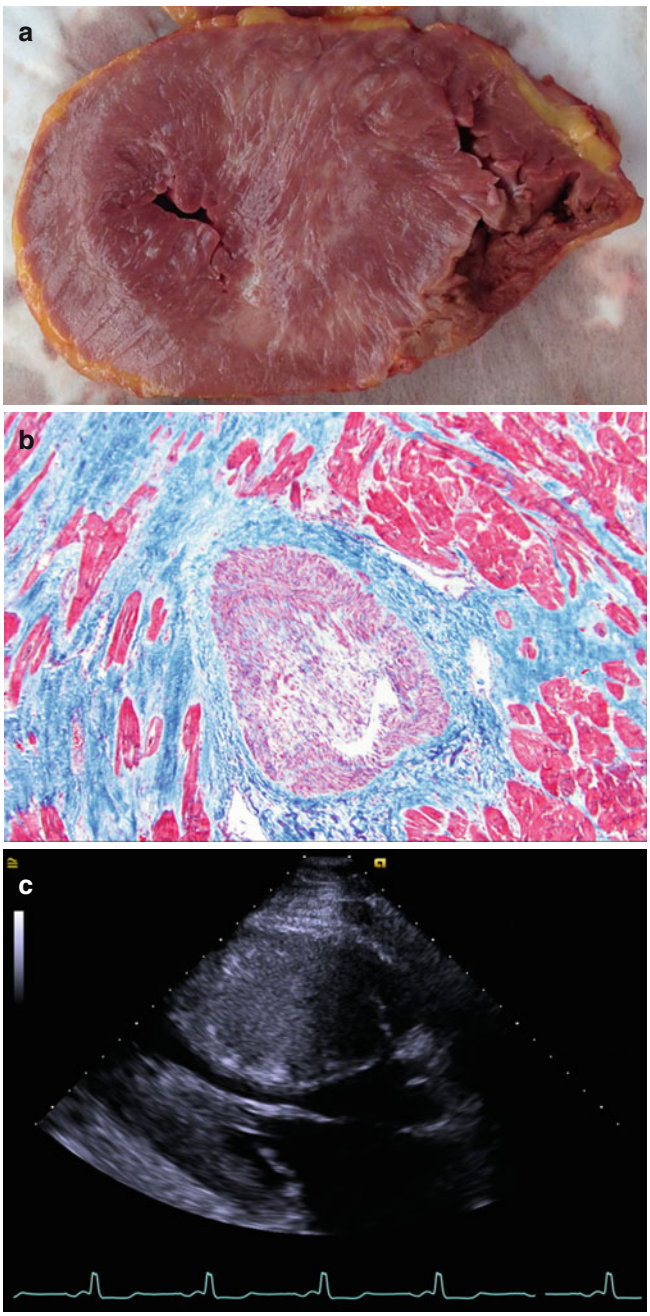

Fig. 20.2 Explanted heart from an 18 year old man with severe HCM diagnosed at age 2 who in recent years had developed massive biventricular hypertrophy, progressive NYHA class III symptoms of heart failure, a mild resting mid ventricular gradient, and increasing frequency of VT/VF and ICD shocks despite antiarrhythmic therapy. Defibrillation thresholds were high and multiple shocks at maximum device output were required to restore sinus rhythm. Due to severe nature of his disease it was determined that transplantation was the most appropriate therapy. He was deemed ineligible for LVAD implant due to the small LV cavity, massive hypertrophy involving both ventricles, and VT/VF. A total artificial heart was successfully implanted and he is awaiting HTx at the time of publication. Image (**a**) is a cross section at the mid ventricular level, showing massive hypertrophy of all walls, small LV and RV cavities, and extensive scarring. Septal dimension = 6.5 cm. Image (**b**) shows myocyte disarray, medial arteriolar hypertrophy, and extensive interstitial fibrosis on trichrome stain. Image (**c**) shows the parasternal long axis transthoracic echocardiogram image prior to implantation of the total artificial heart

not have significant dilatation of their native heart. To date there are no published reports on the use of the total artificial heart as a means of bridging HCM patients to transplant, which is also the case with BiVADs, ECMO, or the IABP.

Adult Heart Transplantation

Cardiac transplantation has proven to be an effective therapy for patients with end stage heart disease from a variety of causes who have no other treatment options (Table 20.1). There remains no other treatment that is as effective at increasing quality and quantity of life in this select patient population. For those with end stage heart failure, intractable arrhythmias, and severe ischemia transplantation can transform one from a state of cardiac debilitation to essentially normal functional capacity.

Table 20.1 Indications for heart transplantation

Severe heart failure
Refractory cardiogenic shock
Dependence on IV inotropic or LVAD support
Functional class III/IV symptoms or ACC/AHA Stage D heart failure
Peak $VO_2 \leq 10$–14 (approximately ≤50 % predicted)
Severe symptoms of ischemia not amenable or responsive to other therapies.
Recurrent symptomatic ventricular arrhythmias unresponsive to all other therapies.

Patients with HCM who undergo transplantation make up a small minority of all transplant patients but reports from various authors have shown that heart transplantation can be an effective long-term therapy for HCM patients. A recent review of the United Network of Organ Sharing (UNOS) database found that 303 (or about 1 %) of over 26,000 patients who were transplanted from 1990 to 2004 had HCM [20]. Long-term outcomes were similar to patients with dilated and restrictive cardiomyopathy and better than those with ischemic heart disease (Fig. 20.3). The 10-year survival for the HCM patients was 61 %.

A single center report by Coutu et al. has shown similar excellent long-term outcomes [21]. Thirteen of 14 patients (7 adults, or 2.7 % of adult transplant done at this center during the period of interest, and 7 children, or 15 % of their pediatric transplants) had undergone transplant for severe heart failure, while 1 had intractable ventricular tachycardia. The average age at the time of transplant was 40 years in the adult population and 13 years in the pediatric population. The median wait time on the transplant list was 9 months. Five, 10, and 15 year survival was 100, 85, and 64 %, respectively, far exceeding the most recent median 11 year survival reported by the International Society for Heart and Lung Transplantation [22]. Another single center report from Italy has reported similar excellent survival [23]. Of 21 adults with HCM listed for transplant, 18 patients (4 % of their total transplants) were eventually transplanted with 5 and 7-year survival of 94 %. Twenty of the 21 listed patients had end stage dilated HCM while 1 had hypotension and poorly tolerated atrial fibrillation. Median age was 45 years and time

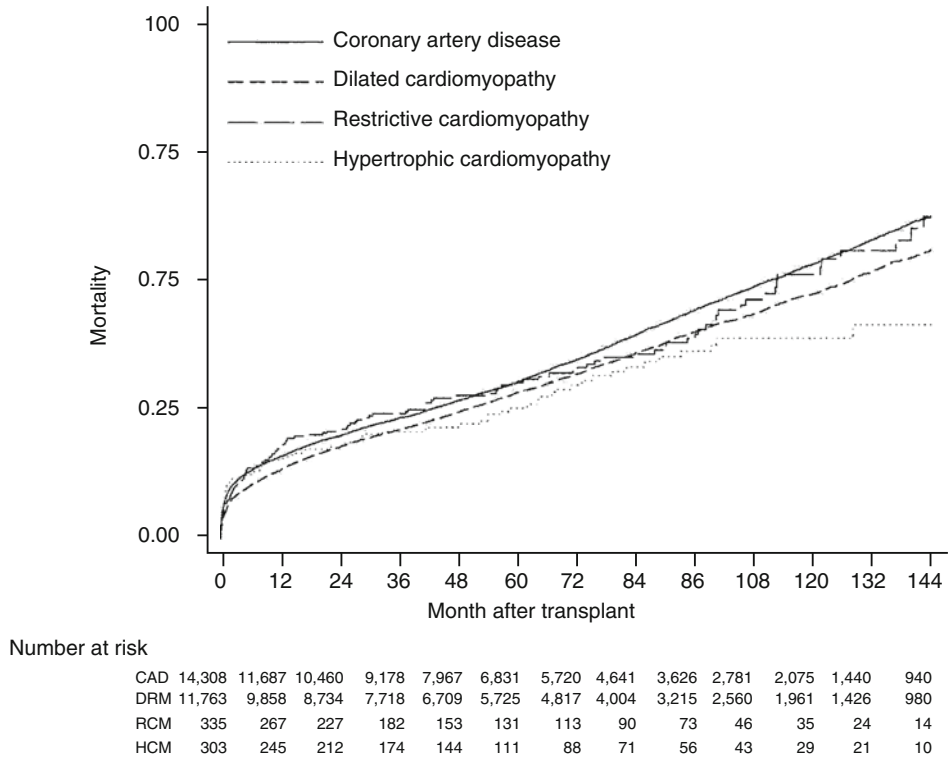

Fig. 20.3 Kaplan–Meier curves for all-cause mortality after cardiac transplantation in patients with HCM, ischemic cardiomyopathy (coronary artery disease), dilated cardiomyopathy, and restrictive cardiomyopathy (Reprinted from Maron et al. [20], with permission)

on the wait list averaged 13 months. For those with the dilated end stage form of the disease the average time from diagnosis of HCM to development of LV dilation was 10 years, while the time from onset of dilation to transplant listing was 5 years. A small series of 9 patients reported from China has also shown good results with 8 patients having good long-term outcome with few complications [24].

One of the largest single center reports evaluated 41 HCM patients who underwent heart transplantation at Columbia University Medical Center from 1999 to 2010 [25]. This represented 5 % of the total transplants done at Columbia during this time frame, which is higher than other reports and was attributed to referral bias since Columbia is both a large transplant center and a HCM referral center. Thirty-nine of the patients had severe heart failure as their indication for transplant, while the remaining 2 had intractable arrhythmia. When the HCM patients were compared to other transplant patients they were found to be younger, more frequently Caucasian, and less frequently supported with LVADs prior to heart transplantation. Interestingly, 27 of the patients had non-dilated hearts with restrictive physiology, low cardiac output, and poor exercise capacity. The time spent on the waiting list for these patients with restrictive end stage HCM was approximately twice as long as that for those with dilated end stage HCM. This difference may be reflective of the disadvantage that severe heart failure patients with normal LVEF and non-dilated hearts have while on the transplant wait list. The 1 and 5-year survival of 90 and 86 %, respectively, in HCM patients was better than those with ischemic cardiomyopathy and similar to those with other heart disease.

It appears that HCM patients undergoing transplantation have key differences when compared to those with dilated forms of cardiomyopathy. Unfortunately most reports do not contain significant pre-transplant clinical such as LV size, wall thickness, LVEF, right ventricular function, valvular function, and hemodynamics. The data from Columbia and individual clinical experience suggest that a significant portion of HCM patients who are transplanted have non dilated ventricles with normal LVEFs but restrictive physiology, low output heart failure and perhaps some degree of pulmonary hypertension. Some of these findings were also reported in a clinical and morphologic comparison of HCM, dilated cardiomyopathy, and ischemic cardiomyopathy patients undergoing heart transplantation [26]. The patients with HCM had a longer period of time from symptom onset to transplant (which may have been related to longer wait times), lower heart weight, and smaller LV cavity size but thicker and more scarred septums, higher LVEFs (45 % vs 20 % for non HCM patients), higher pulmonary artery and pulmonary capillary wedge pressures and larger left atrial dimensions. Unfortunately, there was a significant amount of variation within the 3 groups so in many cases the clinical and morphologic features were not specific enough in differentiating patients in one group from those in another.

Pediatric Heart Transplantation

HCM presenting in the first year of life is associated with increased mortality and morbidity especially when associated with symptoms of heart failure. In addition, children with end-stage dilated HCM, restrictive HCM, inborn errors of metabolism and malformation syndromes are at increased risk of death or need for transplantation [27]. Small LV cavity size and massive LV hypertrophy are also linked to worse outcomes in the very young [28].

Heart transplantation in children is performed less frequently than in adults and HCM as the reason for transplant represents a similarly small percentage of the total number of transplants in children as in adults. Patients with HCM appear to represent approximately 2–3 % of the total patients listed for transplant according to data from the Organ Procurement and Transplantation Network (OPTN) database and the Pediatric Heart Transplant Study [29, 30]. There may be a higher mortality rate for children on the transplant waiting list, perhaps because of challenges in supporting and bridging them to transplant compared to patients with other forms of heart disease. At the time of transplant pediatric HCM patients are more frequently on ECMO and ventilator support and fewer have LVADs. Despite these challenges and difficulties, heart transplantation for children with HCM has been shown to be a viable therapy for children of all ages, including newborns who may have been diagnosed in utero and infants [28, 31]. Survival may be worse than that of children with other forms of heart disease and that of the average for adults, but most of this difference is driven by worse outcomes in those less than 1 year of age. Other risks for death and worse outcome include ventilator or ECMO support and UNOS status 1 at the time of transplant, all markers of a more critically ill patient whom one would expect to be at higher risk [29, 30].

Conclusion

Hypertrophic cardiomyopathy is a heterogeneous disease with variable clinical presentation, anatomical morphology, and long-term clinical course. A minority of patients with HCM may develop LV cavity dilatation and LV systolic dysfunction, a situation that should prompt aggressive medical therapy due to its ominous prognosis. Another group of HCM patients have severe heart failure secondary to diastolic dysfunction and restrictive physiology, a clinical situation with few treatment options. Mechanical support and transplantation are two possible options for HCM patients with severe heart failure or intractable ventricular arrhythmias who have failed all other treatments.

Outcomes of adult HCM patients undergoing transplantation appear to be better than the average for all transplant patients, whereas that for the pediatric HCM patient is worse than other children undergoing transplantation for other indications, primarily due to significantly worse outcomes in patients less than 1 year of age. Prompt recognition of the situation and severity of those with end stage disease is essential, and referral to a HCM center and or transplant center should be strongly considered.

Clinical Pearls

- LV dilation and systolic dysfunction in a patient with HCM is an ominous sign.
- With the onset of end stage dilated HCM medical therapy may change significantly and negative inotropic agents other than beta blockers should be discontinued if possible.
- Bridging patients with diastolic dysfunction and restrictive physiology to transplant will usually require longer wait times and may necessitate more frequent use of certain bridging strategies such as the total artificial heart, intra-aortic balloon pump, and application for exceptions to the usual UNOS listing statuses.
- Referrals to HCM and transplant centers that are made early may not alter immediate treatment but those made too late may greatly limit treatment options.
- LVAD use is an option for those with end-stage dilated HCM either for DT or BTT.
- Approximately 1–2 % of all heart transplants are done for HCM and probably at most 1–2 % of diagnosed HCM patients will be considered for or undergo heart transplantation.

References

1. Biagini E, Coccolo F, Ferlito M, Perugini E, Rocchi G, Bacchi-Reggiani L, et al. Dilated-hypokinetic evolution of hypertrophic cardiomyopathy: prevalence, incidence, risk factors, and prognostic implications in pediatric and adult patients. J Am Coll Cardiol. 2005;46(8):1543–50.
2. Harris KM, Spirito P, Maron MS, Zenovich AG, Formisano F, Lesser JR, et al. Prevalence, clinical profile, and significance of left ventricular remodeling in the end-stage phase of hypertrophic cardiomyopathy. Circulation. 2006;114(3):216–25.
3. Spirito P, Maron BJ, Bonow RO, Epstein SE. Occurrence and significance of progressive left ventricular wall thinning and relative cavity dilatation in hypertrophic cardiomyopathy. Am J Cardiol. 1987;60(1):123–9.
4. Thaman R, Gimeno JR, Murphy RT, Kubo T, Sachdev B, Mogensen J, et al. Prevalence and clinical significance of systolic impairment in hypertrophic cardiomyopathy. Heart. 2005;91(7):920–5.
5. Hamada T, Kubo T, Kitaoka H, Hirota T, Hoshikawa E, Hayato K, et al. Clinical features of the dilated phase of hypertrophic cardiomyopathy in comparison with those of dilated cardiomyopathy. Clin Cardiol. 2010;33(7):E24–8.
6. Olivotto I, Maron BJ, Appelbaum E, Harrigan CJ, Salton C, Gibson CM, et al. Spectrum and clinical significance of systolic function and myocardial fibrosis assessed by cardiovascular magnetic resonance in hypertrophic cardiomyopathy. Am J Cardiol. 2010;106(2):261–7.
7. Maron MS. Clinical utility of cardiovascular magnetic resonance in hypertrophic cardiomyopathy. J Cardiovasc Magn Reson. 2012;14:13.
8. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH, Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation. 1991;83(3):778–86.
9. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey Jr DE, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;62(16):e147–239.
10. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, et al. 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2011;58(25):e212–60.
11. Rogers DPS, Marazia S, Chow AW, Lambiase PD, Lowe MD, Frenneaux M, et al. Effect of biventricular pacing on symptoms and cardiac remodelling in patients with end-stage hypertrophic cardiomyopathy. Eur J Heart Fail. 2008;10(5):507–13.
12. Ashrafian H, Mason MJ, Mitchell AG. Regression of dilated-hypokinetic hypertrophic cardiomyopathy by biventricular cardiac pacing. Europace. 2007;9(1):50–4.
13. Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, et al. Long-term use of a left ventricular assist device for end-stage heart failure. N Engl J Med. 2001;345(20):1435–43.
14. Slaughter MS, Pagani FD, McGee EC, Birks EJ, Cotts WG, Gregoric I, et al. HeartWare ventricular assist system for bridge to transplant: combined results of the bridge to transplant and continued access protocol trial. J Heart Lung Transplant. 2013;32(7):675–83.
15. Miller LW, Pagani FD, Russell SD, John R, Boyle AJ, Aaronson KD, et al. Use of a continuous-flow device in patients awaiting heart transplantation. N Engl J Med. 2007;357(9):885–96.
16. Cho YH, Deo SV, Topilsky Y, Grogan MA, Park SJ. Left ventricular assist device implantation in a patient who had previously undergone apical myectomy for hypertrophic cardiomyopathy. J Card Surg. 2012;27(2):266–8.
17. Wynne E, Bergin JD, Ailawadi G, Kern JA, Kennedy JLW. Use of a left ventricular assist device in hypertrophic cardiomyopathy. J Card Surg. 2011;26(6):663–5.
18. Muthiah K, Phan J, Robson D, Macdonald PS, Keogh AM, Kotlyar E, et al. Centrifugal continuous-flow left ventricular assist device in patients with hypertrophic cardiomyopathy: a case series. ASAIO J. 2013;59(2):183–7.
19. Topilsky Y, Pereira NL, Shah DK, Boilson B, Schirger JA, Kushwaha SS, et al. Left ventricular assist device therapy in patients with restrictive and hypertrophic cardiomyopathy. Circ Heart Fail. 2011;4(3):266–75.
20. Maron MS, Kalsmith B, Udelson JE, Wenjun L, DeNofrio D. Survival after cardiac transplantation in patients with hypertrophic cardiomyopathy. Circ Heart Fail. 2010;3:574–9.
21. Coutu M, Perrault LP, White M, Pelletier GB, Racine N, Poirier NC, et al. Cardiac transplantation for hypertrophic cardiomyopathy:

a valid therapeutic option. J Heart Lung Transplant. 2004; 23(4):413–7.
22. Lund LH, Edwards LB, Kucheryavaya AY, Dipchand AI, Benden C, Christie JD, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirtieth Official Adult Heart Transplant Report—2013; focus theme: age. J Heart Lung Transplant. 2013; 32(10):951–64.
23. Biagini E, Spirito P, Leone O, Picchio FM, Coccolo F, Ragni L, et al. Heart transplantation in hypertrophic cardiomyopathy. Am J Cardiol. 2008;101(3):387–92.
24. Huang XS, Chen LW, Pan YC, Lin F, Wang QM, Huang ZY, et al. Outcome post orthotopic heart transplantation for patients with end-stage hypertrophic cardiomyopathy. Zhonghua Xin Xue Guan Bing Za Zhi. 2011;39(2):114–7.
25. Kato TS, Takayama H, Yoshizawa S, Marboe C, Schulze PC, Farr M, et al. Cardiac transplantation in patients with hypertrophic cardiomyopathy. Am J Cardiol. 2012;110(4):568–74.
26. Waller Md TA, Hiser Md WL, Capehart Md JE, Roberts Md WC. Comparison of clinical and morphologic cardiac findings in patients having cardiac transplantation for ischemic cardiomyopathy, idiopathic dilated cardiomyopathy, and dilated hypertrophic cardiomyopathy. Am J Cardiol. 1998;81(7):884–94.
27. Lipshultz SE, Orav EJ, Wilkinson JD, Towbin JA, Messere JE, Lowe AM, et al. Risk stratification at diagnosis for children with hypertrophic cardiomyopathy: an analysis of data from the Pediatric Cardiomyopathy Registry. Lancet. 2013;382(9908):1889–97.
28. Ragni L, Biagini E, Picchio FM, Prandstraller D, Leone O, Berardini A, et al. Heart transplantation in infants with idiopathic hypertrophic cardiomyopathy. Pediatr Transplant. 2009;13(5): 650–3.
29. Gajarski R, Naftel DC, Pahl E, Alejos J, Pearce FB, Kirklin JK, et al. Outcomes of pediatric patients with hypertrophic cardiomyopathy listed for transplant. J Heart Lung Transplant. 2009;28(12):1329–34.
30. Singh TP, Almond CS, Piercey G, Gauvreau K. Current outcomes in US children with cardiomyopathy listed for heart transplantation. Circ Heart Fail. 2012;5(5):594–601.
31. Prandstraller D, Leone O, Biagini E, Picchio FM, Rapezzi C. Prenatal echographic recognition of hypertrophic cardiomyopathy leading to heart transplantation in the newborn. Eur Heart J. 2008;29(7):845.

Approach to the Initial and Follow-Up Visits

21

Paolo Spirito and Camillo Autore

Abstract

This chapter offers a practical approach to the management of patients with hypertrophic cardiomyopathy (HCM). The first section discusses in detail the initial patient evaluation. The second section examines the clinical criteria on which to base the timing of follow-up visits and the treatment strategies with which to confront disease progression. Algorithms summarize the general assessment and management of HCM patients at initial evaluation and during follow-up. A section of this chapter is also dedicated to patient education regarding lifestyle, family screening for HCM, and genetic testing and counseling.

Keywords

Practical approach • Management • Hypertrophic cardiomyopathy

Key Points

- The initial approach to the evaluation of patients with HCM includes: (A) Reconstruction of family history of the disease focused on identification of affected relatives and sudden death events potentially related to HCM; (B) Assessment of presence and severity of HCM-related symptoms; (C) Evaluation of a recent 12-lead electrocardiogram and 24-h ambulatory (Holter) ECG recording, assessment of cardiac morphology and function by imaging techniques (echocardiography and cardiac magnetic resonance) and, in selected patients, determination of functional capacity using exercise testing.
- The distinction between obstructive and non-obstructive HCM represents a key point in the clinical evaluation of patients with HCM, because disease management is strongly influenced by the presence or absence of LV outflow obstruction and patients with the obstructive form are more likely to develop important heart failure symptoms.
- Risk stratification for sudden death is mandatory in all HCM patients and is generally quantified as high, intermediate or low, based on the identification of a number of major HCM risk factors, as well as the evaluation of the prognostic strength of each individual risk factor.
- Given the lifelong implications of HCM for the patients and their families, issues such as lifestyle, physical activity, family screening, and genetic counseling need to be addressed with the greatest clarity and represent an integral part of the initial clinical evaluation.

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- Patient follow-up is based on serial evaluations and focused on the identification of possible signs of clinical deterioration, including progression of either symptoms and/or morphologic and functional cardiac abnormalities, development of arrhythmias, and changes in the risk profile for sudden death.

Scope of This Chapter

Hypertrophic cardiomyopathy (HCM) is a genetic cardiovascular disease characterized by a greatly diverse clinical presentation and natural history [1, 2]. This marked heterogeneity makes patient management particularly difficult. Purpose of this chapter is to offer a practical and systematic approach to the clinical evaluation and management of patients with HCM. This approach applies to patients with established HCM or a high suspicion of the disease and is based on management strategies used at centers with specific expertise in HCM.

The initial patient evaluation is particularly important, as it represents a reference for subsequent visits. Therefore, the first section of this chapter will discuss in detail the main aspects of the initial patient evaluation, including: confirmation of the diagnosis of HCM, assessment of LV morphology and function, evaluation of symptoms, risk stratification for sudden death, selection of treatment strategy, and patient education regarding lifestyle modification, family screening and genetic testing. The second section of this chapter will discuss how to plan a follow-up program on the basis of the severity of the patient clinical presentation and revise the treatment strategy in relation to disease progression. Inevitably, many parts of the present chapter will cover issues already discussed in detail in previous sections of this book. The aim here is to condense these complex subjects into a format that summarizes the most important clinical points in a practical manner and can be used in the assessment and management of individual patients and families with HCM.

Initial Patient Evaluation

In the most recent ACCF/AHA guidelines, HCM is defined as "a disease state characterised by unexplained LV hypertrophy associated with nondilated ventricular chambers in the absence of another cardiac or systemic disease that itself would be capable of producing the magnitude of hypertrophy evident in a given patient" [1]. Therefore, the first step in the initial patient evaluation is to verify that the clinical presentation is consistent with the definition of the disease reported in the Guidelines. Because this definition is based on cardiac morphologic features, cardiac imaging plays a major role in the initial patient evaluation.

Confirmation of the Diagnosis of HCM

The general approach to the confirmation of the diagnosis of HCM is outlined in Fig. 21.1. In the great majority of patients with HCM, the 12-lead electrocardiogram (ECG) shows QRS and/or S-T segment abnormalities [2–4]. Indeed, an abnormal ECG is often the alteration that has first raised the suspicion of HCM [5]. Therefore, it is important to begin the initial patient evaluation by examining the ECG. Electrocardiographic abnormalities such as deep Q waves (>0.3 mV) with a short duration and/or deep negative T waves in the infero-lateral or precordial leads strongly support a diagnosis of primary cardiomyopathy and exclude ventricular hypertrophy secondary to systemic arterial hypertension or valvular heart disease. On the other hand, absence of ECG abnormalities does not exclude HCM, because some patients have mild and localized ventricular hypertrophy involving a small portion of the left ventricle that can be detected only by cardiac imaging [6, 7].

Clinical evaluation proceeds with a 2-dimensional and Doppler echocardiographic study. The 2-dimensional echocardiogram must be performed with great care to assess the magnitude and distribution of LV hypertrophy, presence and severity of anterior systolic movement (SAM) of the mitral valve, and left atrial dimension [1, 2, 8]. In many patients with HCM, LV remodeling due to ventricular wall and papillary muscle hypertrophy causes secondary alterations of the mitral valve apparatus with elongation and anterior displacement of the chordae and leaflets, which may favor the SAM of the valve into the LV outflow tract and outflow obstruction [9]. Identification of elongated and anteriorly displaced mitral valve leaflets with marked SAM and LV outflow obstruction strongly supports the diagnosis of HCM, because these morphologic and functional alterations are absent in patients with secondary ventricular hypertrophy, and uncommon in patients with ventricular hypertrophy associated with genetic diseases such as storage cardiomyopathies and Fabry disease [10, 11]. Doppler echocardiography allows the assessment of the presence and severity of the LV outflow gradient, mitral or aortic valve regurgitation, and LV diastolic filling abnormalities [1, 2]. Of note, LV outflow obstruction in patients with HCM is quantified in terms of maximum peak instantaneous gradient, rather than mean gradient [12]. The Valsalva maneuver should be performed in each patient to measure the increase in the gradient or to elicit an outflow gradient that may be absent under basal conditions [13]. In patients with heart failure symptoms during routine physical activities and without a significant LV outflow gradient under basal conditions or during the Valsalva

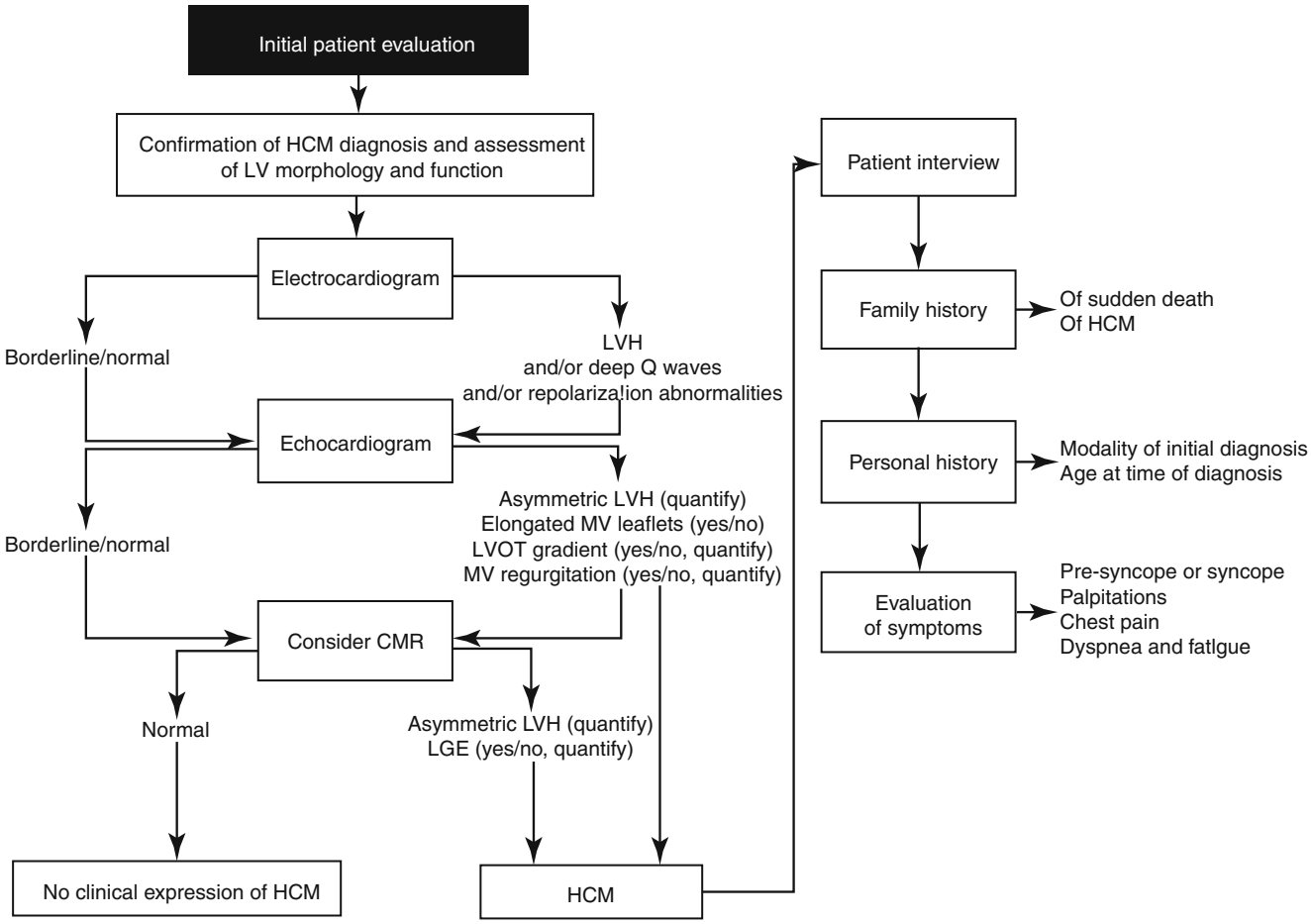

Fig. 21.1 Schematic representation of the general approach to the initial evaluation of patients with hypertrophic cardiomyopathy (*HCM*). *CMR* cardiovascular magnetic resonance, *LGE* late gadolinium enhancement, *LV* left ventricular, *LVH* left ventricular hypertrophy, *LVOT* left ventricular outflow tract, *MV* mitral valve

maneuver, Doppler echocardiography in combination with exercise testing may help to document an exercise-induced gradient [13]. Identification of an inducible LV outflow gradient may have important clinical implications, because in many patients without a gradient under basal conditions symptoms of dyspnea and fatigue during physical activities or after an abundant meal may be explained by the development of an outflow gradient in such circumstances [1, 2, 13].

In recent years, the high resolution of cardiovascular magnetic resonance (CMR) has proved superior to echocardiography in the assessment of the morphologic features of HCM [14]. This technique has also shown that morphologic alterations associated with HCM may not be identified by echocardiography when hypertrophy is confined to certain areas of the left ventricle, such as the anterolateral free wall or apex [14–16]. Therefore, at most HCM centers, CMR is routinely performed as an integral part of the initial patient evaluation to assess LV morphology and magnitude and distribution of LV hypertrophy. In addition, contrast-enhanced CMR with late gadolinium enhancement (LGE) permits the identification of areas of myocardial fibrosis in patients with HCM [17–19]. Several studies have documented that patients with LGE tend to have a more unfavorable prognosis than those without LGE [20–22].

Patient Interview

Family and Patient History of HCM. In most patients, HCM is a genetically transmitted familial disease [1, 2, 23, 24]. Therefore, the patient interview begins with the family history (Fig. 21.1). A history of sudden and unexpected death in young relatives (generally defined as <50 years of age) may have important implications in patient management. Because sudden deaths that occurred decades earlier are often not mentioned by the patient, family history must be investigated meticulously. When a history of one or more sudden and unexpected deaths is identified in the family, detailed information needs to be gathered regarding age and circumstances at the time of the events in order to assess the likelihood that these deaths may have been HCM-related.

As part of the patient personal history, it is important to ascertain the modality of the initial diagnosis of HCM, as a diagnosis during clinical evaluation for development of symptoms is usually associated with a less favorable long-term clinical course than an incidental identification of the disease during routine check-up or family screening. Age at the time of diagnosis is also important and may offer prognostic information, because patients diagnosed with HCM at a young age appear to have a less favorable long-term clinical course and prognosis than those diagnosed later in life [25, 26].

Evaluation of Symptoms. Many patients with HCM have no or only mild symptoms [27–30]. However, when present, symptoms are typically variable and may include pre-syncope or syncope, palpitations, chest pain and dyspnea. Therefore, it is useful to follow a systematic approach when enquiring for the presence of HCM-related symptoms. Below, symptoms are addressed beginning with the least common and ending with dyspnea and fatigue, which are the most common symptoms and have an important impact on patient clinical course and quality of life.

Syncope and pre-syncope are relatively infrequent in patients with HCM but may have important prognostic implications depending on the characteristics of the event. Recent and unexplained syncopal episodes that have occurred in circumstances not clearly consistent with a neurally mediated event have been reported to be associated with an increased risk of sudden death [31]. Such episodes include syncope without apparent explanation at rest, or during ordinary activity, or during an intense effort. Neurally mediated vasovagal syncope has virtually no prognostic implications [31]. Pre-syncope may be reported by patients as lightheadedness/near fainting or the perception that a loss of consciousness was imminent but did not occur. No systematic data are available regarding the prognostic implications of symptoms such as lightheadedness or near fainting (pre-syncope). However, the potential clinical importance of pre-syncopal episodes should not be underestimated and needs to be interpreted within the context of the patient overall clinical presentation [32].

Palpitations are reported by the majority of patients with HCM. Therefore, the interpretation of the clinical significance of this symptom is based on a careful reconstruction of its characteristics, including incidence, duration, intensity, and possible associated symptoms such as shortness of breath, near fainting, or fainting. In the majority of patients with HCM, palpitations are of brief duration and not associated with other symptoms. However, despite a meticulous questioning, the clinical interpretation of reported palpitations remains uncertain in the absence of Holter ECG documentation of the cardiac rhythm at the time of symptoms.

Chest pain or chest discomfort is often reported by patients with HCM. In some patients, the episodes of chest pain are intense, similar in their characteristics to angina pectoris, and develop either at rest or with exertion. More commonly chest pain symptoms are mild, prolonged and atypical for angina pectoris. The available data indicate that myocardial ischemia caused by microvascular dysfunction occurs in patients with HCM [33–35]. This abnormality may play a role in the chest pain symptoms [35, 36]. However, in the absence of associated epicardial coronary artery disease, the prognostic implications of chest pain remain unclear.

Shortness of breath and fatigue are the symptoms that more accurately reflect the severity of the functional abnormalities in patients with HCM. Because management decisions are based on the severity of symptoms [1, 2], and there is a strong and independent relationship between New York Heart Association (NYHA) functional class and prognosis in HCM [37–39], it is particularly important to assess with great care the level of the patient's functional limitation. In selected patients, exercise testing and determination of maximum oxygen consumption may be useful to assess functional capacity more accurately [1, 2, 40].

Management of Symptoms

At this point in the initial patient evaluation, the physician has confirmed the diagnosis of HCM and knows in detail the patient clinical presentation, including personal and family history, characteristics and severity of symptoms, and cardiac morphology and function. The general approach to subsequent management decisions is outlined in Fig. 21.2. Because of the major role of LV outflow obstruction in the clinical course of HCM, patient management is strongly influenced by the presence or absence of outflow obstruction.

LV Outflow Obstruction

In patients with HCM, LV outflow obstruction causes an increase in LV systolic pressure and leads to important functional abnormalities, including elevation of diastolic filling pressure, prolongation of ventricular relaxation, mitral valve regurgitation, left atrial dilatation, decrease in forward output, and myocardial ischemia [1, 2, 41–43]. Of the patients with HCM evaluated at referral centers, 20–25 % have LV outflow obstruction under basal conditions (defined as a maximum peak instantaneous gradient ≥30 mmHg) and 30–35 % may spontaneously generate an outflow gradient during daily activities that can usually be elicited by the Valsalva maneuver or exercise [1, 12, 13]. Several studies have shown that LV outflow obstruction under basal conditions is a strong and independent predictor of disease progression to severe heart failure and atrial fibrillation, as well as death secondary to heart failure or stroke [1, 38, 39]. No data are available regarding the prognostic implications of LV outflow gradients elicited with provocative maneuvers in patients without outflow

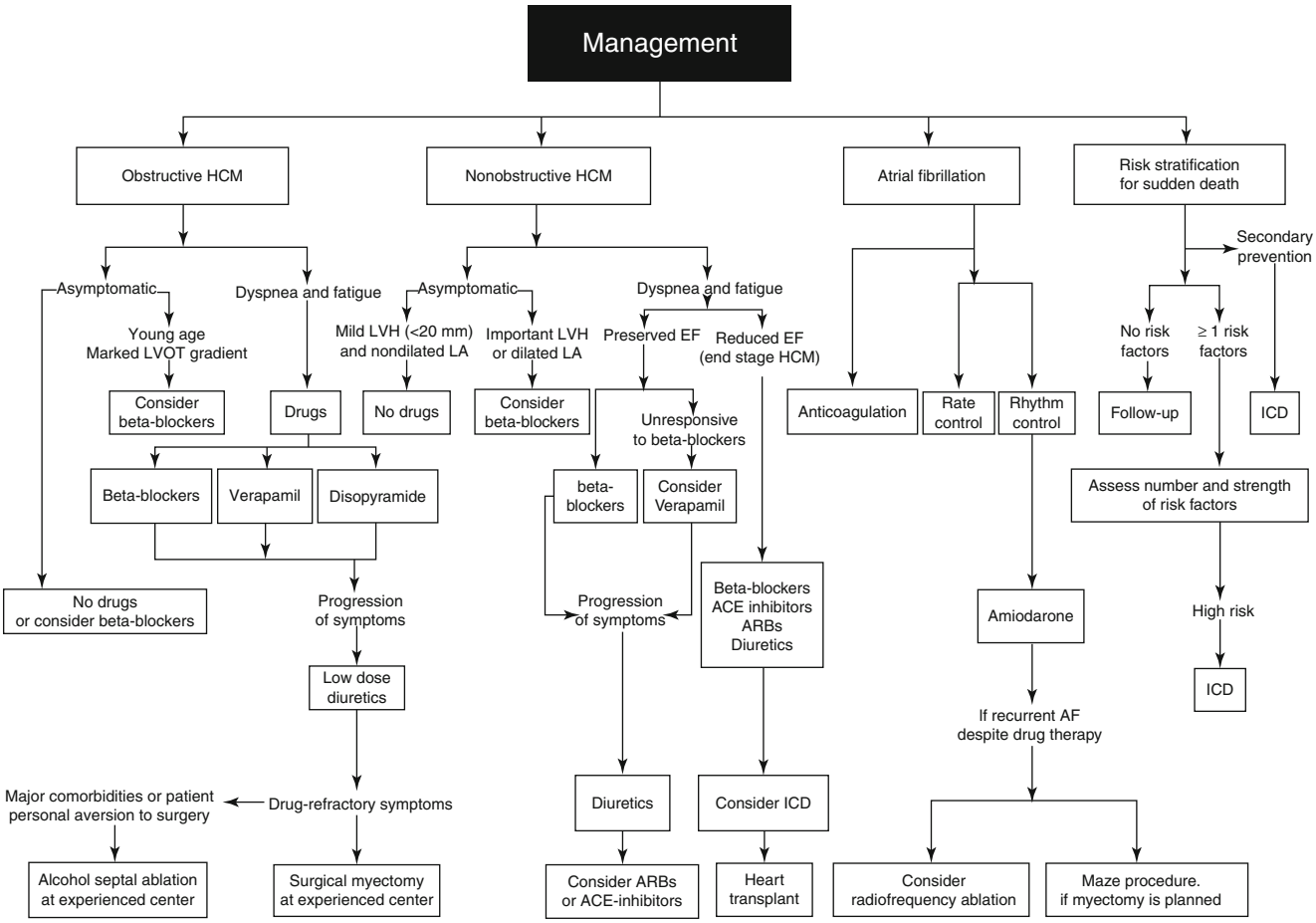

Fig. 21.2 Management of patients with hypertrophic cardiomyopathy (*HCM*) at the time of the initial evaluation. *ARBs* angiotensin receptor blockers, *AF* atrial fibrillation, *EF* ejection fraction, *ICD* implantable cardioverter-defibrillator, *LA* left atrium, *LVH* left ventricular hypertrophy, *LVOT* left ventricular outflow tract

gradients under basal conditions. However, in clinical practice, management strategies are similar in patients with important symptoms of heart failure and either resting or physiologically induced outflow gradients [1].

LV outflow obstruction and symptoms of dyspnea or fatigue. In patients with LV outflow obstruction and symptoms of dyspnea or fatigue, beta-blocking drugs are the medication of choice [1, 2, 4, 44]. Administered at standard dosages, beta blockers may alleviate symptoms through their negative inotropic and chronotropic effects. In patients unable to tolerate beta-blocking drugs or unresponsive to these medications, verapamil may have favorable effects on symptoms [2, 4, 44, 45]. However, in patients with high outflow gradients, verapamil should be used with caution and started at low dosages, because the vasodilative effects of the drug may increase the gradient [1, 2, 46]. When important symptoms of heart failure persist despite treatment with beta blockers or verapamil, diuretics at relatively low dosages may be useful [1, 2, 4]. In some patients who do not respond to beta blockers and verapamil, disopyramide may prove effective in reducing the LV outflow gradient and improving symptoms [1]. However, because of its potential proarrhythmic effects, this medication should be initiated in-hospital and with cardiac monitoring [1]. High-dose diuretics and vasodilator therapy should be avoided or used with caution in patients with resting or provocable obstruction, as these medications may increase outflow obstruction by reducing LV filling, or afterload, respectively [1, 2, 4].

Patients with symptoms uncontrolled by medications and marked gradients (≥50 mmHg), either at rest or with provocation, are candidates to surgical septal myectomy or percutaneous alcohol septal ablation [1, 2]. In recent years, the selection criteria for these two techniques have been a source of controversy. However, the recent ACCF/AHA guidelines report that "Surgical septal myectomy, when performed in experienced centers, can be beneficial and is the first consideration for the majority of eligible patients with HCM with severe drug-refractory symptoms and LV outflow obstruction", and that "When surgery is contraindicated or the risk is considered unacceptable because of serious comorbidities or

advanced age, alcohol septal ablation, when performed in experienced centers, can be beneficial in eligible adult patients with HCM with LV outflow obstruction and severe drug-refractory symptoms (usually NYHA classes III-IV)" [1].

Therefore, surgical myectomy is the primary treatment option and the preferred approach in young patients, while alcohol septal ablation may be preferable in the elderly, or in patients with major comorbidities or strong personal aversion to surgery. However, it is important to reiterate here, as stated by the HCM guidelines, that operator and institutional experience are key determinants of successful outcome for either surgical myectomy or alcohol septal ablation, and all potential candidates to invasive therapy for relief of outflow obstruction must be objectively informed regarding the availability, advantages and limitations of these two techniques.

LV outflow obstruction and no or only mild symptoms. There is no definitive evidence that beta-blocking drugs reduce the LV outflow gradient under basal conditions, delay disease progression or improve prognosis in HCM patients with LV outflow obstruction and no or mild symptoms [1, 2]. However, the decision to initiate pharmacologic treatment in asymptomatic children and adults with outflow tract gradients is justified by the expectation that medications, by reducing heart rate and prolonging diastole, may have a favorable effect on diastolic function and delay the onset of symptoms [1, 2]. It is also important to educate the patients with outflow tract gradients regarding the mechanism of LV outflow obstruction and how to avoid environmental situations that may lead to a marked increase in the LV outflow gradient, as summarized in our section "Patient Education and Counseling".

Nonobstructive HCM

A large proportion of patients with HCM are asymptomatic and have mild LV hypertrophy (<20 mm) and no resting or provocable LV outflow obstruction [27–29]. Many of these patients will have a favorable clinical course with no or mild symptoms and a normal life expectancy [27–29, 47]. However, a minority of asymptomatic patients with the nonobstructive form of HCM may have a less favorable clinical course [1, 2, 41]. Left atrial dimension has an important role in the identification of these latter patients, because an enlarged left atrium usually reflects important diastolic dysfunction and is associated with an increased risk of developing symptoms of heart failure and/or atrial fibrillation [48–50]. Therefore, an enlarged left atrium may justify treatment with beta-blocking drugs even in asymptomatic or mildly symptomatic patients with nonobstructive HCM.

A minority of patients with nonobstructive HCM present with severe symptoms of heart failure [1, 2, 4, 41]. Some of these patients have important diastolic dysfunction with marked left atrial dilatation and preserved systolic function [2, 4, 41]. Such patients have limited therapeutic options (Fig. 21.2). Beta-blocking drugs or verapamil are useful to control heart rate and prolong ventricular diastolic filling [1, 2, 4, 41]. Diuretics and ACE-inhibitors or angiotensin receptor blockers are indicated for treatment of congestive heart failure symptoms [1, 2, 4, 43, 44]. However, the dosage of diuretics should be increased with caution, because patients with severe diastolic dysfunction may need relatively high filling pressures to achieve adequate ventricular filling. Anticoagulation is indicated in HCM patients with documented paroxysmal or chronic AF [1, 2, 50]. Because asymptomatic and prolonged episodes of low rate AF may occur in patients with a markedly dilated left atrium treated with high dosages of beta-blocking drugs or verapamil, anticoagulant therapy for prevention of thromboembolic events may be considered in such patients, even in the absence of documented AF.

A proportion (3–5 %) of patients with nonobstructive HCM and severe heart failure symptoms are in the end stage phase of the disease, characterized by LV remodeling with progressive wall thinning, cavity enlargement and systolic dysfunction [51–53]. In patients with end stage evolution, treatment should be changed to standard medications for heart failure associated with systolic dysfunction, including diuretics, ACE-inhibitors or angiotensin receptor blockers, beta-blocking drugs and other indicated medications [1, 2] (Fig. 21.2). Anticoagulation for prevention of thromboembolic events may be considered. Ultimately, heart transplantation may become necessary in these patients with end stage evolution [1, 2, 4]. In general, heart transplantation is indicated in patients with end stage evolution and advanced heart failure symptoms that are refractory to all other interventions. Long-term outcome after heart transplant in patients with HCM is favorable and does not differ from that of patients with idiopathic dilated cardiomyopathy [53–55]. Because the risk of sudden death is increased in patients with end stage evolution, prophylactic ICD implantation may be considered [53].

Atrial Fibrillation

Atrial fibrillation is a particularly important arrhythmia in HCM. It develops in 20–25 % of adult patients followed at referral centers and is a predictor of unfavorable prognosis with increased risk of heart failure, death and stroke [50, 56, 57]. The risk of developing AF is higher in patients with LV outflow obstruction and/or a dilated left atrium, and it increases with age [50, 58]. While some patients may remain asymptomatic during episodes of AF, many develop symptoms such as prolonged palpitations, shortness of breath, or dizziness. However, the cause-effect relationship between paroxysmal AF and such symptoms can be proved only in those patients in whom 12-lead ECG or Holter ECG documentation of AF is available at the time of symptoms. Hence, patients experiencing recurrent episodes of prolonged

palpitations should be advised to go to an emergency department, without waiting for spontaneous remission of symptoms, primarily for the purpose of obtaining 12-lead ECG documentation of the underlying arrhythmia.

Amiodarone is the most effective antiarrhythmic agent for the prevention of recurrent AF in patients with HCM [1, 2]. The Maze procedure may be considered during surgical myectomy in patients with a history of paroxysmal AF [1]. Radiofrequency ablation may play a role in the management of AF, but the long term benefits of this procedure have not been verified [1]. Chronic AF is often well tolerated, particularly in older patients, if the heart rate is adequately controlled. Beta-blocking drugs or non-dihydropyridine calcium channel blockers are usually efficacious in controlling the heart rate in HCM patients with chronic atrial fibrillation [1, 2].

The risk of thromboembolic events is high in patients with HCM and AF [50, 56, 57]. Therefore, paroxysmal, persistent, or chronic AF is a strong indication to anticoagulation therapy [50, 57]. Because even brief recurrent episodes of AF in HCM have been associated with an important risk of systemic embolization, the threshold for the initiation of anticoagulation should be low and a single episode of AF may justify taking into consideration anticoagulant therapy [1, 2].

Risk Stratification and Prevention of Sudden Death

A systematic approach to risk stratification for sudden death has become mandatory in all patients with HCM in view of the documented efficacy of the ICD for sudden death prevention in this disease, as well as the inefficacy of antiarrhythmic drugs and beta-blockers in reducing the risk of sudden death [1, 2, 59–61]. Although only a minority of patients with HCM die suddenly, all are at risk for sudden and unexpected death independently of the presence or absence of symptoms, including those without sudden death risk factors [59–61]. Therefore, all patients with HCM should undergo risk stratification and be informed that no patient with this disease can be considered at zero risk for sudden death [1, 2, 59–61].

Patients with HCM and prior documented cardiac arrest, ventricular fibrillation, or sustained ventricular tachycardia are candidates to the ICD for secondary prevention of sudden death [1, 2, 60, 62]. Identification of candidates to the ICD for primary prevention of sudden death remains less certain, given the many difficulties in the investigation of risk stratification in HCM, including the relatively uncommon occurrence of the disease, low rate of events, diversity of the clinical presentation in the individual patient and affected families, as well as the variable definition of risk factors in the literature. In clinical practice, risk is stratified as high, intermediate, or low based on a number of major conventional risk factors, including history of ≥1 HCM-related sudden deaths in family members <50 years of age, massive LV hypertrophy (maximal wall thickness ≥30 mm), recurrent or prolonged nonsustained ventricular tachycardia (VT) on ambulatory ECG monitoring, and unexplained (non-vasovagal) recent syncope [1, 2, 31, 37, 59, 61, 63–65]. A failure to increase blood pressure by at least 20 mmHg, or a blood pressure decrease of at least 20 mmHg, during exercise has been reported to be associated with an increased risk of sudden death [66, 67]. Therefore, exercise testing may contribute to the assessment of sudden death risk in the individual patient. Patients with multiple risk markers are generally considered at high risk. Young patients with a single *strong* risk marker, such as one or more HCM-related sudden deaths in first-degree relatives, massive LV hypertrophy (≥30 mm), frequent or prolonged (>10 beats) bursts of rapid nonsustained VT on a recent ambulatory ECG monitoring, or unexplained non-vasovagal syncope within the previous months, are also at important risk and merit consideration for prophylactic implantation of an ICD [1, 60, 61].

In many patients, however, the assessment of risk based on conventional risk factors remains uncertain and the decision to favor the implantation of an ICD over the morbidity associated with the device is a major clinical challenge. In some of these patients, a number of clinical features that may increase the level of risk, including end stage evolution with systolic dysfunction, LV apical aneurysm, or severe LV outflow obstruction at rest, may help in solving uncertain management decisions [53, 68–70]. Preliminary data also indicate that extensive late gadolinium enhancement on CMR may be associated with an increased risk for ventricular tachyarrhythmias and sudden death [20–22]. However, it is important to be aware that, in clinical practice, the level of risk associated with conventional risk markers cannot be evaluated exclusively in terms of number of risk factors, because each risk marker carries an intrinsic quantitative connotation in the individual patient. For example, a history of multiple sudden deaths in a family with a small number of affected relatives may be considered a stronger indicator of increased risk than a single sudden death in a family including many affected relatives each with a benign clinical presentation (i.e., no symptoms, mild LV hypertrophy, no LV outflow obstruction, no risk factors other than the single sudden death in the family). A maximal LV wall thickness that approaches 30 mm in a young patient may be associated with a higher risk than a ≥30 mm wall thickness in an older patient. A prolonged (>10 beats) high rate episode of nonsustained VT in a young patient may carry a stronger prognostic weight than several brief episodes of nonsustained VT in an older patient. These examples show that the final risk assessment relies on the judgment of the managing physician on a case-by-case basis, depending on the patient's individual

clinical and risk profile. It is also important to emphasize that patients' attitudes towards the risk of sudden death and the ICD can vary considerably amongst countries and cultures. Therefore, the final decision must take into account the attitude of the individual patient who has been informed regarding the risk of sudden death, the advantages and potential complications of the ICD, as well as the limitations of risk stratification in HCM.

Patient Education and Counseling

Because of the complexity, clinical heterogeneity and genetic nature of HCM, physicians should make a major effort to inform the patients and their families regarding the disease. In particular, patients should be informed of the important variability in the natural history of HCM, including a favorable clinical course in the absence of symptoms, development of heart failure symptoms, or sudden and unexpected death. Proper information will make it easier to explain and share difficult management decisions with the patients. Given the lifelong implications of HCM for the patients and their families, considerations regarding lifestyle, physical activity, family screening, and genetic counseling should be part of this information and are briefly summarized below.

Lifestyle Considerations

Patients with HCM should be advised not to participate in competitive sports associated with intense exertion or other strenuous physical activities, to avoid situations that may cause excessive vasodilation and to maintain adequate hydration, to keep to a healthy weight for the purpose of reducing the heart workload, and to avoid the excessive use of alcohol or caffeine as well as the use of drugs that increase sympathetic tone. Patients with a favorable clinical profile may participate in recreational sports associated with mild-to-moderate physical activity [1].

Pregnancy is not contraindicated in women with HCM who are asymptomatic, or whose symptoms are well controlled with beta-blocking drugs [71, 72]. In such patients, spontaneous labor and vaginal delivery are common, and caesarian section is usually performed for obstetric reasons. In women with severe LV outflow obstruction under basal conditions, with or without symptoms, pregnancy is associated with an increased risk of morbidity and mortality [71]. In women with advanced heart failure symptoms, pregnancy is associated with high morbidity and mortality, and it should be strongly discouraged [71, 72]. A multidisciplinary team is essential for adequate management of women with HCM throughout pregnancy. Continuous ECG monitoring is indicated during labor and delivery, as well as in the early postpartum period.

Family Screening

HCM is inherited as a Mendelian autosomal dominant trait [24]. Hence, each first-degree relative of a patient with HCM has a 50 % chance of carrying the mutation (or mutations) responsible for the disease and is at risk of developing HCM. Therefore, clinical screening of first-degree relatives and other family members should be encouraged. Purpose of family screening is to identify affected relatives with undiagnosed HCM, as well as to inform relatives without clinical expression of HCM regarding the risk of developing the disease later in life and the indication to periodic clinical screening. The recommended strategies for family screening include 12-lead ECG, echocardiographic and clinical evaluation. In family members in whom a diagnosis of HCM remains uncertain, CMR should also be performed. During adolescence, HCM may develop more rapidly in association with body growth. Therefore, clinical screening is advisable every 2 years for young family members (12–21 years of age) [1]. Because the disease may also develop later in life, it is prudent to recommend screening every 5 years in adults who have a normal 12-lead ECG and echocardiogram at initial evaluation [1].

Genetic Testing and Counseling

The recent HCM guidelines recommend genetic counseling as part of the evaluation of patients with HCM to address the medical, psychological and family aspects of the disease [1]. Genetic testing may be considered in the index patient to facilitate the identification of first-degree family members at risk for developing HCM. Genetic testing is not indicated in family members, when a definitive pathogenic mutation has not been identified in the index patient [1]. In countries in which the results of genetic testing may have consequences for health and life insurance, these issues should be discussed with the index patient and those family members who may be candidates to genetic screening.

Follow-Up Visits

Timing of Visits During Follow-Up

The timing for follow-up visits is based on the initial patient clinical profile, as outlined in Fig. 21.3. In patients with a benign clinical presentation, a routine follow-up evaluation every 1–2 years (including a 12-lead ECG, echocardiogram, and 24-h Holter ECG monitoring) is usually adequate. Clinical presentation is generally considered benign when the patient meets each of the following criteria: no or only mild symptoms, mild LV hypertrophy (<20 mm), no LV outflow

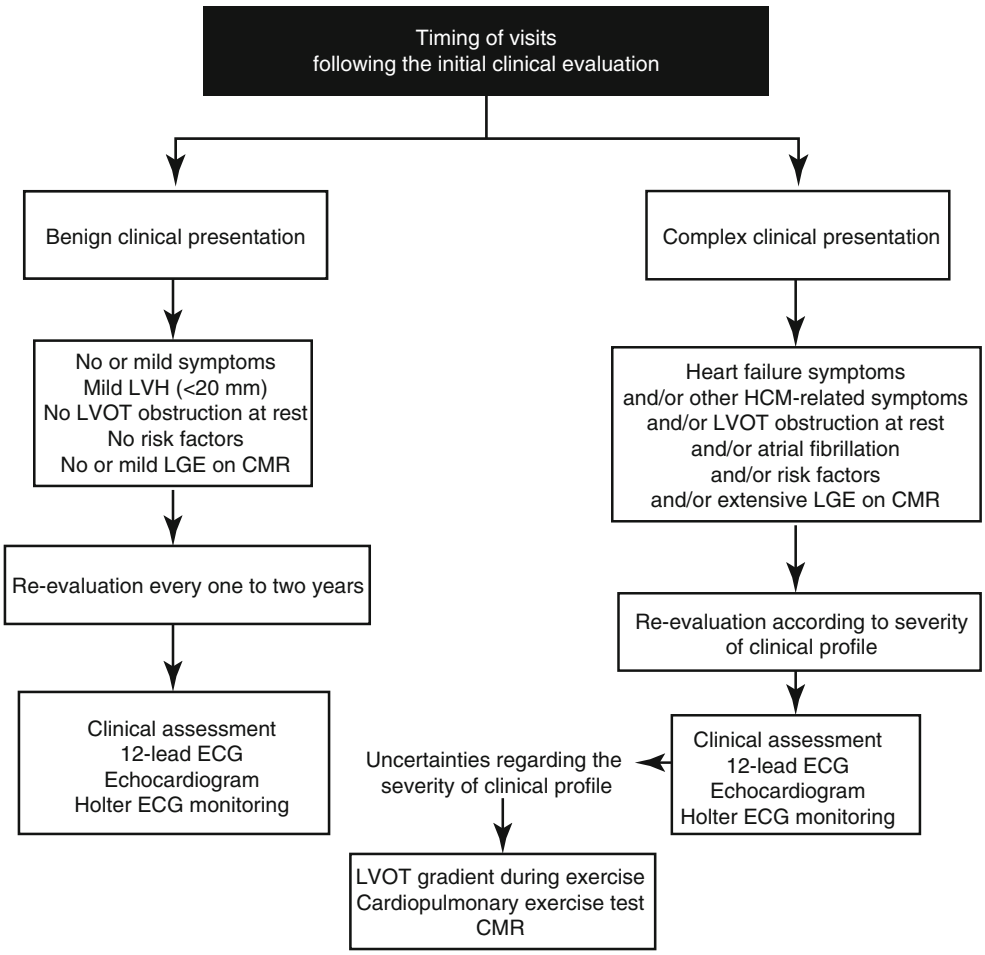

Fig. 21.3 Timing of visits following the initial clinical evaluation. *CMR* cardiovascular magnetic resonance, *ECG* electrocardiographic, *HCM* hypertrophic cardiomyopathy, *LGE* late gadolinium enhancement, *LVH* left ventricular hypertrophy, *LVOT* left ventricular outflow tract

obstruction under basal conditions, no HCM risk factors for sudden death, and no or mild LGE on CMR.

In patients with a more complex clinical presentation, including one or more of the following features: heart failure symptoms, LV hypertrophy ≥20 mm, LV outflow obstruction under basal conditions, paroxysmal or chronic AF, risk factors for sudden death, or extensive LGE on CMR, the timing for subsequent visits should be scheduled in relation to the severity of the individual patient clinical presentation. In some of these patients, additional tests may be included in the routine follow-up evaluation. For example, Doppler echocardiographic measurements of the LV outflow gradient during exercise may be helpful to document an exercise induced gradient in patients without LV outflow obstruction at rest who have heart failure symptoms during physical activities. Determination of maximum oxygen consumption during exercise may be useful in patients in whom uncertainties persist regarding presence or severity of heart failure symptoms and functional limitation. At many HCM referral centers, serial CMR evaluations are becoming a standard component of the follow-up of patients with a complex clinical presentation.

Management of Disease Progression During Follow-Up

The management of patients with clinical deterioration during follow-up is outlined in Fig. 21.4. In patients with development or progression of heart failure symptoms, management options depend on the pathophysiologic and functional expression of the disease. In patients with LV outflow obstruction, it may be necessary to decide whether pharmacologic treatment can be sufficient to control symptoms, or invasive therapy should be taken into consideration to abolish the outflow gradient and reduce or abolish symptoms. In the large majority of patients with the nonobstructive form of HCM and clinical deterioration secondary to diastolic dysfunction, pharmacologic therapy is the only option. In a small number of highly selected patients with preserved systolic function but severe symptoms secondary to restrictive diastolic features, heart transplant may be considered. In patients with end stage evolution and systolic dysfunction, a continuous adjustment of pharmacologic treatment is necessary. Ultimately, most patients with end stage HCM become candidates for heart transplant. In such patients,

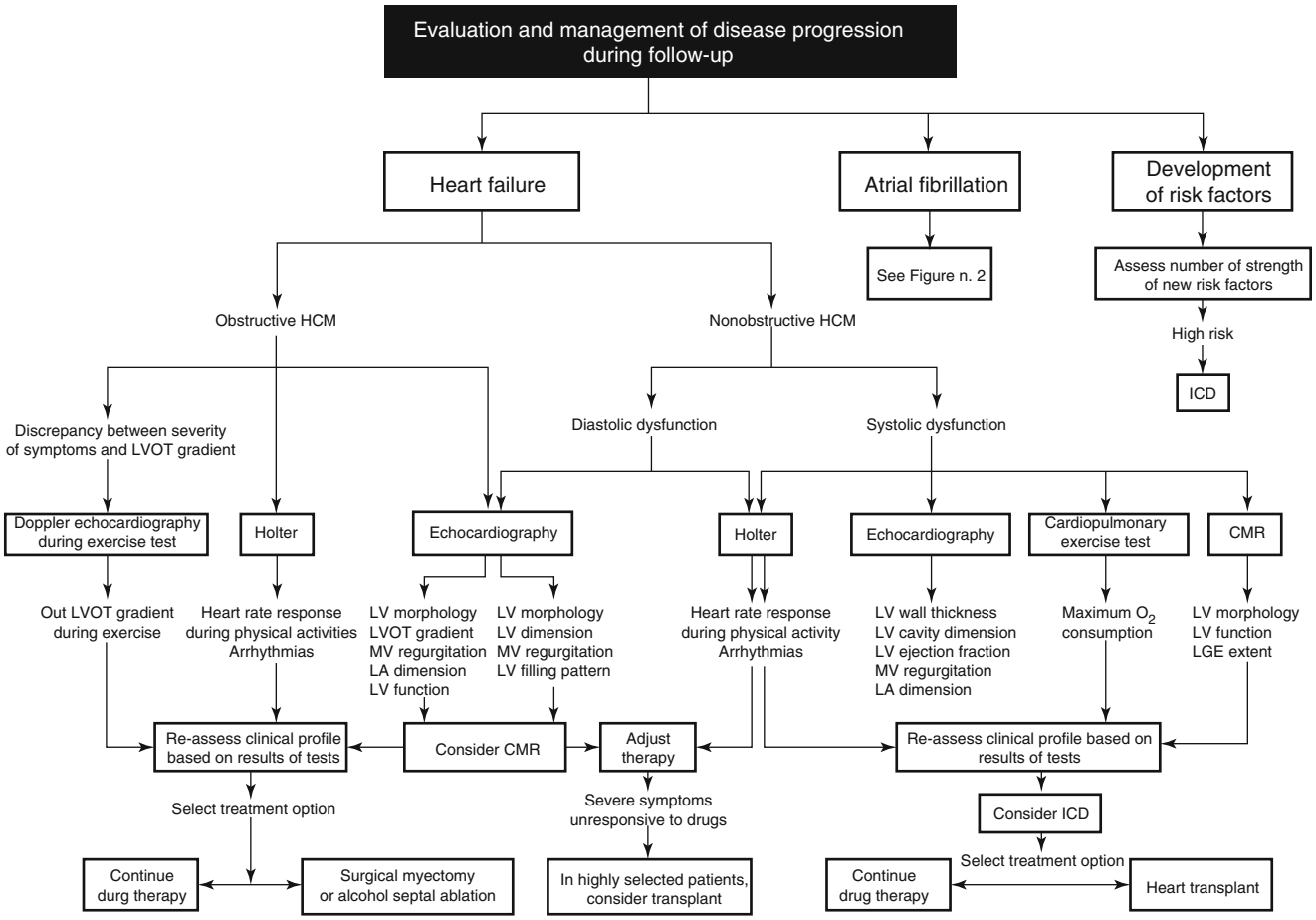

Fig. 21.4 Management of patients with hypertrophic cardiomyopathy (*HCM*) and progression of the disease during follow-up. *CMR* cardiovascular magnetic resonance, *ICD* implantable cardioverter-defibrillator, *LA* left atrium, *LGE* late gadolinium enhancement, *LV* left ventricular, *LVOT* left ventricular outflow tract, *MV* mitral valve

ICD implantation should be considered as a bridge to transplant [1, 2, 53].

In patients who develop AF during follow-up, the issues of anticoagulant therapy and treatment for prevention of recurrent AF or heart rate control need to be addressed. Management of such patients is discussed in detail in the section on AF reported in the present chapter.

In patients with changes in their risk profile for sudden death, the level of risk should be reassessed to decide whether ICD implantation for primary prevention of sudden death may be justified. For example, development of one or more of the following risk factors should raise the issue of ICD implantation: progression of LV hypertrophy to ≥30 mm (or values that approach 30 mm in young patients), recent sudden cardiac death in a young first-degree relative known to be affected by HCM (or in whom HCM may be suspected as the most likely cause of the event), documentation of alarming ventricular tachyarrhythmias such as frequent or prolonged (>10 beats) bursts of rapid nonsustained VT on Holter ECG monitoring, or recent (within months) unexplained non-vasovagal syncope in a young patient [1, 2, 31, 37, 61, 65].

Echocardiographic Assessment During Follow-Up

During follow-up, serial echocardiographic and Doppler evaluations allow the identification of changes in cardiac morphology and LV function secondary to disease progression. In children, attention is focused on a possible substantial increase in the LV wall thickness. This morphologic evolution is frequently associated with rapid body growth during adolescence and may occur within the space of 1–2 years, or even a few months [73]. In adults, progression of LV hypertrophy has seldom been reported during follow-up [74, 75]. At the opposite extreme of the morphologic evolution of the disease, LV wall thinning and/or cavity dilatation with development of systolic dysfunction and progression to end stage HCM may occur in patients of all

ages, including adolescents [51–53]. The incidence of LV wall thinning and systolic dysfunction has been reported to be 3–5 % in patients followed at HCM referral centers and appears to be more common in some HCM families [51–53].

Serial measurements of left atrial size are helpful in the follow-up evaluation of patients with HCM. In most patients with the obstructive form of the disease, left atrial dimension increases progressively as a consequence of the long-term impact of the LV outflow gradient on the hemodynamics of the left ventricle, including elevation of LV systolic and diastolic pressure, and mitral valve regurgitation. In patients with the nonobstructive form of HCM, left atrial dimension closely reflects the severity of LV diastolic function. Progressive left atrial enlargement indicates deterioration in the LV hemodynamics, increased risk of atrial fibrillation, and the need for reassessment of the clinical profile and treatment strategy [48–50, 76].

Continuous wave Doppler echocardiography allows the identification of changes in the LV outflow gradient during follow-up. Because of the dynamic nature of LV outflow obstruction in HCM, modest changes in the magnitude of the outflow gradient have no clinical relevance. However, repeated documentation of a significant outflow gradient under basal conditions and prolonged systolic mitral-septal contact in patients previously known to have the nonobstructive form of the disease generally reflects a permanent transition to obstructive HCM. This evolution is usually the consequence of a progressive increase in LV wall thickness with a decrease in outflow tract dimension and development of secondary alterations in the mitral valve apparatus. No data are available regarding the incidence of the evolution from nonobstructive to obstructive HCM. At the other extreme of the functional spectrum, loss of the LV outflow gradient can be an early sign of evolution towards end stage HCM.

Doppler echocardiography is routinely used to assess mitral valve regurgitation and diastolic function in patients with HCM. In most patients, mitral valve regurgitation is secondary to LV remodeling and outflow obstruction and may have an important impact on the clinical course of the disease [1, 42, 43]. In a minority of patients, mitral regurgitation is due to primary abnormalities of the valve apparatus [77]. Impairment of diastolic filling has an important role in the pathophysiology of HCM [2, 4]. However, Doppler indexes of diastolic function have limited clinical implications in most HCM patients, because they are strongly influenced by the LV loading conditions. These diastolic indexes may be useful under certain circumstances, such as the assessment of atrial function in patients with marked left atrial enlargement, or the documentation of a restrictive LV filling pattern in patients with clinical evidence of severe diastolic dysfunction.

Holter ECG Monitoring During Follow-Up

Evaluation of heart rate during 24-h Holter ECG monitoring can be useful for titration of therapy with beta-blocking drugs or verapamil. For example, a mean heart rate ≥70–75 beats/min may indicate the need to increase drug dosage in patients with persistent important dyspnea despite pharmacologic treatment, while a mean heart rate <45–50 beats/min with a peak rate <80–85 beats/min suggests excessive drug related bradycardia and chronotropic incompetence as the possible explanation for persistent symptoms. Identification of supraventricular arrhythmias may suggest the need to modify pharmacologic treatment. Documentation of frequent or prolonged (>10 beats) bursts of rapid nonsustained VT alters the patient risk profile and may have important management implications in terms of risk stratification and prevention of sudden death [1, 2, 61].

Exercise Testing During Follow-Up

In patients who develop heart failure symptoms during follow-up, exercise testing may be useful in the assessment of their functional limitation [1]. In particular, in those patients without a significant LV outflow gradient under basal conditions, exercise testing in combination with Doppler echocardiography may help to assess the potential role of an exercise-induced LV outflow gradient in the development of heart failure symptoms [13]. In patients who develop one or more of the main HCM risk factors during follow-up, documentation of an abnormal blood pressure response during exercise testing may contribute to the overall assessment of the sudden death risk [66, 67].

CMR During Follow-Up

Because of the high tomographic resolution of magnetic resonance, serial CMR evaluations in patients with HCM allow a high degree of accuracy in the identification of: (1) Progression of LV hypertrophy; (2) LV remodeling with wall thinning and decrease in systolic function; (3) Development of apical aneurism; and (4) Assessment of LV outflow tract morphology and characterization of the mitral valve and papillary muscle apparatus in candidates to surgical myectomy [78–82]. Comparison of LGE distribution in serial CMR evaluations may allow identification of an increase in the extent of myocardial fibrosis, a possible sign of disease progression and augmented risk of ventricular tachyarrhythmias [19, 20, 22, 82]. Current guidelines, however, do not advocate routine CMR evaluation during follow-up.

Clinical Pearls

- The first clinical evaluation of a patient with a suspected diagnosis of HCM should always begin with the examination of the 12-lead ECG, because 90–95 % of patients with HCM have ECG abnormalities, which usually include deep Q waves (>0.3 mV) with a short duration, deep negative T waves, and/or increased amplitude of the QRS complex. *Absence* of any ECG abnormalities on the 12-lead ECG makes a diagnosis of HCM unlikely in individuals without family history of HCM.
- In patients with HCM, an enlarged left atrium usually reflects augmented LV filling pressures and is associated with an increased risk of developing heart failure symptoms and/or atrial fibrillation. Therefore, left atrial dimension has an important role in the clinical evaluation of patients with HCM.
- The word "obstruction" recurs continuously in the conversation between physicians and patients with the obstructive form of HCM. Therefore, physicians should make the utmost effort to explain to the patient, in everyday language, the mechanism of LV outflow obstruction. Drawing simple sketches of the heart, hypertrophied septum and systolic anterior motion of the mitral valve may be helpful for this purpose.
- The patient's psychological attitude towards risk of sudden death and ICD implantation varies greatly and plays an important role in the final management decision. Therefore, patients judged to be at high or moderate risk should be explained, in simple words, their level of risk, the advantages and potential complications of the ICD, as well as the persisting limitations of risk stratification in HCM. Patients judged to be at low risk should be explained that their clinical profile does not justify ICD implantation, because the risk of ICD complications would be substantially higher than that of sudden death. *However*, *all patients should be informed that no individuals with HCM are at zero risk of sudden death*, *including those judged to be at low risk*.
- General considerations regarding lifestyle, family screening and genetic testing, as well as pregnancy for affected young women, should represent an integral part of the initial evaluation of a patient diagnosed with HCM.

References

1. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, et al. American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines; American Association for Thoracic Surgery; American Society of Echocardiography; American Society of Nuclear Cardiology; Heart Failure Society of America; Heart Rhythm Society; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011;124:2761–96.
2. Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, Seidman CE, et al. American College of Cardiology/European Society of Cardiology Clinical Expert Consensus Document on Hypertrophic Cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. J Am Coll Cardiol. 2003;42:1687–713.
3. Maron BJ. The electrocardiogram as a diagnostic tool for hypertrophic cardiomyopathy: revisited. Ann Noninvasive Electrocardiol. 2001;6:277–9.
4. Spirito P, Seidman CE, McKenna WJ, Maron BJ. The management of hypertrophic cardiomyopathy. N Engl J Med. 1997;336:775–85.
5. Panza JA, Maron BJ. Relation of electrocardiographic abnormalities to evolving left ventricular hypertrophy in hypertrophic cardiomyopathy during childhood. Am J Cardiol. 1989;63:1258–65.
6. McLeod CJ, Ackerman MJ, Nishimura RA, Tajik AJ, Gersh BJ, Ommen SR. Outcome of patients with hypertrophic cardiomyopathy and a normal electrocardiogram. J Am Coll Cardiol. 2009;54:229–33.
7. Ho CY. Hypertrophic cardiomyopathy in 2012. Circulation. 2012;125:1432–8.
8. Klues HG, Schiffers A, Maron BJ. Phenotypic spectrum and patterns of left ventricular hypertrophy in hypertrophic cardiomyopathy: morphologic observations and significance as assessed by two-dimensional echocardiography in 600 patients. J Am Coll Cardiol. 1995;26:1699–708.
9. Klues HG, Maron BJ, Dollar AL, Roberts WC. Diversity of structural mitral valve alterations in hypertrophic cardiomyopathy. Circulation. 1992;85:1651–60.
10. Monserrat L, Gimeno-Blanes JR, Marin F, Hermida-Prieto M, García-Honrubia A, Pérez I, et al. Prevalence of Fabry disease in a cohort of 508 unrelated patients with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2007;50:2399–403.
11. Maron BJ, Roberts WC, Arad M, Haas TS, Spirito P, Wright GB, et al. Clinical outcome and phenotypic expression in LAMP2 cardiomyopathy. JAMA. 2009;301:1253–9.
12. Nishimura RA, Holmes Jr DR. Clinical practice. Hypertrophic obstructive cardiomyopathy. N Engl J Med. 2004;350:1320–7.
13. Maron MS, Olivotto I, Zenovich AG, Link MS, Pandian NG, Kuvin JT, et al. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. Circulation. 2006;114:2232–9.
14. Rickers C, Wilke NM, Jerosch-Herold M, Casey SA, Panse P, Panse N, et al. Utility of cardiac magnetic resonance imaging in the diagnosis of hypertrophic cardiomyopathy. Circulation. 2005;112:855–61.
15. Moon JC, Fisher NG, McKenna WJ, Pennell DJ. Detection of apical hypertrophic cardiomyopathy by cardiovascular magnetic resonance in patients with non-diagnostic echocardiography. Heart. 2004;90:645–9.
16. Maron MS, Maron BJ, Harrigan C, Buros J, Gibson CM, Olivotto I, et al. Hypertrophic cardiomyopathy phenotype revisited after 50 years with cardiovascular magnetic resonance. J Am Coll Cardiol. 2009;54:220–8.
17. Moon JC, Reed E, Sheppard MN, Elkington AG, Ho SY, Burke M, et al. The histologic basis of late gadolinium enhancement cardiovascular magnetic resonance in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2004;43:2260–4.

18. Choudhury L, Mahrholdt H, Wagner A, Choi KM, Elliott MD, Klocke FJ, et al. Myocardial scarring in asymptomatic or mildly symptomatic patients with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2002;40:2156–64.
19. Rubinshtein R, Glockner JF, Ommen SR, Araoz PA, Ackerman MJ, Sorajja P, et al. Characteristics and clinical significance of late gadolinium enhancement by contrast enhanced magnetic resonance imaging in patients with hypertrophic cardiomyopathy. Circ Heart Fail. 2010;3:51–8.
20. Moon JC, McKenna WJ, McCrohon JA, Araoz PA, Ackerman MJ, Sorajja P, et al. Toward clinical risk assessment in hypertrophic cardiomyopathy with gadolinium cardiovascular magnetic resonance. J Am Coll Cardiol. 2003;41:1561–7.
21. Adabag AS, Maron BJ, Appelbaum E, Harrigan CJ, Buros JL, Gibson CM, et al. Occurrence and frequency of arrhythmias in hypertrophic cardiomyopathy in relation to delayed enhancement on cardiovascular magnetic resonance. J Am Coll Cardiol. 2008;51:1369–74.
22. O'Hanlon R, Grasso A, Roughton M, Moon JC, Clark S, Wage R, et al. Prognostic significance of myocardial fibrosis in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2010;56:867–74.
23. Teare D. Asymmetrical hypertrophy of the heart in young adults. Br Heart J. 1958;20:1–8.
24. Seidman JG, Seidman C. The genetic basis for cardiomyopathy: from mutation identification to mechanistic paradigms. Cell. 2001;104:557–67.
25. Maron BJ, Casey SA, Hauser RG, Aeppli DM. Clinical course of hypertrophic cardiomyopathy with survival to advanced age. J Am Coll Cardiol. 2003;42:882–8.
26. Maron BJ, Rowin EJ, Casey SA, Haas TS, Chan RH, Udelson JE, et al. Risk stratification and outcome of patients with hypertrophic cardiomyopathy >= 60 years of age. Circulation. 2013;127:585–93.
27. Spirito P, Chiarella F, Carratino L, Zoni Berisso M, Bellotti P, Vecchio C. Clinical course and prognosis of hypertrophic cardiomyopathy in an outpatient population. N Engl J Med. 1989;320:749–55.
28. Cannan CR, Reeder GS, Bailey KR, Melton 3rd LJ, Gersh BJ. Natural history of hypertrophic cardiomyopathy: a population-based study, 1976 through 1990. Circulation. 1995;92:2488–95.
29. Maron BJ, Casey SA, Poliac LC, Gohman TE, Almquist AK, Aeppli DM. Clinical course of hypertrophic cardiomyopathy in a regional United States cohort. JAMA. 1999;281:650–5.
30. Sorajja P, Nishimura RA, Gersh BJ, Dearani JA, Hodge DO, Wiste HJ, et al. Outcome of mildly symptomatic or asymptomatic obstructive hypertrophic cardiomyopathy: a long-term follow-up study. J Am Coll Cardiol. 2009;54:234–41.
31. Spirito P, Autore C, Rapezzi C, Bernabò P, Badagliacca R, Maron MS, et al. Syncope and risk of sudden death in hypertrophic cardiomyopathy. Circulation. 2009;119:1703–10.
32. Musumeci MB, Spirito P, Cauti FM, Autore C. High risk for sudden death identified by electrocardiographic loop recording in a patient with hypertrophic cardiomyopathy without major risk factors. Am J Cardiol. 2011;107:1558–60.
33. Maron BJ, Wolfson JK, Epstein SE, Roberts WC. Intramural ("small vessel") coronary artery disease in hypertrophic cardiomyopathy. J Am Coll Cardiol. 1986;8:545–57.
34. Cecchi F, Olivotto I, Gistri R, Lorenzoni R, Chiriatti G, Camici PG. Coronary microvascular dysfunction and prognosis in hypertrophic cardiomyopathy. N Engl J Med. 2003;349:1027–35.
35. Maron MS, Olivotto I, Maron BJ, Prasad SK, Cecchi F, Udelson JE, et al. The case for myocardial ischemia in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2009;54:866–75.
36. Cannon III RO, Rosing DR, Maron BJ, Leon MB, Bonow RO, Watson RM, et al. Myocardial ischemia in patients with hypertrophic cardiomyopathy: contribution of inadequate vasodilator reserve and elevated left ventricular filling pressures. Circulation. 1985;71:234–43.
37. Spirito P, Bellone P, Harris KM, Bernabò P, Bruzzi P, Maron BJ. Magnitude of left ventricular hypertrophy and risk of sudden death in hypertrophic cardiomyopathy. N Engl J Med. 2000;342:1778–85.
38. Maron MS, Olivotto I, Betocchi S, Casey SA, Lesser JR, Losi MA, et al. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. N Engl J Med. 2003;348:295–303.
39. Autore C, Bernabò P, Barillà CS, Bruzzi P, Spirito P. The prognosis importance of left ventricular outflow obstruction in hypertrophic cardiomyopathy varies in relation to the severity of symptoms. J Am Coll Cardiol. 2005;45:1076–80.
40. Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF, et al. Clinician's guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. Circulation. 2010;122:191–225.
41. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. JAMA. 2002;287:1308–20.
42. Wigle ED, Sasson Z, Henderson MA, Ruddy TD, Fulop J, Rakowski H, et al. Hypertrophic cardiomyopathy: the importance of the site and the extent of hypertrophy: a review. Prog Cardiovasc Dis. 1985;28:1–83.
43. Wigle ED, Rakowski H, Kimball BP, Williams WG. Hypertrophic cardiomyopathy: clinical spectrum and treatment. Circulation. 1995;92:1680–92.
44. Fifer MA, Vlahakes GJ. Management of symptoms in hypertrophic cardiomyopathy. Circulation. 2008;117:429–39.
45. Bonow RO, Rosing DR, Bacharach SL, Green MV, Kent KM, Lipson LC, et al. Effects of verapamil on left ventricular systolic function and diastolic filling in patients with hypertrophic cardiomyopathy. Circulation. 1981;64:787–96.
46. Epstein SE, Rosing DR. Verapamil: its potential for causing serious complications in patients with hypertrophic cardiomyopathy. Circulation. 1981;64:437–41.
47. Cecchi F, Olivotto I, Montereggi A, Santoro G, Dolara A, Maron BJ. Hypertrophic cardiomyopathy in Tuscany: clinical course and outcome in an unselected regional population. J Am Coll Cardiol. 1995;26:1529–36.
48. Yang H, Woo A, Monakier D, Jamorski M, Fedwick K, Wigle ED, et al. Enlarged left atrial volume in hypertrophic cardiomyopathy: a marker for disease severity. J Am Soc Echocardiogr. 2005;18:1074–82.
49. Nistri S, Olivotto I, Betocchi S, Losi MA, Valsecchi G, Pinamonti B, et al. Prognostic significance of left atrial size in patients with hypertrophic cardiomyopathy (from the Italian Registry for Hypertrophic Cardiomyopathy). Am J Cardiol. 2006;98:960–5.
50. Olivotto I, Cecchi F, Casey SA, Dolara A, Traverse JH, Maron BJ. Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. Circulation. 2001;104:2517–24.
51. Spirito P, Maron BJ, Bonow RO, Epstein SE. Occurrence and significance of progressive left ventricular wall thinning and relative cavity dilatation in hypertrophic cardiomyopathy. Am J Cardiol. 1987;60:123–9.
52. Biagini E, Coccolo F, Ferlito M, Perugini E, Rocchi G, Bacchi-Reggiani L, et al. Dilated-hypokinetic evolution of hypertrophic cardiomyopathy: prevalence, incidence, risk factors, and prognostic implications in pediatric and adult patients. J Am Coll Cardiol. 2005;46:1543–50.
53. Harris KM, Spirito P, Maron MS, Zenovich AG, Formisano F, Lesser JR, et al. Prevalence, clinical profile, and significance of left ventricular remodeling in the end-stage phase of hypertrophic cardiomyopathy. Circulation. 2006;114:216–25.
54. Biagini E, Spirito P, Leone O, Picchio FM, Coccolo F, Ragni L, et al. Heart transplantation in hypertrophic cardiomyopathy. Am J Cardiol. 2008;101:387–92.

55. Maron MS, Kalsmith BM, Udelson JE, Li W, DeNofrio D. Survival after cardiac transplantation in patients with hypertrophic cardiomyopathy. Circ Heart Fail. 2010;3:574–9.
56. Maron BJ, Olivotto I, Spirito P, Casey SA, Bellone P, Gohman TE, et al. Epidemiology of hypertrophic cardiomyopathy related death: revisited in a large non-referral-based patient population. Circulation. 2000;102:858–64.
57. Maron BJ, Olivotto I, Bellone P, Conte MR, Cecchi F, Flygenring BP, et al. Clinical profile of stroke in 900 patients with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2002;39:301–7.
58. Losi MA, Betocchi S, Aversa M, Lombardi R, Miranda M, D'Alessandro G, et al. Determinants of atrial fibrillation development in patients with hypertrophic cardiomyopathy. Am J Cardiol. 2004;94:895–900.
59. Elliott PM, Poloniecki J, Dickie S, Sharma S, Monserrat L, Varnava A, et al. Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. J Am Coll Cardiol. 2000;36:2212–8.
60. Maron BJ, Spirito P, Shen WK, Haas TS, Formisano F, Link MS, et al. Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy. JAMA. 2007;298:405–12.
61. Maron BJ. Sudden death in hypertrophic cardiomyopathy. Contemporary insights and strategies for risk stratification and prevention. Circulation. 2010;121:445–56.
62. Elliott PM, Sharma S, Varnava A, Poloniecki J, Rowland E, McKenna WJ. Survival after cardiac arrest or sustained ventricular tachycardia in patients with hypertrophic cardiomyopathy. J Am Coll Cardiol. 1999;33:1596–601.
63. Bos JM, Maron BJ, Ackerman MJ, Haas TS, Sorajja P, Nishimura RA, et al. Role of family history of sudden death in risk stratification and prevention of sudden death with implantable defibrillators in hypertrophic cardiomyopathy. Am J Cardiol. 2010;106:1481–6.
64. Elliott PM, Gimeno Jr B, Mahon NG, Poloniecki JD, McKenna WJ. Relation between severity of left-ventricular hypertrophy and prognosis in patients with hypertrophic cardiomyopathy. Lancet. 2001;357:420–4.
65. Monserrat L, Elliott PM, Gimeno JR, Sharma S, Penas-Lado M, McKenna WJ. Non-sustained ventricular tachycardia in hypertrophic cardiomyopathy: an independent marker of sudden death risk in young patients. J Am Coll Cardiol. 2003;42:873–9.
66. Sadoul N, Prasad K, Elliott PM, Bannerjee S, Frenneaux MP, McKenna WJ. Prospective prognostic assessment of blood pressure response during exercise in patients with hypertrophic cardiomyopathy. Circulation. 1997;96:2987–91.
67. Olivotto I, Maron BJ, Montereggi A, Mazzuoli F, Dolara A, Cecchi F. Prognostic value of systemic blood pressure response during exercise in a community-based patient population with hypertrophic cardiomyopathy. J Am Coll Cardiol. 1999;33:2044–51.
68. Maron MS, Finley JJ, Bos JM, Hauser TH, Manning WJ, Haas TS, et al. Prevalence, clinical significance, and natural history of left ventricular apical aneurysms in hypertrophic cardiomyopathy. Circulation. 2008;118:1541–9.
69. Elliott PM, Gimeno JR, Tome MT, Shah J, Ward D, Thaman R, et al. Left ventricular outflow tract obstruction and sudden death risk in patients with hypertrophic cardiomyopathy. Eur Heart J. 2006;27:1933–41.
70. McLeod CJ, Ommen SR, Ackerman MJ, Weivoda PL, Shen WK, Dearani JA, et al. Surgical septal myectomy decreases the risk for appropriate implantable cardioverter defibrillator discharge in obstructive hypertrophic cardiomyopathy. Eur Heart J. 2007;28:2583–8.
71. Autore C, Conte MR, Piccininno M, Bernabò P, Bonfiglio G, Bruzzi P, et al. Risk associated with pregnancy in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2002;40:1864–9.
72. Thaman R, Varnava A, Hamid MS, Firoozi S, Sachdev B, Condon M, et al. Pregnancy related complications in women with hypertrophic cardiomyopathy. Heart. 2003;89:752–6.
73. Maron BJ, Spirito P, Wesley Y, Arce J. Development and progression of left ventricular hypertrophy in children with hypertrophic cardiomyopathy. N Engl J Med. 1986;315:610–4.
74. Obeid AI, Maron BJ. Apical hypertrophic cardiomyopathy developing at a relatively advanced age. Circulation. 2001;103:1605.
75. Maron BJ, Niimura H, Casey SA, Soper MK, Wright GB, Seidman JG, et al. Development of left ventricular hypertrophy in adults in hypertrophic cardiomyopathy caused by cardiac myosin-binding protein C gene mutations. J Am Coll Cardiol. 2001;38:315–21.
76. Tsang TS, Barnes ME, Gersh BJ, Bailey KR, Seward JB. Left atrial volume as a morphophysiologic expression of left ventricular diastolic dysfunction and relation to cardiovascular risk burden. Am J Cardiol. 2002;90:1284–9.
77. Zhu WX, Oh JK, Kopecky SL, Schaff HV, Tajik AJ. Mitral regurgitation due to ruptured chordae tendineae in patients with hypertrophic obstructive cardiomyopathy. J Am Coll Cardiol. 1992;20:242–7.
78. Maron MS, Appelbaum E, Harrigan CJ, Buros J, Gibson CM, Hanna C, et al. Clinical profile and significance of delayed enhancement in hypertrophic cardiomyopathy. Circ Heart Fail. 2008;1:184–91.
79. Harrigan CJ, Appelbaum E, Maron BJ, Buros JL, Gibson CM, Lesser JR, et al. Significance of papillary muscle abnormalities identified by cardiovascular magnetic resonance in hypertrophic cardiomyopathy. Am J Cardiol. 2008;101:668–73.
80. Kwon DH, Setser RM, Thamilarasan M, Popovic ZV, Smedira NG, Schoenhagen P, et al. Abnormal papillary muscle morphology is independently associated with increased left ventricular outflow tract obstruction in hypertrophic cardiomyopathy. Heart. 2008;94:1295–301.
81. Rowin EJ, Maron BJ, Lesser JR, Rastegar H, Maron MS. Papillary muscle insertion directly into the anterior mitral leaflet in hypertrophic cardiomyopathy, its identification and cause of outflow obstruction by cardiac magnetic resonance imaging, and its surgical management. Am J Cardiol. 2013;111:1677–9.
82. Maron BJ, Maron MS. Hypertrophic cardiomyopathy. Lancet. 2013;381:242–55.

Evaluation and Management of Hypertrophic Cardiomyopathic Patients Through Noncardiac Surgery and Pregnancy

22

Nadia B. Hensley and Theodore P. Abraham

Abstract

Due to the prevalence of hypertrophy cardiomyopathy (HCM) (1:500), anesthesiologists, cardiologists, surgeons and obstetricians will encounter these patients and need to thoroughly understand their disease in order to understand the risk that noncardiac surgery and pregnancy imposes upon them. Patients with HCM have genotypic and phenotypic variability. Indeed a subgroup of these patients exhibits the HCM genotype but not the phenotype (left ventricular hypertrophy). There are a number of treatment modalities for these patients including pharmacotherapy to control symptoms, implantable cardiac defibrillators to manage malignant arrhythmias, and surgical myectomy and alcohol septal ablation to decrease the left ventricular hypertrophy and outflow obstruction. In this chapter, we will discuss how management of these patients perioperatively is vital to improving their survivability and morbidity when they undergo noncardiac surgery, either electively or emergently. We will also discuss the peripartum management of the HCM patient since the physiologic changes of pregnancy can have either a salubrious or detrimental effect on the pathophysiology of HCM.

Keywords

Hypertrophic cardiomyopathy • Preoperative evaluation • Peripartum evaluation • Noncardiac surgery • Emergent surgery • Left ventricular outflow tract obstruction

Key Points

- HCM patients are at increased risk for sudden death, stroke, congestive heart failure and arrhythmias; therefore preoperative assessment involves a thorough history and physical exam to assess risk for noncardiac surgery or pregnancy.
- Progression and severity of HCM symptomatology (dyspnea, presyncope or syncope, palpitations and angina), duration of symptoms, and functional status currently are most valuable in assessing risk of HCM patients perioperatively or peripartum.

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- Beta-blockers, calcium channel blockers, i.e., verapamil or diltiazem, and disopyramide, should be continued in the perioperative period in HCM patients undergoing noncardiac surgery, including day of surgery.
- For patients with provocable obstruction, with or without congestive heart failure symptoms, attention must be paid to optimal volume status intraoperatively, especially in high risk surgeries with large fluid shifts. Consideration of intraoperative placement of TEE or PA catheters may assist the anesthesiologist in determining optimal cardiac left-sided filling pressures.
- The anesthesiologist should avoid medications that dramatically decrease systemic vascular resistance. Pure alpha-agonists, such as phenylephrine, are preferred over inotropes in the setting of decreased end-diastolic volumes or systemic vascular resistance.
- Physiologic changes of pregnancy can potentially worsen left ventricular outflow tract obstruction in HCM patients due to increased contractility and decreased systemic vascular resistance from the low resistance placenta.
- NYHA Class prior to pregnancy is generally the best indicator of whether or not the parturient will hemodynamically tolerate the physiologic changes of pregnancy. End-stage HCM patients with NYHA Class III/IV prior to pregnancy should consider termination of pregnancy given the risk of mortality to both fetus and mother.

Introduction

Given the prevalence of hypertrophic cardiomyopathy (HCM) being relatively high (1:500 in the general population) across all races and regions, physicians will encounter these individuals preoperatively prior to noncardiac surgery as well as in the setting of pregnancy [1]. It is well known that the anesthetic and surgical perturbations in the setting of HCM pathophysiology can result in increased morbidity and mortality, yet there are few studies that have examined the risk involved. Hreybe et al., examined the risk of acute myocardial infarction (MI) and in-hospital mortality after noncardiac surgery in HCM patients. The risk of in-hospital MI and death was higher in the HCM patients than in the control group (6.7 % vs. 2.5 % [$P<0.001$] for death and 2.2 % vs. 0.3 % [$P<0.001$] for MI) [2]. Haering et al., conducted a retrospective study of HCM patients undergoing noncardiac surgery and found 40 % had one or more adverse perioperative cardiac events, most commonly congestive heart failure (CHF) (16 %) [3]. Therefore, this chapter will review how to assess HCM patients for risk of post-operative or peri-pregnancy complications, and how best to manage such patients, including when surgery or pregnancy may be contraindicated.

Preoperative Evaluation for Noncardiac Surgery

Most HCM patients can be managed through surgery, including high risk operations. The baseline function, including symptoms and degree of heart failure, is likely the most significant discriminating factor on whether a patient with HCM will tolerate surgery. Those who are asymptomatic or mildly symptomatic, including those in NYHA Class 1 and 2, are likely to have fewer complications than those with higher degrees of dysfunction and symptoms. Accordingly, a thorough understanding of the patient prior to surgery is required.

Preoperative Clinical Presentation and Diagnostic Imaging

Patients with HCM are at increased risk for sudden death, stroke, congestive heart failure and arrhythmias such as atrial fibrillation, ventricular tachycardia and fibrillation and atrial reentrant tachycardia [2] and therefore a thorough history should be conducted to help determine risk [4]. Some patients may already have a genetic diagnosis, however, due to the genetic heterogeneity [1], phenotypic expression depends not only on the mutation but also environmental factors [5], such as diet and exercise [6]. A subgroup of HCM patients has emerged with genetic mutations but without left ventricular hypertrophy and the clinical ramifications and natural history of this subgroup are yet unknown [1]. However, since the risk of clinical symptoms increases with age, this subgroup of patients should be periodically screened with serial ECG, 2D-transthoracic echocardiography, and clinical assessments [7]. If there is a strong family history of HCM and the patient is asymptomatic with normal phenotype, genetic testing should be considered to help establish this genotype positive, phenotype negative status and help determine a treatment strategy [5]. If genetic testing is not possible, first degree relatives and other family members of known HCM patients should be assessed by 2D-transesophageal or transthoracic echocardiography (TEE or TTE) or cardiovascular MRI [8] prior to noncardiac surgery and pregnancy [5]. However, general consensus is currently that patients with genotype positive, phenotype negative disease are at very low risk of peri-operative or other HCM-related events, and can be managed similar to the non-HCM population.

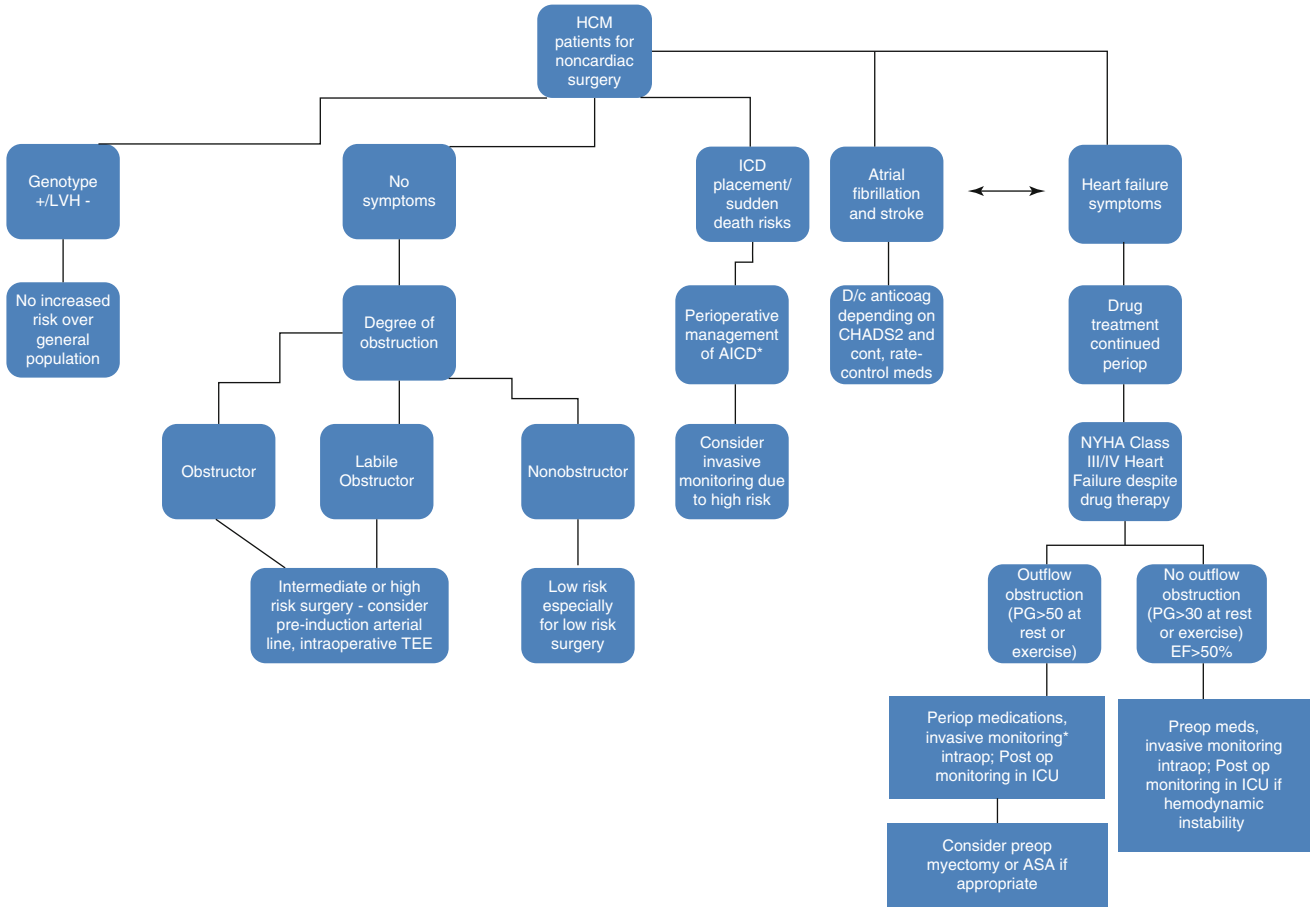

Fig. 22.1 Suggested algorithm for risk stratification and intraoperative monitoring of HCM patients going for noncardiac surgery (Adapted from Ref. [1]). Primary prevention markers for AICD: (1) Family history of sudden cardiac death; (2) unexplained recent syncope; (3) multiple repetitive nonsustained ventricular tachycardia; (4) hypotensive response to exercise; (5) massive LVH ≥ 30 mm; (6) extensive and diffuse late gadolinium enhancement. Invasive monitoring* = intra-arterial catheter, TEE, pulmonary artery catheter, or central venous pressure monitoring. *PG* pressure gradient, *LVH* left ventricular hypertrophy, *ASA* alcohol septal ablation

Since symptoms can occur anytime between infancy and the ninth decade, even the asymptomatic patient with HCM can be at increased risk under general anesthesia or during the physiologic alterations that occur in pregnancy [9]. Indeed, sudden death usually occurs in asymptomatic or mildly symptomatic patients [10]. However, the more severe symptomatology can signify further progressed disease. Most HCM patients' symptomatology involves dyspnea, presyncope or syncope, palpitations and angina [11]. Progression and duration of symptoms, as well as current functional status should be assessed in a preoperative work-up. Those patients that have NYHA Class III or IV symptoms most likely have increased LVOT gradients (resting or provoked) of >30 mmHg [12] and/or atrial fibrillation [13] and/or diastolic dysfunction [14], all of which increases perioperative risk, particularly of heart failure but also of arrhythmias [5]. Any history of arrhythmias, cardioversion, radiofrequency ablations and placement of an implantable defibrillator should also be ascertained [1]. Those with angina, especially the elderly, should undergo cardiac catheterization to stress testing to rule out concomitant coronary artery disease. Current medications, such as antiarrhythmics, rate-control drugs, or anticoagulants, should be assessed as these may need to be continued or withdrawn perioperatively. Patients with uncontrolled or controlled vascular congestion are also at increased risk for worsening of congestive heart failure after non-cardiac surgery.

Risk Stratification of the HCM Patient for Noncardiac Surgery

HCM patients should be risk-stratified during preoperative evaluation, including diagnostic exams such as TTE, TEE or cardiac MRI. They should be categorized as far as their degree of obstruction: (1) nonobstructors, (2) labile obstructors with provocable LVOT peak pressure gradients of ≥30 mmHg and (3) obstructors with resting LVOT peak pressure gradients ≥30 mmHg (See Figs. 22.1 and 22.2). Haering et al., found that factors associated with adverse

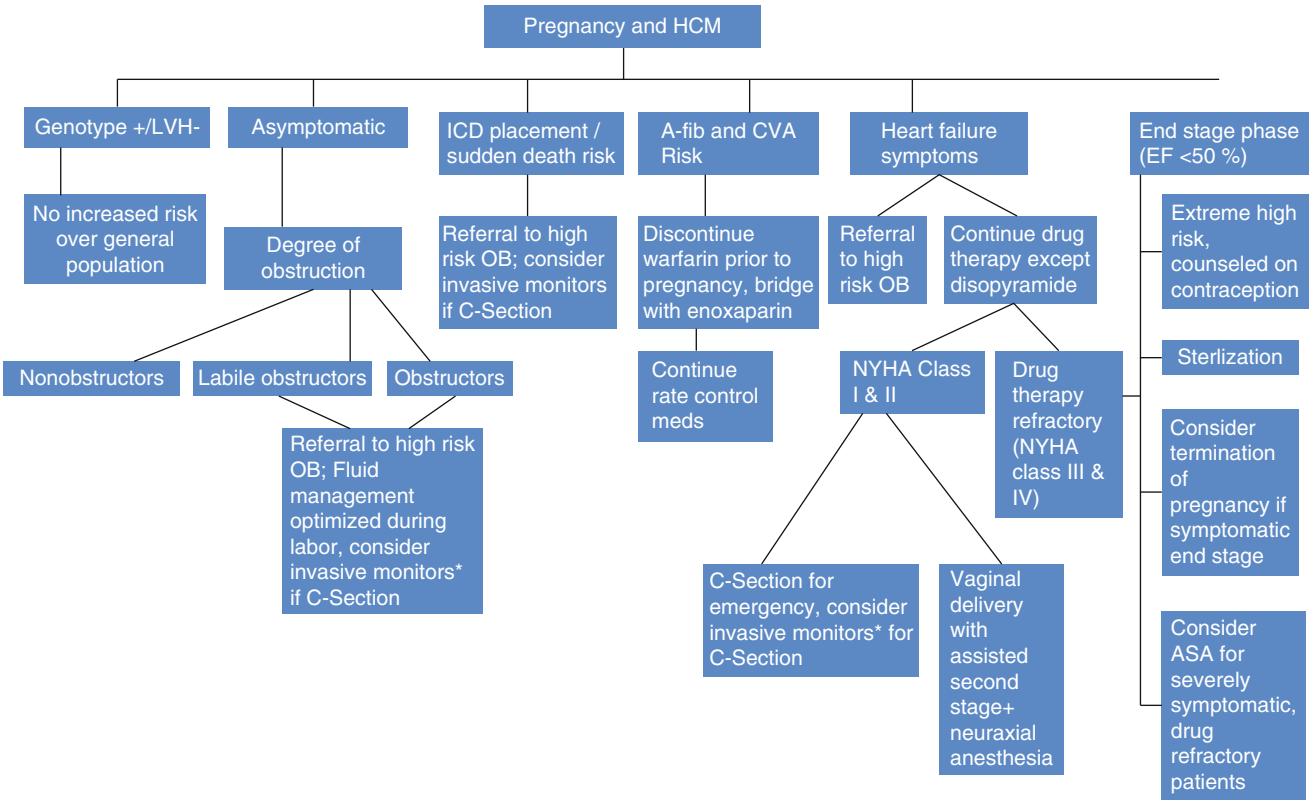

Fig. 22.2 Suggested algorithm for risk stratification and monitoring of HCM Patients during pregnancy and delivery. +=assisted second stage with low forceps or vacuum-assisted delivery. *C-section* cesarean section, *ASA* alcohol septal ablation

cardiac events in this population undergoing noncardiac surgery were increasing length of surgical time and intermediate- to high-risk surgery [3]. Intermediate- to high-risk surgery was defined as major vascular, orthopedic, open peritoneal, and head and neck surgeries [15]. Risk stratifying HCM patients prior to noncardiac surgery should follow AHA/ACC guidelines for preoperative evaluation [15]. If a known HCM patient is undergoing intermediate- to high-risk surgery and has not had a recent 2D-TTE or TEE or if there is a progression in severity of symptoms or new arrhythmias, then further work-up should be completed.

2D-TTE or TEE should focus on the degree of resting and provoked LVOT obstruction, mitral regurgitation and systolic anterior motion of the mitral valve, abnormalities of the mitral valve and subvalvular apparatus, degree of diastolic dysfunction, chamber enlargement, and LV systolic function. Recent studies have examined the use of 2D-strain analysis or speckle tracking to be able to better differentiate between left ventricular hypertrophy and HCM [16]. Outflow track gradients of 30 mmHg or more under resting conditions (measured by continuous wave Doppler) are independent determinants of symptoms of progressive heart failure and death [17] and thus risk factors for increased perioperative cardiac morbidity and mortality. HCM patients may have significant or even severe angina, which may be due to microvascular dysfunction, excessive wall tension or epicardial disease. Older patients with risk factors may require stress testing or cardiac catheterization prior to noncardiac surgery.

Table 22.1 Clinical features of the functional (benign) heart murmur

Location: left sternal border and nonradiating[a]
Timing: mid or early systole[b]
Intensity: grade 2 or lower
No unexplained cardiac or pulmonary symptoms (eg. dyspnea, chest pain, orthopnea, syncopy)
No additional unexplained cardiac signs (eg. rales, S3, significant peripheral edema)
No electrocardiographic or chest radiograph evidence of ventricular hypertrophy)

Adapted from Ref. [18]
[a]Murmurs radiating into the neck should be considered due to aortic stenosis or HCM and are thus not functional
[b]Diastolic murmurs are always considered pathological

For those without a clear diagnosis, murmurs that are dynamic and do not meet the criteria for a benign murmur (Table 22.1) should be referred for echocardiographic review [18]. The typical features of the murmur in HCM is a systolic murmur heard loudest at left sternal border, does not radiate to neck and increases with exercise, valsalva or standing [18]. A 12-lead ECG should be performed, however the

Table 22.2 Nonspecific EKG changes accompanying HCM

Left ventricular hypertrophy (S wave in V1; R wave in V5 > 35 mm)
Left axis deviation
Intraventricular conduction delay (QRS > 0.12 ms)
Left atrial enlargement (broad notched P wave in Lead II; deeply inverted P wave in V1)
ST segment & T wave abnormalities
Poor R wave progression in precordial leads
Supraventricular arrhythmias (most commonly atrial fibrillation)

changes in ECG seen with HCM patients are often nonspecific (Table 22.2). A 12-lead ECG is abnormal in 75–95 % of HCM patients [19] and can help identify arrhythmias or evidence of prior myocardial infarcts.

HCM patients found to have atrial fibrillation are at increased risk of stroke and most likely will be anticoagulated with coumadin or direct Xa inhibitors, such as dabigatran [7]. Coumadin should be stopped within 5 days and direct Xa inhibitors at least 2 days prior to elective surgery to decrease the bleeding risk [20] if they are considered low risk for perioperative stroke [21]. Although rare, HCM patients with a history of easy bruising and increased bleeding may actually have an acquired von Willebrands disorder due to dynamic LVOT obstruction-related shearing of large multimers of von Willebrand factor [22]. This bleeding propensity may be significant depending on the type of surgery and should be kept in mind in preoperative planning.

Preoperative Management in HCM

Patients with significant LVOT obstruction (resting gradient >30 mmHg or more) and exertional heart failure symptoms should be started on pharmacological treatment with beta-blockers or, if contraindication, verapamil [7]. Verapamil should be used with caution in those patients with severe LVOT gradients at rest and advanced heart failure [23]. Disopyramide is another pharmacotherapy used to treat symptomatic HCM patients that has been shown to reduce outflow gradients at rest as well as on provocation [24]. Beta-blockers, calcium channel blockers, i.e., verapamil or diltiazem, and disopyramide should be continued in the perioperative period in the HCM patient undergoing noncardiac surgery, including on the day of surgery. The decrease in heart rate and inotropy and thus optimization of the myocardial supply–demand curve and minimization of LVOT obstruction that beta-blockade allows is particularly advantageous in the setting of surgery and sympathetic stimulation.

Patients with severe obstructive physiology who require high-risk surgery should be optimized from a symptom standpoint and volume standpoint prior to undertaking such surgery. This includes ideally a titration of medications, and possibly a right and left heart catheterization to optimize fluid status and hemodynamics. In patients with severe resting or provocable obstruction refractory to optimal medical therapy, in whom the risks of major non-cardiac surgery remain high, consideration to pre-operative surgical myectomy or alcohol septal ablation should be given. The ideal timing of non-cardiac surgery after surgical myectomy or alcohol septal ablation is unknown.

Intraoperative Management of the Low-Risk HCM Patient

The low-risk HCM patients presenting for noncardiac surgery are those that are asymptomatic or have very mild symptoms. The subclass of HCM that is genotype positive, phenotype negative is also a low-risk population. These patients are lower risk for hemodynamic instability perioperatively and therefore, may not need any additional monitoring than an otherwise healthy patient would need for the same surgery. It should be kept in mind, however, that they have coronary microvascular dysfunction and diastolic dysfunction by the pathophysiologic mechanism of their disease, with exception of the genotype positive/LVH negative patients. In addition to congestive heart failure, the anesthesiologist should be vigilant to any ECG changes concerning for ischemia or arrhythmias perioperatively.

Intraoperative Management of the HCM Labile Obstructors or Resting Obstructors

For patients with provocable obstruction and no pre-existent congestive heart failure, attention must be paid to optimal volume status, as intra-operative or post-operative volume depletion may stimulate worsening obstruction and progressive hypotension. All patients who are hypovolemic or euvolemic should be maintained on sufficient hydration to minimize the possibility of worsening LVOT obstruction. If there is a suspicion or concern, or a procedure with significant fluid shifts or volume losses, then consideration to intraoperative TEE or pulmonary artery catheter during surgery should be given. This is particularly true of patients with large gradients, or significant NYHA class symptoms at baseline, who are undergoing high-risk surgery. In addition, the anesthesiologist should avoid medications with pure afterload-reducing properties, and should prioritize alpha agonists over inotropes in the setting of hypovolemia or decreased systemic vascular resistance. Intra-aortic balloon pumps are contraindicated due to the possibility of promoting and exacerbating outflow tract obstruction, and causing a paradoxical worsening of hypotension, in patients with resting or labile obstruction.

For patients with severe obstructive physiology, the anesthesiologist must understand that hypotension may be a consequence of preload reduction or due to profound obstruction. When there is doubt, a swan ganz catheter can be helpful in assuring appropriate filling pressures. If pressors are required, a pure arterial vasoconstrictor, such as phenylephrine, is preferable, given its ability to improve outflow tract obstruction and blood pressure. Inotropes should be avoided, including epinephrine and norepinephrine, unless patients have been documented to be non-obstructive by intra-op TEE.

Intraoperative Management of HCM Non-obstructors

Patients with non-obstructive HCM may also be at risk of peri-operative complications, including exacerbation of heart failure. Such patients typically require higher filling pressures due to severe diastolic dysfunction, but may also be easily pushed into frank pulmonary edema if aggressively hydrated during surgery. In addition, cardiac output is often times normal in minimally-symptomatic patients, but may be severely reduced in patients with severe diastolic dysfunction. Apical HCM patients may also fit this category, due to a both small ventricular chamber size from apical obliteration and myocardial diastolic failure. In such patients, a Swan Ganz catheter may be helpful in order to maintain optimal filling pressures, especially when high risk surgeries with large fluid shifts are planned. Intra-operative TEE may be particularly helpful in difficult cases of hypotension, in order to understand physiology acutely, and to reconfirm that no obstruction is present. Patients with non-obstructive HCM are also at risk of ischemia and arrhythmias, and should be monitored for these complications as well.

Post-operative Management of HCM Patients After Noncardiac Surgery

Post-operatively, patients with pre-existent severe symptoms, or intra-operative hypotension or arrhythmia, should be managed in an intensive care unit setting, especially after high risk surgery with large fluid shifts or aggressive hydration. As previously discussed, arterial vasoconstrictors and hydration are the mainstays of hypotension treatment, unless the patient is already in pulmonary congestion. IABP is contraindicated in patients with outflow tract obstruction. Patients should be maintained or re-initiated on their outpatient medications, including beta-blockers, and fluid resuscitation or diuretics may be utilized as needed, keeping in mind that the optimal filling pressures in patients with HCM are typically higher than in the normal population. Pulmonary artery catheters may be helpful to document and titrate filling pressures to balance reduction in outflow tract obstruction physiology with avoidance of pulmonary vascular congestion in those with obstructive physiology, but may also be helpful in non-obstructive HCM patients with severe diastolic dysfunction and reduced cardiac output.

Managing HCM Through Pregnancy

There are very few studies, most of which are more than 30 years old, that examine the cardiac risks involved in HCM patients that become pregnant [25, 26]. A recent retrospective review by Autore et al. looked at the risk of mortality and morbidity in this population [17]. They found that there was increased risk of death compared to the general population; however, the absolute maternal death rate was low [17]. In their study, two deaths occurred in particularly high-risk females, one of which had NYHA class III symptoms with a previous pregnancy and the other had strong family history of sudden death in several close relatives [17]. For the most part, pregnancy is not absolutely contraindicated in HCM patients and those that are asymptomatic or have mild HCM typically tolerate pregnancy well [17].

Physiologic Changes in Pregnancy and HCM

The hemodynamic changes that occur during pregnancy can have either a salubrious or detrimental effect in the HCM parturient [27]. Increases in circulating blood volume (50 % increase in plasma volume and 30 % increase in red blood cell mass) and increased left ventricular end-diastolic diameter associated with increased stroke volume can be of benefit [27] by reducing LVOT obstruction. However, patients with baseline congestive heart failure may see a worsening of congestion with expansion of plasma volume. In addition, worsening obstruction can occur due to increased cardiac contractility and decreased systemic vascular resistance due to the low resistance placenta [27] and high estrogen/progestin levels. Meticulous attention to hemodynamics, volume status and clinical symptoms, and adjustment of medications, may be required particularly in the third trimester of pregnancy.

Physiologic changes during labor and delivery can exacerbate heart failure symptoms in HCM patients as well. Pain and anxiety can result in tachycardia which decreases diastolic filling time in patients with already impaired diastolic relaxation [27, 28]. Increases in preload can be dramatic due to the lack of IVC compression and redistribution of blood from the lower extremities, especially during contractions, which can cause pulmonary edema in those at the brink of the Frank-Starling curve [28]. There is an increase in cardiac

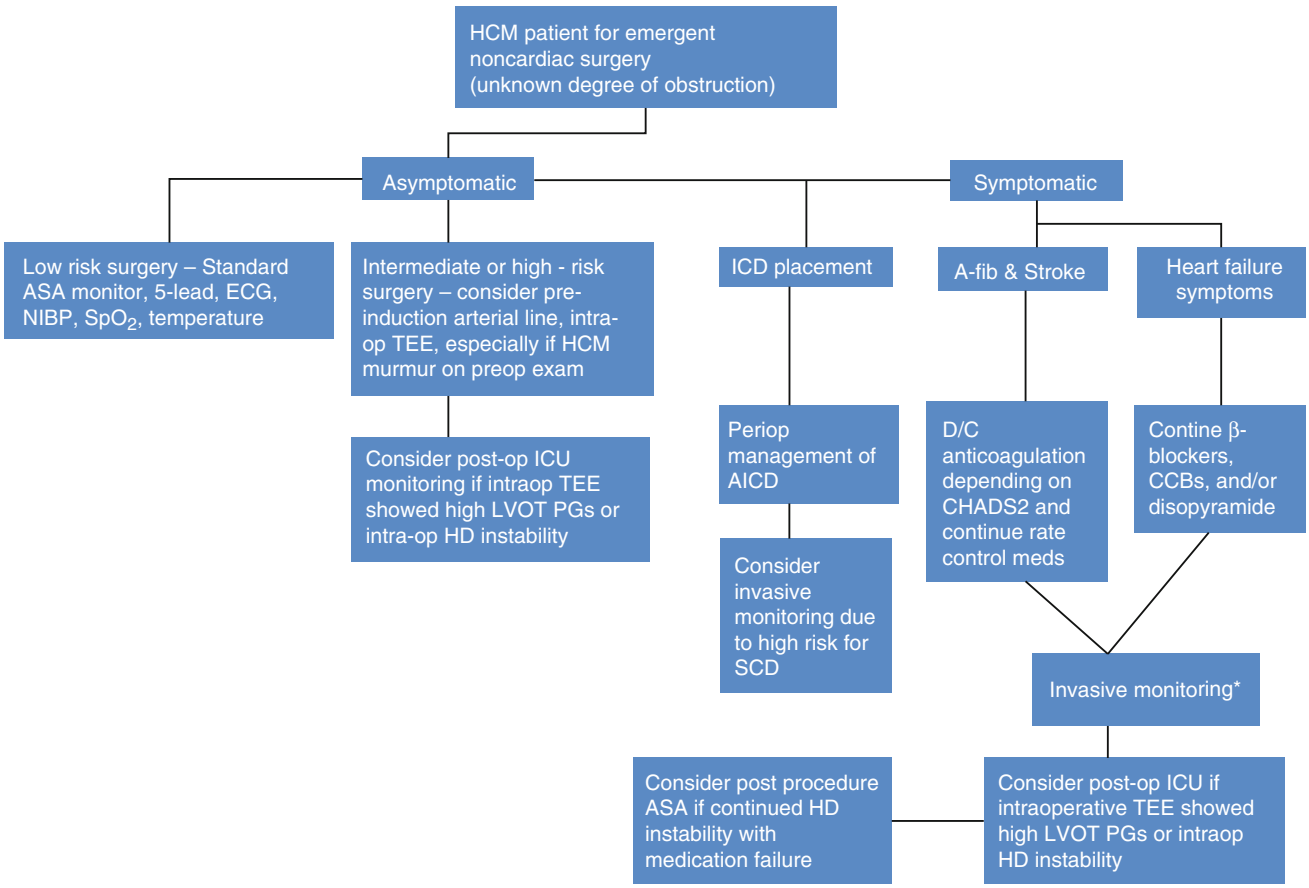

Fig. 22.3 Suggested algorithm for HCM patient requiring emergent/urgent surgery. * = Intra-arterial catheter, central venous catheter, +/– TEE. *LVOT* left ventricular outflow tract, *PG* pressure gradient, *HD* hemodynamic, *AICD* automated internal cardioverter defibrillator, *SCD* sudden cardiac death, *TEE* transesophageal echocardiography, *A-fib* atrial fibrillation, *CCD* calcium channel blocker

output of up to 50 % above pre-delivery values during the second stage of labor and as high as 80 % above pre-labor within the first hour of delivery [27]. Cardiac output slowly declines over the next 2 weeks. These peripartum hemodynamic pertubations place the HCM parturient at risk of new or increased left ventricular outflow tract obstruction (LVOTO), arryhthmias, and CHF [28].

General Management Before or During Pregnancy in HCM

Ideally before pregnancy, there should be a clinical assessment of HCM-related risks, including which category of LVOTO HCM the patient falls into: (1) nonobstructor, (2) obstructor at rest or (3) labile obstructor. Those with significant obstruction (>30 mmHg at rest) are at increased risk for morbidity and mortality [7, 17, 29] (See Fig. 22.3). Even though degree of obstruction can correlate with functional capacity, this may not always be the case. There are few studies and numerous case reports on pregnancy outcomes in HCM parturients. These generally show that NYHA class prior to pregnancy directly relates to maternal morbidity [17].

For patients (mother or father) with HCM, genetic counseling should be offered pre-conception [7]. In addition, some institutions are offering genetic testing of the fetus or pre-implantation for family planning purposes. Other assessments should be made regarding current medications, current or history of arryhthmias, implantable defibrillators, previous surgical or nonsurgical treatments such as myectomy or alcohol septal ablations. In patients who have undergone myectomy or alcohol septal ablation, in particular, an assessment should be made for the degree of any residual LVOT obstruction. Most patients with resolved obstruction, in whom diastolic dysfunction may have also improved, can tolerate pregnancy better than prior to such procedures, although confirmatory data are lacking.

Women with resting or provocable LVOT gradients >50 mmHg or NYHA Class > II should be referred to a high-risk maternal fetal medicine obstetrician [7, 27]. If HCM patients are currently on beta-blockers, most can be continued during the peripartum period. Atenolol is the exception due to the higher incidence of fetal growth restriction

compared with other beta-blockers [28]. Increased surveillance for fetal bradycardia and intrauterine growth restriction is prudent [7, 30]. For those parturients on verapamil, it can also be continued with the same precautions as in a nonparturient, i.e., it should be used with caution if functional status starts to deteriorate or those with severe LVOT gradients at rest [1, 28]. HCM patients on disopyramide prepregnancy should stop taking the medication prior to becoming pregnant due to its ability to possibly induce uterine contractions [28]. In those patients with history of atrial fibrillation and being anticoagulated, coumadin should be stopped due to its teratogenic effects [28] and they should be transitioned to therapeutic doses of enoxaparin [31].

In those patients with increased LVOT gradients (>30 mmHg at rest) and NYHA Class III or IV symptoms, it should be impressed upon them that they are at high risk for adverse maternal and fetal outcomes. They should be educated on methods of safe contraception to avoid becoming pregnant and placing themselves and the fetus at such risk. Estrogen and progesterone contraceptives can potentiate prothrombotic risks in HCM patients. These combined hormonal contraceptives are given WHO (World Health Organization) Class 2 rating which suggests the benefit outweighs the risk in those with HCM without atrial arrhythmias [27]. Other options include progestin-only formulations, intrauterine devices, barrier methods and sterilization [27]. In patients with severe symptoms that are likely to get prohibitively worse during the second or third trimesters, or post-partum, consideration to terminating the pregnancy should be given, in order to reduce maternal and fetal mortality.

Management During Labor and Delivery

The decision regarding the timing and mode of delivery (cesarean sections vs. vaginal) should be based on the hemodynamic status of the patient. Most HCM patients that are asymptomatic or have had mild, stable symptoms can be allowed to spontaneously progress into the stages of labor [27, 28]. If there are concerns about the functional adequacy of the heart to withstand the physiological changes of pregnancy, labor can be induced in a more controlled fashion with more availability of staff and monitoring capabilities. In the decompensating patient, a discussion between the cardiologist, obstetrician and anesthesiologist should occur that weighs the risks of continuing pregnancy to both the mother and fetus and the risk of delivery [27]. Vaginal delivery with its associated less blood loss is preferred over cesarean section unless there is fetal distress or the parturient is rapidly deteriorating hemodynamically [27].

Neuraxial anesthesia can dramatically decrease afterload, but careful titration of local anesthetics and opioids with adequate fluid administration prior to placement has been used successfully in HCM parturients [27]. In fact, the decrease in pain and sympathetic stimulation that neuraxial anesthesia allows can decrease cardiac contractility and heart rate which would benefit the HCM patient. Hemodynamic management following a spinal anesthetic may be more challenging and slow titration using a continuous spinal, decreased dose of intrathecal local anesthetic, advanced fluid loading, and patient positioning are critical aspects of management [32].

For a mandatory Cesarean section, arterial line placement is recommended. Depending on the degree of LVOTO, functional status, recent worsening of symptoms, arryhthmias, and emergent nature, it may be necessary to induce general anesthesia. If it is an emergent cesarean section, there is significant increased risk due to the cardiovascular instability that can occur with a rapid sequence induction and intubation. TEE would be of benefit in the scenario of a rapidly deteriorating or critically ill parturient undergoing general anesthesia for cesarean section. Similarly, a pulmonary artery catheter may prove beneficial to adequately monitor and manage fluid status and pressors, if needed. In particular, TEE could guide fluid management to maintain normovolemia, as well as assist in determining new causes of hemodynamic instability by allowing assessment of regional wall motion, degree of mitral regurgitation or LVOT obstruction. Pulmonary artery catheters could help assess left sided filling pressures and be useful post-operatively in the critical care setting.

Postpartum HCM patients may need a higher level of monitoring, i.e., an intensive care setting if the patient had significant hemodynamic changes during delivery or significant decline in functional status prior to delivery. Synthetic oxytocin administration after delivery to assist with uterine contractions should be administered slowly due to its side effect of decreasing systemic vascular resistance [27]. The elevated cardiac output and large fluid shifts postpartum can be especially precarious in the HCM patient and therefore hemodynamic monitoring for 12–24 h is advised [27].

The AHA/ACC guidelines on the use of pulmonary artery catheters in cardiac patients for noncardiac surgery (cesarean section) suggest that they can be used if the patient is at risk for major hemodynamic disturbances that can be detected by a PA catheter [15]. If the patient will be going to an ICU setting and has severely compromised LV dysfunction, PA catheter insertion can be considered if the ability to measure cardiac left- sided filling pressures and SvO_2 monitoring can assist the providers in determining causation for hemodynamic instability. This is often times indeed the case for patients with severe HCM with obstructive physiology, especially with resting obstruction. Intraoperatively, TEE may provide improved capabilities over PA catheters in HCM patients due to ability to assess biventricular function,

new or increasing LVOT obstruction, new regional wall motion abnormalities and degree of mitral regurgitation.

In conclusion, HCM is not an absolute contraindication to pregnancy and the most significant predictor of the parturient to tolerate the physiologic changes peripartum is the functional status of the patient prior to becoming pregnant. Cesarean section should only be performed if absolutely needed for the well being for the fetus and mother at the time of delivery, i.e., rapid deterioration in mother's hemodynamic status or severe fetal bradycardia. TEE and PA catheters can be utilized in the general anesthetic cesarean section HCM patient to help guide fluid management and/or the need for pressors.

Clinical Pearls

- Intra-aortic balloon pump is absolutely contraindicated in the HCM patient with left ventricular outflow tract obstruction (LVOTO) due to its ability to promote and potentially worsen obstruction.
- Myectomy and alcohol septal ablation could be considered in patients with peak LVOT gradients ≥30 mmHg at rest or ≥50 mmHg provoked prior to high-risk noncardiac surgery or patients contemplating pregnancy, especially if drug-refractory.
- Neuraxial anesthesia for the HCM parturient can be beneficial due to its ability to diminish the sympathetic response to pain (tachycardia and inotropy) and therefore decrease the risk of causing LVOTO. Slow titration of local anesthetic is warranted due to their side effect of decreasing afterload.
- Forceps-assisted or vacuum-assisted delivery of the fetus may be considered in the second stage of labor due to decreasing the amount of valsalva/pushing required of the HCM parturient, which would otherwise potentially worsen the LVOTO.

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Conflict of Interest

None of the authors have any conflicts.

References

1. Maron BJ, Maron MS. Hypertrophic cardiomyopathy. Lancet. 2013;381(9862):242–55.
2. Hreybe H, et al. Noncardiac surgery and the risk of death and other cardiovascular events in patients with hypertrophic cardiomyopathy. Clin Cardiol. 2006;29(2):65–8.
3. Haering JM, et al. Cardiac risk of noncardiac surgery in patients with asymmetric septal hypertrophy. Anesthesiology. 1996;85(2):254–9.
4. Fleisher LA, et al. ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery) Developed in Collaboration With the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. J Am Coll Cardiol. 2007;50(17):1707–32.
5. Maron BJ, et al. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. J Am Coll Cardiol. 2003;42(9):1687–713.
6. Olivotto I, et al. Obesity and its association to phenotype and clinical course in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2013;62(5):449–57.
7. Gersh BJ, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011;124(24):2761–96.
8. Maron MS, et al. Hypertrophic cardiomyopathy phenotype revisited after 50 years with cardiovascular magnetic resonance. J Am Coll Cardiol. 2009;54(3):220–8.
9. Maron BJ, et al. Clinical course of hypertrophic cardiomyopathy in a regional United States cohort. JAMA. 1999;281(7):650–5.
10. Spirito P, et al. The management of hypertrophic cardiomyopathy. N Engl J Med. 1997;336(11):775–85.
11. Maron MS, et al. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. Circulation. 2006;114(21):2232–9.
12. Maron MS, et al. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. N Engl J Med. 2003;348(4):295–303.
13. Olivotto I, et al. Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. Circulation. 2001;104(21):2517–24.
14. Maron BJ, et al. Noninvasive assessment of left ventricular diastolic function by pulsed Doppler echocardiography in patients with hypertrophic cardiomyopathy. J Am Coll Cardiol. 1987;10(4):733–42.
15. Fleisher LA, et al. 2009 ACCF/AHA focused update on perioperative beta blockade incorporated into the ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American college of cardiology foundation/American heart association task force on practice guidelines. Circulation. 2009;120(21):e169–276.
16. Afonso L, et al. Two-dimensional strain profiles in patients with physiological and pathological hypertrophy and preserved left ventricular systolic function: a comparative analyses. BMJ Open. 2012;2(4).
17. Autore C, et al. The prognostic importance of left ventricular outflow obstruction in hypertrophic cardiomyopathy varies in relation to the severity of symptoms. J Am Coll Cardiol. 2005;45(7):1076–80.
18. Angelotti T, et al. Anesthesia for older patients with hypertrophic cardiomyopathy: is there cause for concern? J Clin Anesth. 2005;17(6):478–81.

19. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. JAMA. 2002;287(10):1308–20.
20. Wysokinski WE, McBane 2nd RD. Periprocedural bridging management of anticoagulation. Circulation. 2012;126(4): 486–90.
21. Douketis JD, et al. The perioperative management of antithrombotic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008; 133(6 Suppl):299S–339.
22. Blackshear JL, et al. Hypertrophic obstructive cardiomyopathy, bleeding history, and acquired von Willebrand syndrome: response to septal myectomy. Mayo Clin Proc. 2011;86(3): 219–24.
23. Udelson JE, et al. Verapamil prevents silent myocardial perfusion abnormalities during exercise in asymptomatic patients with hypertrophic cardiomyopathy. Circulation. 1989;79(5): 1052–60.
24. Sherrid MV, et al. Multicenter study of the efficacy and safety of disopyramide in obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol. 2005;45(8):1251–8.
25. Turner GM, Oakley CM, Dixon HG. Management of pregnancy complicated by hypertrophic obstructive cardiomyopathy. Br Med J. 1968;4(5626):281–4.
26. Oakley GD, et al. Management of pregnancy in patients with hypertrophic cardiomyopathy. Br Med J. 1979;1(6180):1749–50.
27. Stergiopoulos K, Shiang E, Bench T. Pregnancy in patients with preexisting cardiomyopathies. J Am Coll Cardiol. 2011;58(4):337–50.
28. Sebastien K, van der Smagt JJ, van den Berg MP. Systematic review of pregnancy in women with inherited cardiomyopathies. Eur J Heart Fail. 2011;13:584–94.
29. Avila WS, et al. Influence of pregnancy on clinical course and fetal outcome of women with hypertrophic cardiomyopathy. Arq Bras Cardiol. 2007;88(4):480–5.
30. Frishman WH, Chesner M. Beta-adrenergic blockers in pregnancy. Am Heart J. 1988;115(1 Pt 1):147–52.
31. Rowan JA, et al. Prophylactic and therapeutic enoxaparin during pregnancy: indications, outcomes and monitoring. Aust N Z J Obstet Gynaecol. 2003;43(2):123–8.
32. Pryn A, et al. Cardiomyopathy in pregnancy and caesarean section: four case reports. Int J Obstet Anesth. 2007;16(1):68–73.

Constructing a Hypertrophic Cardiomyopathy Center of Excellence

23

B. Robinson Williams III

Abstract

Over the past two decades, a network of regional hypertrophic cardiomyopathy (HCM) centers has been established. The primary goal of these centers is to provide state-of-the-art longitudinal care and consistent outcomes for patients with HCM. The comprehensive care at an HCM center is a result of collaboration amongst a multidisciplinary team that includes specialists in adult and pediatric cardiology, electrophysiology, interventional cardiology, cardiac surgery and genetic counseling, all with particular expertise in treating the patient with HCM. Additional benefits of having a network of regional HCM centers is that it encourages consistency of treatment algorithms and outcomes, as well as collaborative research between institutions.

Keywords

HCM center • Multidisciplinary • Genetic counseling • Septal myectomy • Alcohol septal ablation • Cardiac electrophysiology

Abbreviations

HCM	Hypertrophic cardiomyopathy
HCMA	Hypertrophic Cardiomyopathy Association
ICD	Implantable cardioverter defibrillator
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
SCD	Sudden cardiac death
TEE	Transesophogeal echocardiography
VUS	Variants of unknown significance

Key Points

1. A national network of referral centers has been established for patients with hypertrophic cardiomyopathy (HCM) both adult and pediatric.
2. The goal of these centers is to improve clinical care for patients with HCM by concentrating expertise and patient volume and to facilitate both investigator-initiated and large scale randomized controlled trial research.
3. Key components of an HCM center include HCM specialists in adult and pediatric cardiology electrophysiology, cardiac imaging, cardiac surgery, interventional cardiology, advanced heart failure therapy, genetic counseling, and an administrative HCM coordinator. Administrative support for marketing and programmatic development is similarly important.

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4. An HCM center offers expertise in advanced therapies for HCM patients such as surgical myectomy and alcohol septal ablation meeting national standards for competency and clinical outcomes for both procedures.

Introduction

In the 2011 ACCF/AHA guidelines for the diagnosis and treatment of hypertrophic cardiomyopathy (HCM), the following paragraph is devoted to the concept of the HCM center:

> The writing committee considers it important to emphasize that HCM is a complex disease entity with a broad (and increasing) clinical and genetic spectrum. Although HCM is one of the most common forms of genetic heart disease and relatively common in the general population, this disease entity is infrequent in general clinical practice, with most cardiologists responsible for the care of only a few patients with HCM. This principle has led to an impetus for establishing clinical programs of excellence—usually within established centers—in which cardiovascular care is focused on the management of HCM (i.e., "HCM centers"). Such programs are staffed by cardiologists and cardiac surgeons familiar with the contemporary management of HCM and offer all diagnostic and treatment options, including genetic testing and counseling, comprehensive transthoracic echocardiogram (TTE), CMR imaging, both surgical septal myectomy and alcohol ablation, and the management of atrial fibrillation (AF)/atrial flutter, and ICDs. Another advantage is the potential to perform outcomes research on large groups of patients [1].

In this paragraph, the guidelines writing committee emphasizes the importance of regional referral centers dedicated to the care of patients with HCM. The "HCM Centers of Excellence" serve to provide comprehensive medical care for patients and their families as well as facilitate the formation of a national network of centers that can collaborate in multicenter research studies. In this chapter, we will discuss the evolution of the concept of "Centers of Excellence" and discuss the components of an HCM center.

The concept of regional centers of excellence in healthcare in the United States can be traced back to the National Cancer Institute (NCI), a division of the National Institutes of Health (NIH). During the first half of the twentieth century, the public and the medical community began to focus more of their attention on cancer, a disease that seemed to be rapidly increasing in prevalence and appeared to have no cure. In 1960, the NCI recommended the formation of government-sponsored cancer centers. The goal was to unify the research being done at various academic centers around the country. In 1971, the National Cancer Act was signed, which established fifteen NCI-designated cancer centers. These centers were distributed throughout the United States at various institutions based on population, geography and medical science expertise. Their mandate was to conduct "clinical research, training and demonstration of advanced diagnostic and treatment methods relating to cancer" [2].

Today, there are more than 60 NCI-designated cancer centers across the country. In order to obtain this designation, a center must meet various criteria set forth by the NCI both in terms of clinical expertise and research capabilities. Regional centers of excellence not only allow for collaboration between institutions, but also allow patients to have access to world-class clinical care within driving distance. In the decades that have followed, other national organizations have followed the highly successful "center" model adopted by the NCI. Both the Hypertrophic Cardiomyopathy Association (HCMA) and the Children's Cardiomyopathy Foundation (CCF) follow this model for patients with HCM.

The HCMA was founded in 1996 with the stated goal of providing "support, advocacy and education to patients and their family members, the medical community and the public about hypertrophic cardiomyopathy" [3]. The HCMA was founded by Lisa Salberg, herself an HCM patient who had lost multiple family members to the disease. One of the goals of the HCMA was to establish a national network of HCM centers. They have been very successful in this regard. Prior to the founding of the HCMA, there were only a handful of institutions with multidisciplinary expertise in the diagnosis and treatment of HCM. Currently, there are twenty-seven HCM centers recognized by the HCM in nineteen states (Fig. 23.1).

Much like the NCI-designated cancer centers, HCM centers allow patients to have access to state of the art care closer to home. The HCMA has established criteria that an institution must meet in order to qualify. In addition, many HCM centers have collaborated to form a powerful research network. The remainder of this chapter will be spent discussing the components that comprise an HCM center as well as the role of an HCM center in education and research.

Another organization specifically for the pediatric population is the Children's Cardiomyopathy Foundation (CCF). The CCF was founded by Lisa Yue after her son died from HCM and has similarly begun instituting the Center of Excellence concept for cardiomyopathies, including HCM. The goal, similar to the HCMA, is to foster a network of centers that can address HCM in the pediatric population, including advanced therapies. The CCF has likewise identified institutions with particular expertise in HCM care, especially as it relates to the pediatric population. While there is significant overlap between the two lists, there are some differences (Fig. 23.2).

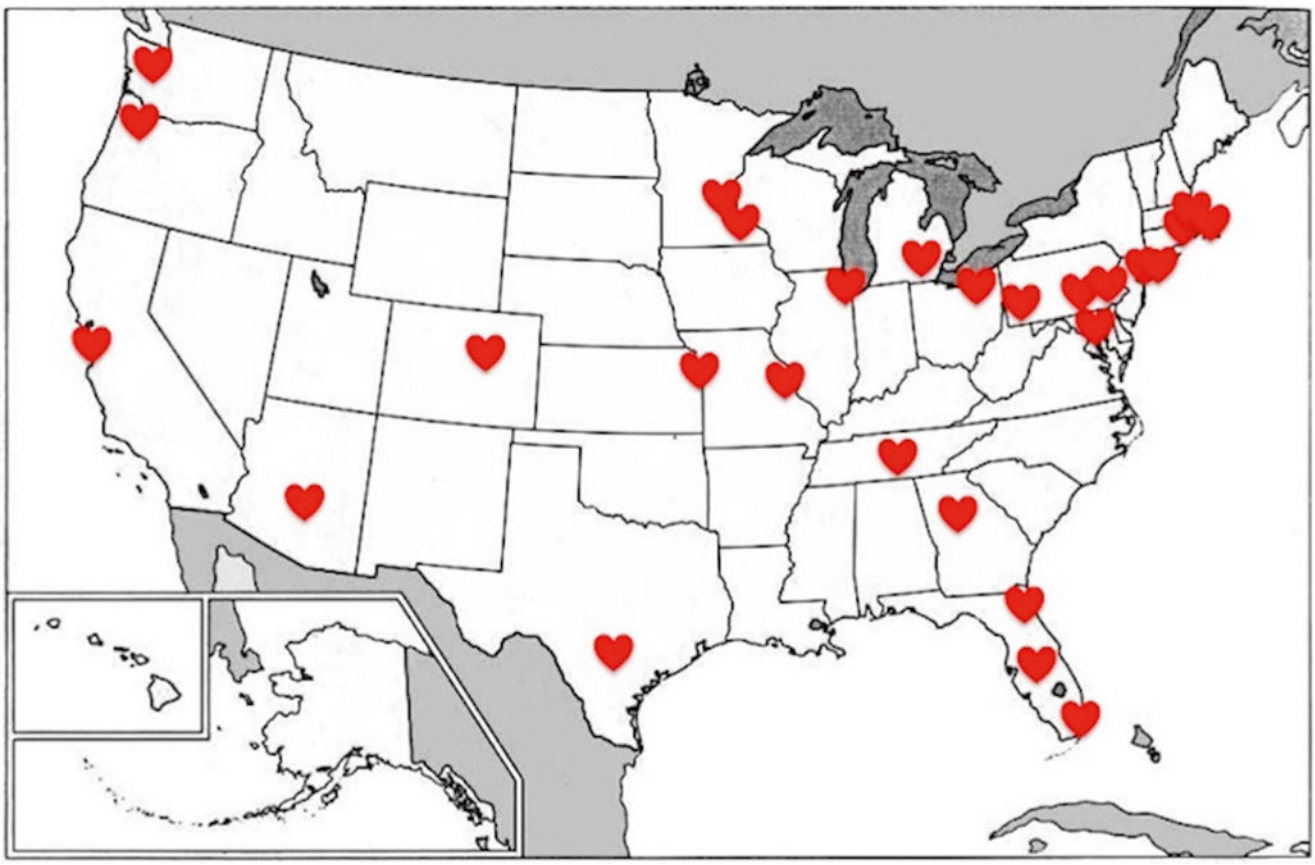

Fig. 23.1 Location of HCM centers currently recognized by the Hypertrophic Cardiomyopathy Association (HCMA)

Of course, the centers recognized by the HCMA and CCF are not the only centers caring for patients with HCM. Several well-known HCM centers have not been selected, but remain active and well-respected both clinically and through research, with large patient volumes and longstanding experience. Thus, the listed centers are not meant to be a comprehensive listing, but rather two examples of networks for HCM. Indeed, there is excellent and comprehensive care being provided to HCM patients at centers throughout the United States and countries throughout the world not on these lists for a variety of reasons, but all follow the concepts outlined herein in terms of the components and goals of such centers.

Components of an HCM Center

HCM is a heterogeneous and unpredictable disease that is encountered relatively infrequently in a general cardiology practice. Having regional centers allows for cardiologists and surgeons to gain expertise by caring for large volumes of patients. Furthermore, caring for patients and families with HCM requires a multidisciplinary team approach. Ideally, an HCM center should include a medical director, adult and pediatric cardiology, cardiac imaging (echocardiography and cardiac magnetic resonance imaging), electrophysiology, cardiac surgery, interventional cardiology, cardiac transplant and genetic counseling (see Table 23.1). A clinical coordinator that helps patients through the system, and enhances communication with referring physicians, is also important.

HCM Specialist

The medical director of an HCM center is the individual with expertise in the diagnosis and management of patients with HCM. This individual typically devotes a significant percentage of his clinical time to the care of patients with this complex disease, and is involved in the vision and direction of the program and the accumulation and maintenance of knowledge regarding HCM. He or she is also responsible for coordinating the clinical care of patients at their institution. A large medical center will often already have most or all of the components needed for an HCM center, although significant time will need to be devoted to growing and maintaining the HCM expertise of each of these individuals. The medical director will also ensure that these components work in

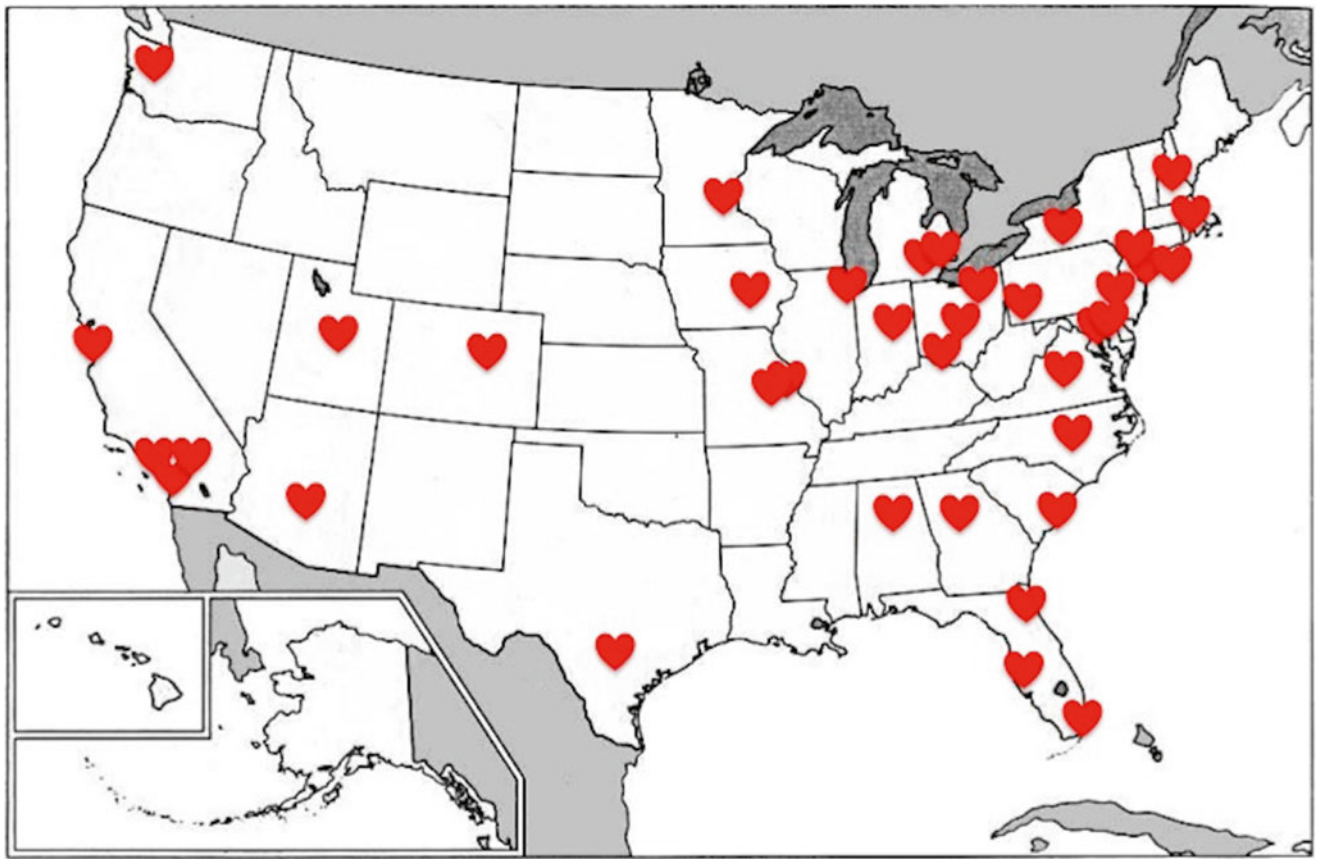

Fig. 23.2 Location of pediatric HCM centers recognized by the Children's Cardiomyopathy Foundation (CCF)

Table 23.1 Components of an HCM Center

HCM Coordinator
HCM Specialist
Pediatric Cardiology
Cardiac Imaging (Echocardiography and Cardiac MRI)
Cardiac Electrophysiology
Cardiac Surgery
Interventional Cardiology
Advanced Heart Failure/Transplant
Genetic Counseling

concert and continue to accrue specific knowledge and experience regarding HCM treatment.

Traditionally, the medical director is a general cardiologist, often with an expertise in cardiac imaging. However, a cardiology subspecialist such as an electrophysiologist or interventional cardiologist could certainly serve in this role. The medical director is often the first physician that the patient will encounter at the HCM center. The medical director will then refer the patient to other members of the team as he or she sees fit. In addition, the medical director is responsible for keeping the lines of communication open among the team members, often with multidisciplinary conferences. The medical director often supervises the HCM-related clinical research being performed at the center and is typically the director of the HCM-related educational efforts. She or he is also responsible for making sure the Center is prioritized within the institution, including administrative and financial support to maintain and grow the program. The HCM director is oftentimes the face of the program, interacting external from marketing and development standpoints, including raising awareness of HCM.

Pediatric Cardiology

Pediatric cardiology is another integral part of any HCM center. Hypertrophic cardiomyopathy is a genetic disease that can affect multiple members of the same family, including children. It is also the leading cause of sudden cardiac death in children and young people under the age of 35. While the HCM phenotype most commonly manifests itself during the second or third decade of life, the disease can present at any age. Infants diagnosed with HCM at a very young age (<1 year) tend to have more severe disease and higher mortality rates [4]. Children and adolescents with HCM may develop symptoms, and/or need advanced care,

such as implantable defibrillators or surgery. The pediatric cardiologist is responsible for managing these patients, and coordinating care, sometimes with outside institutions.

In addition to caring for affected children, pediatric cardiologists play a pivotal role in screening the adolescent first-degree relatives of HCM patients. For patients less than 12 years of age (or prior to the onset of puberty) with a first degree relative with HCM, screening is optional unless there is clinical suspicion for early onset (e.g. murmur or syncope), a malignant family history of premature death from HCM or the child is involved in high-risk competitive athletics [1]. It is recommended that adolescents undergo screening every 12–18 months. Screening typically involves history and physical examination, electrocardiography and echocardiography. Lifestyle factors and social implications are particularly important in children; therefore, the pediatric cardiologist must have access to social and/or psychology services, and work closely with the parents of the children to address any and all concerns, including sports participation, social isolation, and other psychological issues.

The introduction of genetic testing of families with HCM has resulted in the creation of a group of patients that are genotype-positive for HCM but phenotype-negative. The majority of these genotype-positive, phenotype-negative individuals will be children or adolescents and will need rigorous monitoring by a pediatric cardiologist for the development of the HCM phenotype.

Cardiac Imaging

Expertise in cardiac imaging is another important component of an HCM center. Although multiple imaging modalities are utilized, echocardiography is the predominant modality for diagnosis and management of patients with HCM. As mentioned in the previous section, echocardiography is the test of choice when screening first-degree relatives of HCM patients. Echocardiography is also important in assessing those with known HCM as well. Echocardiography is used determine if left ventricular outflow tract (LVOT) obstruction is present and accurately measure gradients, determine maximum wall thickness, assess diastolic and systolic left ventricular function and assess response to therapy. Newer echocardiographic techniques such as strain-rate imaging, three-dimensional echocardiography and left atrial volume index are also useful in the assessment of HCM patients.

Echocardiography is also used frequently during alcohol septal ablation to help guide the interventional cardiologist. Intra-operative transesophogeal echocardiography (TEE) is frequently utilized to guide surgeons during septal myectomy. A sonographer or interpreting physician at a high-volume HCM center is more likely to have a full grasp of the subtleties of diagnosing and assessing HCM with echocardiography. Sonographers should use a consistent protocol when imaging an HCM patient, including Doppler assessment from multiple views with and without provocation and the use of myocardial contrast agents when indicated to assist in defining endocardial borders and determining wall thickness. In addition, sonographers at a high-volume HCM center should be familiar with utilizing exercise echocardiography to assess functional capacity and provokable LVOT obstruction.

In addition to echocardiography, cardiac magnetic resonance imaging (MRI) plays a crucial role in the assessment of patients with HCM. Over the past decade, cardiac MRI has become an increasingly important study not only for establishing the diagnosis of HCM but also in risk stratification for sudden cardiac death. Cardiac MRI has higher special resolution than echocardiography and the ability to image the heart in a tomographic fashion. It is useful in establishing the diagnosis in patients with difficult echo images or with focal hypertrophy in areas that are often not well visualized with echo (anterolateral wall or apex). Cardiac MRI is useful in risk stratification in HCM by being able to accurately measure maximum wall thickness and assess the extent of left ventricular delayed enhancement. Late gadolinium enhancement in HCM is associated with adverse clinical outcomes, including all-cause mortality [5]. Cardiac MRI can also be used to establish the diagnosis of HCM in patients that have equivocal echocardiograms or to provide a more accurate measurement of wall thickness in those with severe hypertrophy by echocardiogram. A wall thickness of $\geq$3.0 cm has been associated with an increased risk of sudden cardiac death (SCD) and may be an indication for implantation of an implantable cardioverter defibrillator (ICD). Cardiac MRI is emerging as an essential component of the evaluation of HCM patients and a center should have expertise in this imaging modality.

Cardiac Electrophysiology

Cardiac electrophysiology is a subspecialty available in most cardiology practices and cardiac centers. It is also a critical component of an HCM center. As discussed elsewhere in this textbook, HCM patients are at increased risk of SCD when compared to the general population, with an average incidence of 1 % annually. Many HCM patients will be deemed to be at high risk for SCD and require an ICD. Often, HCM patients who require an ICD are younger and more active than the typical adult cardiology patient and this must be taken into consideration by the electrophysiologist. By virtue of their age, HCM patients are more likely to need multiple generator exchanges over their lifetime. Lead failure is also more common in HCM patients. This is likely a result of the patients' higher activity levels and possibly due to the

hyperdynamic contraction of the hypertrophic heart. Being exposed to multiple procedures over their lifetime increases the cumulative risk for HCM patients. Having an experienced electrophysiologist will mitigate this increased risk.

In addition to an increased risk for ventricular tachyarrhythmias and SCD, patients with HCM are at high risk for atrial arrhythmias such as atrial fibrillation and flutter. An electrophysiologist may be needed to help guide antiarrhythmic therapy or perform ablation procedures to treat the atrial or ventricular arrhythmias. In contrast to patients with other underlying heart diseases, ablation procedures in HCM patients may have unique challenges due to very large atria or extreme hypertrophy of the left ventricle. Thus, specialized expertise in the care of HCM patients is also needed in this regard.

Finally, pacemakers are also often required in patients with HCM. Elderly patients may benefit from pacemakers to reduce outflow tract obstruction, or allow higher doses of atrio-ventricular nodal blocking drugs (i.e. beta-blockers or calcium-channel blockers). In addition, patients following both alcohol septal ablation and surgical myectomy may require pacemakers for heart block or severe conduction disease.

Cardiac Surgery

Cardiac surgery, with specific expertise in the septal myectomy procedure, is another important component of an HCM center. The isolated septal myectomy procedure is considered the gold standard in the United States for treating symptomatic patients with LVOT obstruction that is resistant to medical therapy. Like any surgical procedure, operator experience is critical to obtaining good clinical results and low complication rates. However, given the relative scarcity of HCM in most cardiac centers, it is difficult for surgeons to obtain the surgical volumes necessary to become proficient except in the setting of a high-volume HCM center. The 2011 ACCF/AHA guidelines recommend operator volume of at least 20 cases and the center should achieve a mortality rate of <1 % and a major complication rate of <3 % [1]. The HCMA does not require the presence of an on-site septal myectomy surgeon at an HCM center. A center may have an established referral pathway to an established high-volume surgical center. Surgeons should be experienced in complex mitral valve repair, including modifications to papillary muscles and chords, in order to avoid the need for mechanical mitral valve replacement. In many instances, formal on-site proctoring by an established HCM surgeon may be required.

Interventional Cardiology

In addition to surgical septal myectomy, the other invasive treatment for symptomatic HCM patients with LVOT obstruction is alcohol septal ablation. This procedure, covered in depth in Chap. 19, is a catheter-based procedure performed by an interventional cardiologist. An HCM center should offer this as an option for their patients with LVOT obstruction that fail medical therapy. This procedure should be considered in those patients whose surgical risk may be unacceptably high due to comorbidities or a less-invasive option for those patients who refuse surgical therapy. Like surgical myectomy, high operator volumes are associated with better clinical outcomes and fewer complications. Similar to surgical myectomy, the 2011 ACCF/AHA guidelines also recommend an operator volume of at least 20 cases for those that perform alcohol septal ablations [1]. These high volumes are most easily attained in the setting of a high-volume HCM center. Similar to surgical myectomy, a center may have an established referral pathway to an established high-volume interventional cardiologist with expertise in alcohol septal ablation. Also as with surgery, formal proctoring in the performance of alcohol septal ablation, either on-site or by way of national courses, may be required.

In addition to performing alcohol septal ablation, the interventional cardiologist should be adept at advanced hemodynamic assessment techniques, including a comprehensive hemodynamic evaluation to determine and isolate HCM physiology in the symptomatic patient. As alcohol septal ablation or surgery is only a viable option in those in whom severe obstructive physiology is the rate-limiting step in the patient's clinical symptoms, this assessment is absolutely vital to understanding how to manipulate medications, devices and other invasive therapies in order to improve patient outcome.

Advanced Heart Failure and Transplant

Each year, 1–2 % of HCM patients will progress to "end-stage" HCM. This is defined as the development of systolic dysfunction (left ventricular ejection fraction of ≤50 %) and is thought to be due to progressive myocardial fibrosis. End-stage HCM is discussed in detail in Chap. 20. The mortality rate for this patient population is high (11 % per year) [6]. Many of the end-stage patients will develop progressive heart failure despite optimal medical therapy and some will undergo cardiac transplantation. Some patients with advanced diastolic dysfunction (non-obstructive) may also progress to end-stage heart failure with preserved ejection fraction. For these reasons, an established advanced heart failure program with transplant capability is an asset for an HCM center.

The advanced heart failure specialist is vital in comprehensive assessment of these patients with end-stage diastolic or systolic heart failure, performance and tracking of cardiopulmonary exercise testing results, titration of advanced medications and therapies, and the timing of listing for heart transplantation, if required. For such patients,

the heart failure specialist often becomes the primary treating physician. In many cases, the HCM heart failure and transplant specialist is at a different but nearby institution, but works in close collaboration with both the regional HCM specialist and the local cardiologist.

Genetic Counseling

Genetic testing and genetic counseling is an important service offered by an HCM center. HCM is a genetic disease caused by a mutation in one of several genes encoding for sarcomere proteins. The disease is transmitted in an autosomal dominant fashion. Therefore, when an individual is diagnosed with HCM, all first-degree family members should be screened for the disease. Family screening is discussed in detail in Chap. 13. A genetic counselor can determine when to utilize genetic testing and aid in interpreting the results. They can help explain the ramifications of a positive test, negative test or variants of unknown significance (VUS) to patients and family members, including implications on life expectancy, complications, life and health insurance, as well as future transmission of disease.

HCM Coordinator

An HCM center benefits tremendously from a dedicated HCM coordinator. Such an individual accepts all calls from HCM patients and referring physicians, triages and schedules patients for clinical visits, and helps coordinate testing. In particular, patients from distant locations may require multiple tests or office visits on a single day, or may require complex insurance authorizations. A coordinator experienced in these aspects assures a smooth running center, and enhances both the patient and physician experience. HCM coordinators are also helpful in the research and educational missions of the center, organizing conferences, and facilitating the work of all members of the HCM team.

Research at HCM Centers

We have discussed the advantages of the multidisciplinary approach of a high-volume HCM center and how this improves clinical care. Another advantage of regional HCM centers is that it facilitates research. HCM centers have the ability to establish large clinical databases that allow for longitudinal outcomes research. Furthermore, centers can combine their databases to form even more powerful observational or randomized prospective studies. Much of what we know today about HCM is a result of these observational studies. The rate of SCD in HCM, the effectiveness of ICD therapy in HCM patients, and outcomes from surgical myectomy and alcohol septal ablation have been demonstrated by registries from HCM centers in the United States and elsewhere.

Over the past 30 years or so, the effectiveness of therapies for other cardiac diseases like coronary artery disease and congestive heart failure have been demonstrated in large, prospective randomized clinical trials. These diseases are very prevalent and therefore easier to study in this manner. Due to a relative scarcity of patients, prospective randomized trials for HCM are uncommon. One of the benefits of a national network of HCM centers is the ability to pool patients for randomized clinical trials.

In addition to large-scale research across centers, individual centers with particular expertise (such as with surgical myectomy or pediatrics) may be able to perform individual investigator-initiated research to advance the field. Such findings can then be extrapolated to other regions of the country for the benefit of all patients with HCM.

Education at HCM Centers

In addition to providing quality clinical care and conducting research, an HCM center also should be engaged in educating fellow health care professionals and patients about HCM. Education can come in many forms, including a local conference devoted to HCM, speaking at local hospitals and medical centers and information sessions for patients and their families. Certain centers with particular excellence can also be national leaders, educating others at national cardiovascular, surgical, heart failure or interventional meetings. Accordingly, education includes participating in national cardiology meetings such as the American College of Cardiology and the American Heart Association as well as meetings devoted specifically to HCM like the International Summit of Hypertrophic Cardiomyopathy and the HCMA Annual Meeting.

Education serves two main purposes. Naturally, it raises the awareness of HCM among local physicians and other health care providers and likely improves care of HCM patients. Second, it provides exposure for the HCM center and makes other health care professionals aware that this national network of referral centers exists. In this regard, certain advertising such as radio commercials or website development can serve an educational function.

Conclusion

Over the past two decades, a national network of HCM Centers of Excellence has been established. The goal of the centers is to improve clinical care for HCM patients, encourage HCM research and improve HCM-related awareness and education. A successful HCM center utilizes a multidisciplinary team with a wide array of expertise, including HCM specialists in adult and pediatric cardiology, electrophysiology, cardiac imaging,

cardiac surgery, interventional cardiology, advanced heart failure therapy and genetic counseling, all of it managed by a dedicated HCM coordinator.

This multidisciplinary team brings their broad skill set together to care for patients with a complex and unpredictable disease. The existence of HCM centers also facilitates collaboration between institutions. High-volume centers have established databases and can collaborate with other centers to form even larger databases. This results in meaningful outcomes research and randomized clinical trials. The type of collaboration that occurs within *and* between HCM centers will undoubtedly advance our understanding of the disease and help HCM patients live longer, better lives.

The intent of the HCM centers is not to replace the local cardiologist in caring for HCM patients. Instead, the centers are meant to be a resource for referring providers and patients. They can offer a second opinion on patients that have symptoms that are difficult to manage or assist in assessing risk for SCD. An HCM center will likely offer services such as genetic counseling or expertise in septal myectomy or alcohol septal ablation that are not readily available in most cardiology practices. An HCM center is also available to assume care of patients or families with more severe forms of the disease. However, many patients will continue to be followed by their local cardiologist after visiting an HCM center. This may be the preferred strategy in patients who do not live in close proximity to an established center, or in patients with a variety of comorbidities. Effective communication between the center and local cardiologist is imperative to ensure the HCM patient continues to receive high-quality care.

References

1. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy. J Am Coll Card. 2011;58:2703–38.
2. National Cancer Act of 1971, Pub. L. No. 92–218, (Dec 23, 1971).
3. 4hcm.org [website]. New Jersey: Hypertrophic Cardiomyopathy Association; [updated 7/1/2009]. Available from https://www.4hcm.org/hcma-the-organization/about-the-hcma/3079-mission-and-vision-statement.html.
4. Colan SD, Lipschultz SE, Lowe AM, Sleeper LA, Messere J, Cox GF, et al. Epidemiology and cause-specific outcome of hypertrophic cardiomyopathy in children: findings from the Pediatric Cardiology Registry. Circulation. 2007;115:773–81.
5. Green JJ, Berger JS, Kramer CM, Salerno M. Prognostic value of late gadolinium enhancement in clinical outcomes for hypertrophic cardiomyopathy. J Am Coll Cardiol Img. 2012;5(4):370–7.
6. Harris KM, Spirito P, Maron MS, Senovich AG, Formisano F, Lesser JM, et al. Prevalence, clinical profile, and significance of left ventricular remodeling in the end-stage phase of hypertrophic cardiomyopathy. Circulation. 2006;114:216–25.

Longitudinal Case Based Presentations in HCM

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Abstract

A significant volume of data has been published over the past several years regarding HCM, yet only recently in 2011 has the ACCF/AHA issued guidelines for management and diagnosis. Nonetheless, the acute and chronic management of HCM is highly nuanced, based on collective experience of a large number of patients. In order to elucidate the subtleties of management, seven carefully selected cases from our HCM center attempt to depict the medical decision making process at various stages of illness. Case 1 is a middle-aged male with refractory NYHA Class III symptoms who eventually improved after undergoing surgical septal reduction. Case 2 is a young female with history of sudden death and refractory symptoms who required invasive therapy and a successful alcohol septal ablation was performed due to strong patient preference. Case 3 is a young female without significant outflow tract obstruction but with advanced diastolic heart failure who eventually required a heart transplant. Case 4 depicts severe obstructive HCM in a female with advanced age who after an extended course of medical therapy eventually improved post alcohol septal ablation. Case 5 is a relatively young female post ICD for SCD with ICD lead complications and atrial fibrillation well managed medically. Case 6 is a middle aged male with severe obstructive HCM who required invasive therapy eventually and preferred alcohol septal ablation to surgery. Case 7 is a patient with obstructive HCM referred for alcohol septal ablation who was subsequently determined to have a subaortic membrane and ultimately required surgical treatment. As will become clear, appropriate care of HCM patients requires an individualized and comprehensive approach keeping in view their specific and oftentimes changing presentation, currently available data, and guidelines, all within the confines of a dedicated HCM center.

Keywords

Case series • Hypertrophic cardiomyopathy • Long-term • Follow-up

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Abbreviations

ACCF	American college of cardiology foundation
AHA	American heart association
CMRI	Cardiac magnetic resonance imaging
CPR	Cardiopulmonary resuscitation
DCCV	Direct current cardioversion
ETT	Exercise treadmill test
HCM	Hypertrophic cardiomyopathy
HOCM	Hypertrophic obstructive cardiomyopathy
ICD	Implantable cardioverter defibrillator
INR	International normalized ratio
LBBB	Left bundle branch block
LGE	Late gadolinium enhancement
LVOT	Left ventricular outflow tract
MR	Mitral Regurgitation
NSVT	Non-sustained ventricular tachycardia
NYHA	New York Heart Association
RBBB	Right bundle branch block
SAM	Systolic anterior motion of mitral valve
SCD	Sudden cardiac death
TEE	Transesophageal echocardiography
TTE	Transthoracic echocardiography
VT	Ventricular tachycardia

Introduction

Hypertrophic cardiomyopathy (HCM) has been well recognized since the 1950s. However, only recently has the frequent prevalence of this condition been recognized, affecting roughly 1 in 500 people. The complex pathophysiology continues to be delineated, and includes diastolic dysfunction, outflow tract obstruction, mitral regurgitation, congestive heart failure and pulmonary hypertension, as well as other sequelae including atrial fibrillation or stroke. Nonetheless, significant advances have been made in understanding this disease, including its genetic basis. Indeed, various mutations have been identified to help screen individuals and their families, to both help identify affected individuals and also determine who is safe to exclude from further testing.

Numerous anatomic, physiologic and clinical variables are now known to exist that can lead to a variety of presentations, ranging from no phenotypic expression of the disease in a gene positive individual to sudden cardiac death in a massively hypertrophied individual. Alternatively, more chronic presentations including refractory heart failure requiring heart transplant are also noted. The complex interplay of various factors like diastolic dysfunction, dynamic left ventricular outflow tract obstruction, mitral valve apparatus abnormalities, pulmonary hypertension, and arrhythmias leads to a fascinating range of presentations which, if not properly managed, may progress through the life of the patient causing increased morbidity or mortality. Severely symptomatic patients present with exertional dyspnea, lower extremity swelling, orthopnea, syncope or more crippling conditions such as cardioembolic stroke, advanced heart failure and/or life threatening arrhythmias. Coexistent medical conditions like obesity, hypertension and lung pathologies may sometimes even further confuse the picture by causing similar and overlapping symptoms. In many cases, symptoms are ascribed to these alternate diagnoses for years prior to a firm diagnosis of HCM. The problem is compounded by the fact that many cardiologists and echo-cardiographers are not exposed to HCM patients in their routine clinical practice and hence this condition is oftentimes picked up only after referral to a second or third specialist, by which time the symptoms, morphology and function may have become even more debilitating, and thus limiting potential treatments and expected quality of life or survival benefits. Indeed, methods aimed at increased awareness and early diagnosis and treatment are needed in this field.

Management of certain select populations like younger patients who participate in competitive sports, who have prospects of a long productive life ahead of them, as well as pregnant women, may be more challenging. Fortunately, after HCM is recognized in a patient, they can be referred to a high volume HCM center and most of the time symptoms may be abated by various non-invasive and/or invasive approaches, including appropriate pharmacotherapy and lifestyle modifications, as outlined elsewhere in this book and within the current HCM guidelines.

A challenge in the dissemination of information regarding the treatment of HCM patients is the wide variability in clinical presentations, anatomy, cardiac function, and individual responses to therapies in a population that is overall relatively rare and oftentimes misunderstood. Accordingly, much of the treatment expertise resides in a few individuals at even fewer HCM Centers of Excellence. Since the management of this disease is learned through one patient at a time, the purpose of this chapter is to simulate clinical experience by case presentations. Accordingly, this chapter lays out seven cases with their initial presentations and longitudinal followup over several years at our HCM center, and depicts the range of presentations of these patients and how they were managed. It is anticipated that this approach will be complementary to the didactic descriptions of diagnosis and management found elsewhere in this textbook. Importantly, as this is a single-center experience, some of the decisions will be based on local experience and outcomes; therefore, the point of the chapter is not to suggest the perfect course for a group of patients, but to document one such course for the given patient.

Each case is organized starting with their initial encounter, including any relevant historical information, and following the patient through to the most recent office visit. Through the presentations we will pause for clinical decision-making discussions, as well as clinical pearls, so the reader gets a firm understanding of the reasoning behind each of the clinical decisions and some of the nuanced care.

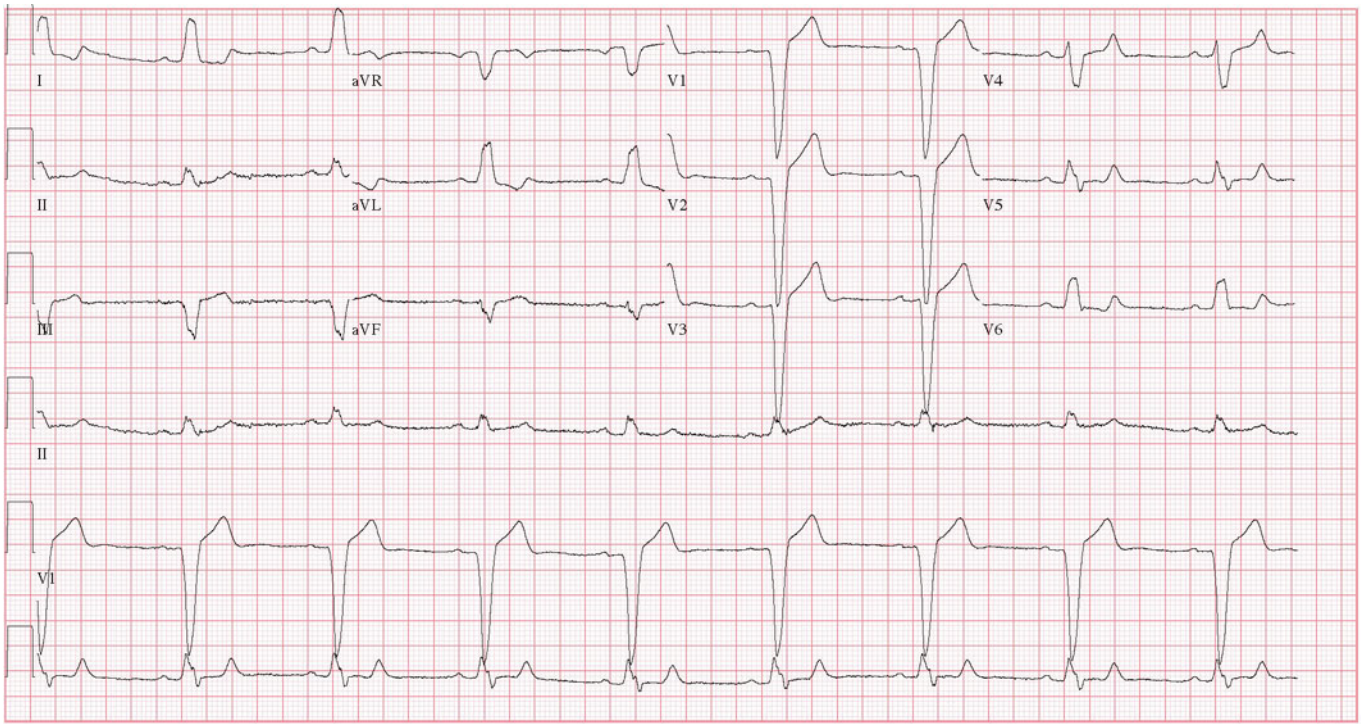

Fig. 24.1 Case 1: Electrocardiogram with left bundle branch block

Case 1: A 58 Year Old Man with Refractory HCM Symptoms

A 58 year-old Caucasian male with past medical history of hypertension presented after being recently diagnosed with hypertrophic obstructive cardiomyopathy. He reported previously being very physically active with good exercise tolerance. However over the past 1 year, he had increasing shortness of breath and dyspnea on exertion that had progressed to recurrent presyncopal episodes associated with exertion for the last 6 months. There were no reports of syncope or chest discomfort but palpitations had been frequent. During his initial evaluation, the patient expressed dyspnea on exertion after climbing one flight of stairs consistent with NYHA Class III symptoms. A 12 lead electrocardiogram showed sinus rhythm with a left bundle branch block (Fig. 24.1). An echocardiogram revealed moderate mitral regurgitation, preserved left ventricular systolic function with a 2.1 cm basal septum, a normal posterior wall, and a left ventricular outflow tract obstruction at 40 mmHg that augmented to 130 mmHg with Valsalva maneuver, consistent with HCM obstructive physiology. Subsequently, a 24-h ambulatory electrocardiographic monitor was recommended.

Clinical Decision Making—When to recommend 24-h ambulatory (Holter) electrocardiographic monitoring in HCM patients

Ambulatory electrocardiographic monitoring should routinely be included in the initial evaluation of patients with HCM [1]. Ambulatory electrocardiography monitoring for detection of ventricular tachyarrhythmias is important for risk stratification of asymptomatic and symptomatic patients with HCM. This is because episodes of nonsustained ventricular tachycardia (NSVT) on ambulatory EKG monitoring, besides identifying patients at elevated risk of subsequent SCD events, can also help identify candidates for ICD therapy [1]. However, on its own, NSVT is a Class IIb indication for ICD implantation and usually requires other modifiers of risk in order to justify ICD placement. Alternatively, a relatively long and fast run of NSVT may be sufficient to prompt ICD implantation, especially in the patient with symptoms or outflow tract obstruction. Holter monitoring may also identify atrial fibrillation, which is a common etiology of stroke and clinical decompensation in HCM patients. Holter monitoring for subsequent annual evaluations in an asymptomatic patient is less useful, but may be considered. More often, subsequent Holter, event or loop monitors are indicated for the symptomatic patient in order to elucidate etiology of symptoms.

Following normal Holter monitoring, the patient underwent diagnostic cardiac catheterization. Right heart catheterization revealed normal right and left-heart filling pressures with borderline elevated pulmonary pressures. There was evidence of HCM obstructive physiology with

no resting gradient but a provocable gradient of 90 mmHg after combined Brockenbrough and Valsalva maneuvers. Cardiac output was preserved and coronary angiography demonstrated non-obstructive mid-LAD disease with a <30 % stenosis lesion. The patient was continued on combination therapy with aggressive beta-blockade and Disopyramide. In addition, a CMRI confirmed a discrete septal bulge measuring 2.2 cm with no evidence of late gadolinium enhancement.

Clinical Decision Making—When to recommend CMRI in HCM patients?

Accurate characterization of the HCM phenotype by CMRI may be useful in management decisions for invasive therapies (septal myectomy or alcohol septal ablation) by more precisely defining the location and magnitude of hypertrophy. Additionally, in selected patients, when SCD risk stratification is inconclusive and high-risk status for SCD remains uncertain, CMR imaging with assessment of LGE may be considered in resolving clinical decision-making. Several studies have shown that approximately 50 % of HCM patients have LGE suggestive of areas of fibrosis that in some patients may occupy on average 10 % of the left ventricular myocardium [2, 3]. Importantly, patients with HCM with evidence of LGE on CMRI tend to have more markers of risk of SCD, such as NSVT on ambulatory EKG monitoring than patients without LGE. Accordingly, the presence and extent of LGE may aid in determination of ICD implantation, as a risk modifier. CMRI is also useful in confirming the diagnosis of HCM, or discerning HCM from athlete's heart, by its ability to image the entirety of the heart and obtain fine measurements of thickness. In addition, areas poorly visualized by echo, chiefly the apex and lateral wall are easier to discern, as are associated structures such as papillary muscles or membranes. Finally, as maximal thickness >3.0 cm is an indication of sufficient risk to warrant an ICD, patients with borderline high maximal thickness (between 2.5 and 2.9 cm) may benefit from CMRI to determine whether areas >3.0 cm are present. Some HCM centers CMRI routinely on all patients with HCM, while others have a more selective approach.

As a result of severe drug-refractory symptoms and dynamic LVOT obstruction, the patient was considered for septal reduction therapy. Ultimately, a decision was made to proceed with septal myectomy based on the patient's age, HCM phenotype, and underlying left bundle branch block, which would make the patient extremely high risk for complete heart block and pacemaker requirement if a RBBB developed after alcohol septal ablation. A generous resection of the asymmetric hypertrophy was performed with intraoperative transesophageal confirming relief of the left ventricular outflow tract obstruction. Postoperatively (post-operative TTE in Figs. 24.2, 24.3, and 24.4), the patient did well and beta-blockade was continued upon discharge from the hospital.

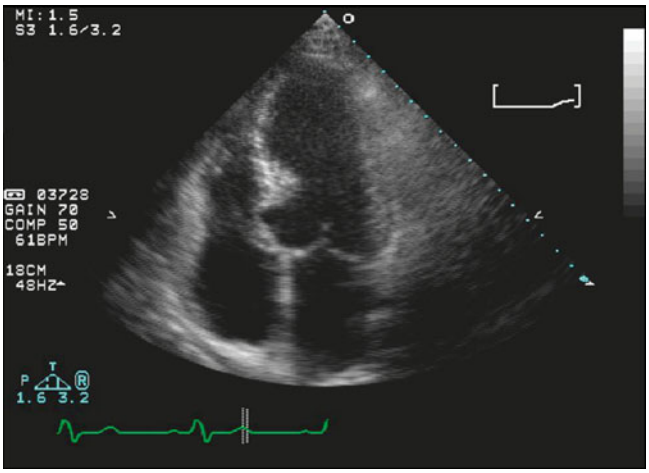

Fig. 24.2 Case 1: Post-op TTE depicting septal reduction

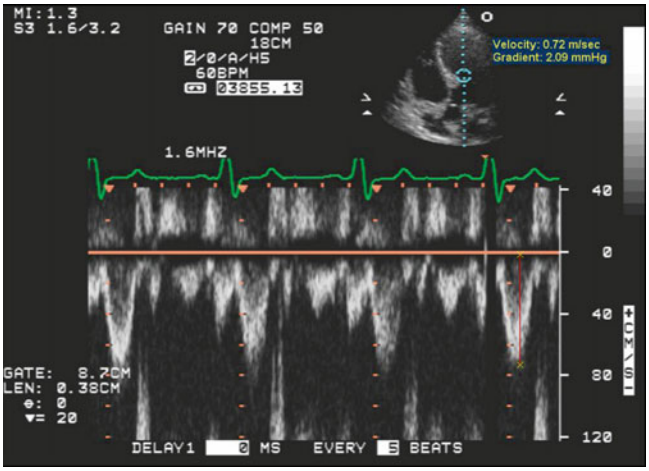

Fig. 24.3 Case 1: Post-op TTE 4 chamber view showing no LVOT gradient

Clinical Pearl—Do atrioventricular conduction patterns affect the choice of invasive therapy?

In patients with a left bundle-branch block at baseline, surgical myectomy may be the preferred approach to septal reduction therapy as opposed to alcohol septal ablation as the latter would severely increase the risk of permanent pacemaker placement, due to the development of concomitant right bundle branch block

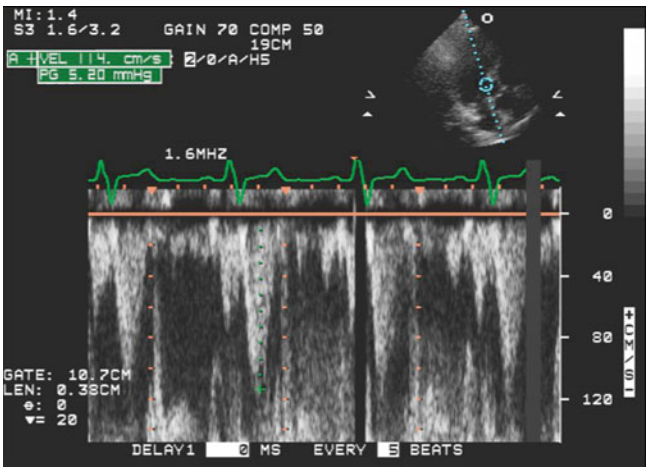

Fig. 24.4 Case 1: Post-op TTE 3 chamber view showing no significant LVOT gradient

and resultant complete heart block. In one small study [4] (n = 52) comparing effects of alcohol septal ablation vs. surgical septal myectomy on the atrioventricular conduction patterns, out of 4 patients with pre-existing LBBB, 3 developed complete heart block (CHB) post alcohol septal ablation, while out of 10 patients with pre-existing LBBB, none developed CHB post-surgery. This was in contrast to patients with no underlying AV conduction abnormalities in both groups where 40 % developed RBBB in the alcohol septal ablation group and 46 % developed LBBB in surgical myectomy group; there was no significant difference in normal conduction patterns after either procedure between the two groups (53 and 54 % respectively) [4]. Further 3 out of 5 patients (60 %) with preexisting RBBB in the surgical group developed CHB in contrast to none in the alcohol septal ablation group (n = 2) [4]. Therefore, patients with pre-existent RBBB should be referred for alcohol septal ablation while those with pre-existent LBBB should be referred for surgery, if all other considerations are equal.

However, approximately 2 weeks after undergoing septal myectomy, the patient began to experience multiple syncopal episodes. He empirically underwent ICD implantation for primary prevention of SCD, which had not been preceded by an electrophysiology study. Over the next few months the patient continued to experience repeated syncopal episodes and subsequent device interrogation yielded no evidence for an arrhythmogenic etiology. Echocardiography also failed to reveal resting or provoked outflow obstruction (Figs. 24.2, 24.3, and 24.4).

Clinical Decision Making—What is the indication for an ICD in HCM?

At the initial evaluation of a patient with known or suspected HCM, an evaluation of SCD risk should always take place. As per the ACCF/AHA guidelines [1], high risk is composed of one or more of the following criteria: (1) a personal history for ventricular fibrillation, sustained VT, or SCD events, including appropriate ICD therapy for ventricular tachyarrhythmias; (2) a family history for SCD events in a first degree relative with HCM below the age of 50; (3) unexplained recurrent syncope; (4) documented NSVT defined as 3 or more beats at greater than or equal to 120 bpm on ambulatory ECG; (5) maximal LV wall thickness greater than or equal to 30 mm. During follow up evaluations, ambulatory EKG monitoring, exercise treadmill tests (for hypotension or arrhythmia) and echocardiograms are usually performed, together with repeat family and personal history, in order to determine whether any of the high-risk markers, or confluence of high and lower risk markers, exist that would warrant consideration of ICD implantation. In contrast, EPS is not indicated as a risk stratification tool for patients with HCM. In the current case, the "unexplained syncope" was utilized to place the ICD. However, this patient had recent surgery, and the etiology of the syncope was not adequately determined prior to placement of the ICD. The ICD interrogation and echo ruled out arrhythmogenic and obstructive etiologies, leaving autonomic instability as the remaining culprit.

Clinical Pearl

"Unexplained" and "recurrent" syncope is a marker for SCD [1] in patients with HCM. Due to its multifactorial and complex etiology in HCM patients, a careful clinical history should be elicited to thoroughly assess patients with unexplained and recurrent syncope who are at high risk for SCD before placing an ICD. Possible etiologies of syncope in HCM patients include: (1) arrhythmogenic: ventricular and supraventricular tachyarrhythmias, (2) mechanical: dynamic LVOT obstruction causing a sudden sharp reduction in systolic blood pressure (e.g., provoked by exertion), (3) neurally mediated and (4) iatrogenic causes e.g., medications that interfere with AV conduction as well as treatments that affect loading conditions. Another iatrogenic etiology is unrecognized heart block after surgery or alcohol septal ablation. In one study, syncope that was unexplained or thought to be consistent with arrhythmia demonstrated a significant independent association with SCD only when the events occurred in the recent past (<6 months) but not if they occurred >5 years before the clinical visit [5].

The patient's syncope resolved with discontinuation of his beta-blocker, implicating a neurogenic cause (autonomic instability) for his syncope. Echocardiogram continued to reveal no evidence for obstruction, and no arrhythmias were noted on ICD interrogation. Over the next several months, there was no recurrence of syncope or presyncope, and the patient attained NYHA functional class I. The patient was complaining of chest wall discomfort at the ICD insertion site requiring prolonged use of narcotics.

Given a paucity of indications for continuing ICD therapy for primary prevention in this now asymptomatic patient, coupled with an exercise treadmill test yielding excellent exercise tolerance, a decision was made to refer the patient to an electrophysiologist for ICD extraction (per the patient's wishes). He was also advised that since the device is already implanted, it may be wise to keep it. Importantly, however, the patient was told to wait at least 6 months to make sure that no arrhythmias were found and symptoms did not recur. Following a lengthy discussion evaluating the risks and benefits of ICD removal, the patient ultimately underwent system explantation without further complications. One year subsequent to this, the patient remains asymptomatic.

Case 2: Alcohol Septal Ablation in a 38 Year Old Woman with History of Peri-partum SCD

Patient A. B. presented to the hypertrophic cardiomyopathy center in June of 2010 at the age of 38, after a recent pregnancy. She was an uninsured Caucasian female with a history of hypertension and tobacco use, though she had quit 6 months prior (25 pack-years). She was taking metoprolol succinate 100 mg q.d. after a recent diagnosis of HCM. She had two pregnancies and had a 12 years old and a 2-month-old child. Neither child had yet been tested for HCM at this time. Her medical history is divided below in two phases; the first phase describes events prior to presentation to our hypertrophic cardiomyopathy center and the second phase describes decisions taken after she presented to us in 2010.

Her first cardiac encounter was in 2004 when her family doctor noted that she had a systolic ejection murmur. The murmur appropriately prompted an echocardiogram, which was interpreted as having borderline left ventricular hypertrophy. Shortly afterwards, the patient developed chest pain and dyspnea that became worse on exertion. She was found to have New York Heart Association Class II heart failure symptoms and was started on a small dose Metoprolol and Aspirin. It is unclear what the physician's primary diagnosis was at the time, however; no further testing was performed.

In 2006 she underwent her first cardiac catheterization for persistent chest pain on exertion. The patient reported that the results were "unremarkable" and no explanation was found for her chest pain; she continued to have chest pain post catheterization. Two years later she complained of angina at rest in the substernal region associated with shortness of breath. Her symptoms worsened after she became pregnant in 2009, even though reportedly she had sought medical attention prior to getting pregnant and had been advised that pregnancy would be safe for her. Due to a lack of health insurance coverage she did not seek medical care until she was 31 weeks pregnant. At this point she was experiencing syncopal episodes on a daily basis and persistent shortness of breath. This prompted further work up during a hospital stay, where she was finally diagnosed with severe Hypertrophic Obstructive Cardiomyopathy after an echocardiogram revealed a septal thickness of 2.4 cm, with obstructive physiology. The cardiology and obstetrics teams taking care of her debated over the merits of an earlier Cesarean section and whether or not the heart could withstand the remaining duration pregnancy or C-section. This period was marked by repeated hospitalizations until delivery was finally scheduled by C-section at 36 weeks of pregnancy. She was not referred to a high-risk obstetrics program. It is unclear whether there was evidence for congestion or volume overload at this time. Unfortunately, the C-section was complicated by sudden cardiac arrest intra-operatively. She was successfully resuscitated after CPR and defibrillation. An implantable cardioverter defibrillator was inserted, she was started on metoprolol and the remaining post-pregnancy course was relatively unremarkable. After discharge from the hospital, the dose of metoprolol was increased gradually to 100 mg q.d.

Clinical Decision Making—Was implantation of the cardioverter defibrillator (ICD) appropriate for this patient?

HCM may account for as much as 48 % of SCD in patients aged <35 years [6]. In fact, SCD may be the initial presentation. ICDs provide a mortality benefit in patients at high risk of sudden cardiac death (SCD). All HCM patients should therefore be screened for risk of SCD and possible need for ICD. At this time, clinical factors rather than genetic factors are used in risk stratification for SCD in HCM patients, although a family history of SCD in first-degree patients with HCM can be associated with a 5-fold increased risk of SCD [7]. In one series, patients with a range of genotypes were phenotypically indistinguishable, thus making prognostication on basis of genotype unreliable [8, 9]. The Class I ACCF/AHA indications for an ICD include a positive component in any of the following elements in history: personal history of ventricular fibrillation arrest, sustained ventricular tachycardia, sudden cardiac death, family history of sudden cardiac

deaths (especially in first degree relatives <50), recent unexplained syncope (<6 months) or maximal left ventricular thickness of greater than 30 mm [1]. Although one could argue that the ventricular arrhythmia and cardiac arrest were precipitated by anesthesia and the stress of delivery in this patient who would otherwise have been contraindicated for pregnancy, any patient who sustains SCD with a diagnosis of HCM typically warrants ICD placement. Of note, while NSVT was considered a major risk factor at one time, it alone is a Class IIb for ICD implanatation; the same goes for abnormal blood pressure response by exercise treadmill testing.

Clinical Decision Making—What is the risk involved in patients seeking to get pregnant who are known to have HCM?

Women with HCM can safely experience pregnancy if asymptomatic, or symptoms are mild or moderate, while NYHA Class III or IV predicts maternal mortality and morbidity [10]. 10 to 30 % of mothers with moderate to severe symptoms worsen clinically during the course of the pregnancy, especially if LVOT obstruction is present, while gradients >100 mmHg carry the highest risk of deterioration [11, 12]. Cesarean section delivery and special medical care (high risk obstetrics) is not necessary for patients with pre-existent mild to moderate symptoms, unless active heart failure or significant obstructive physiology develops during the course of pregnancy, but should be the mainstay for anyone with higher degrees of symptoms who become pregnant. Maternal mortality is limited to patients with advanced disease, including progressive heart failure, severe systolic or diastolic dysfunction, ventricular tachycardia, supraventricular tachycardia, or marked LVOT obstruction. These women require care of a high-risk maternal/fetal medical team with close involvement of a cardiologist preferably specialized in HCM. Beta-blockers or Disopyramide should not be stopped during pregnancy if needed to control symptoms and close monitoring should be done for fetal bradycardia. ACCF/AHA guidelines stress genetic testing and counseling for any women of childbearing age with HCM as well as counseling of parents (mother or father) with HCM regarding risks of pregnancy prior to conception [1]. Patients with NYHA Class III symptoms should be discouraged from pregnancy, while NYHA Class IV is an absolute contraindication. Spinal blocks that drop afterload are also contraindicated, and anesthesia should be well versed on medications that precipitate obstruction and medications that can be used to improve outflow tract obstruction acutely.

The patient was referred to the Hypertrophic Cardiomyopathy Center in 2010. Exam revealed her blood pressure to be 112/60 mmHg, heart rate was regular at 60 bpm, and she weighed 230 lb and was morbidly obese. She did not have any jugular venous distension, bruits or masses in her neck. She had a 3/6 systolic murmur at the left sternal border that increased with Valsalva maneuver. There was trace edema in both of her legs. She had NYHA Class III symptoms of dyspnea. Review of systems revealed absence of syncope but she did have dizziness and palpitations on exertion, in addition to one flight of stairs exertional dyspnea. A 12 lead electrocardiogram revealed that she was AV paced at 60 bpm.

At this consultation an echocardiogram was recommended to evaluate for asymmetric septal hypertrophy, the degree of hypertrophy, systolic anterior motion of mitral valve leaflet, mitral regurgitation, and the extent of outflow tract obstruction at rest and during provocation. Besides this, Metoprolol succinate was increased to 100 mg AM & 50 mg PM due to significant symptoms and presumed obstruction, with consideration to add Disopyramide in future for better control of symptoms. There was also discussion of possible invasive therapy (alcohol septal ablation or septal reduction surgery) should severe symptoms persist. Based on ACCF/AHA guidelines and her young age (38 years) surgical septal myomectomy would be recommended over alcohol septal ablation, and was discussed specifically.

At her 2 week follow up the echocardiogram (Fig. 24.5) was discussed; it revealed an ejection fraction 65–70 %, grade 2 diastolic dysfunction, and isolated basal septal hypertrophy (2.4 cm). There was systolic anterior motion of the mitral valve with left ventricular outflow tract obstruction, peak resting gradient across the left ventricular out-flow tract of 80 mmHg, right ventricular systolic pressure of 40–45 mmHg, mild to moderate mitral regurgitation and a severely dilated left atrium. The patient remained in NYHA Class III symptoms, and thus Disopyramide CR 150 mg bid was initiated in order to further reduce outflow tract obstruction.

Despite this, the patient continued to have NYHA Class III symptoms of dyspnea, episodic lightheadedness, and class II angina 1 month later. Therefore, a cardiac catheterization was performed (Fig. 24.6) which revealed normal coronary anatomy, mildly elevated right and left heart filling pressures, mild pulmonary

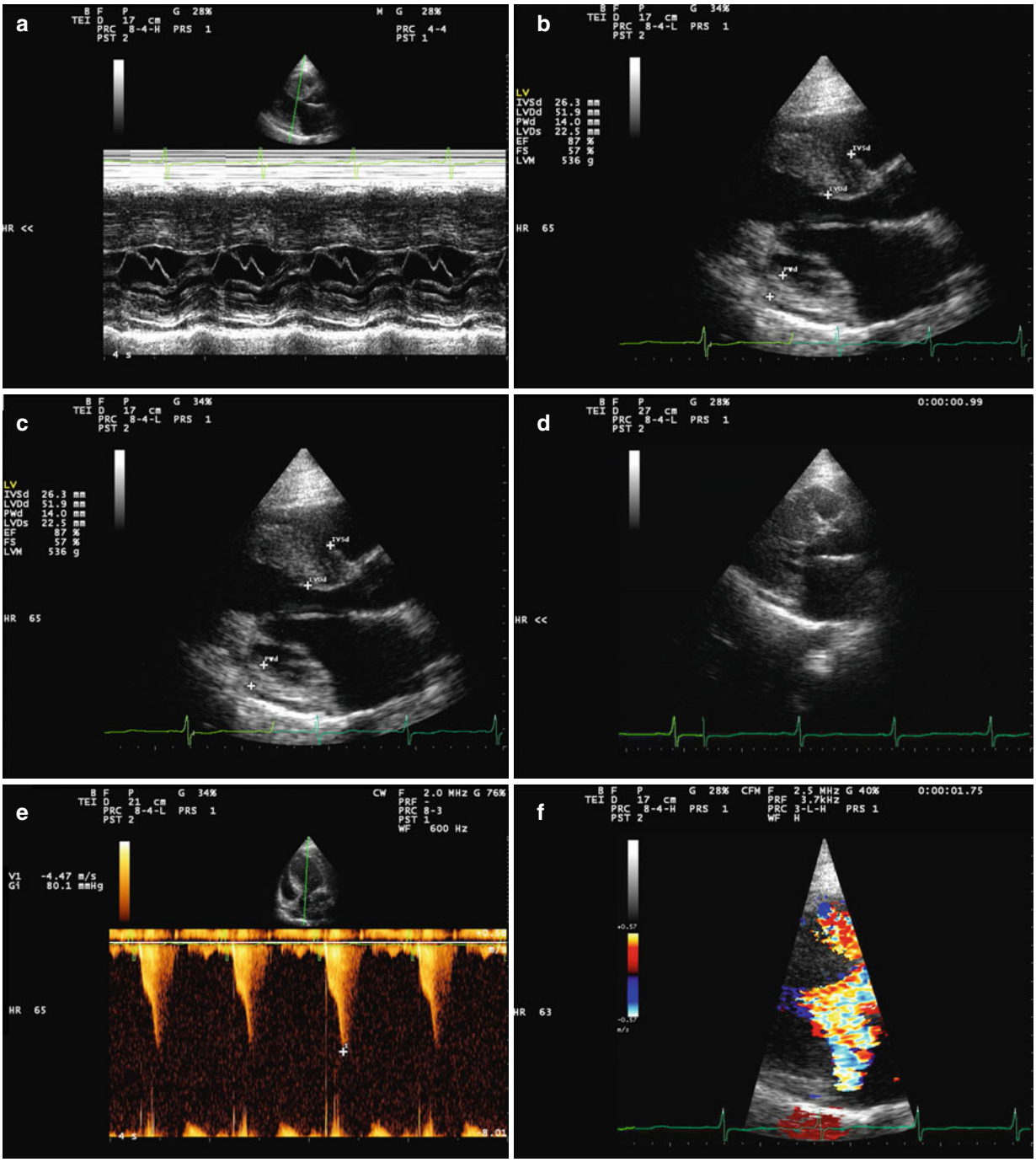

Fig. 24.5 Case 2: (**a**) TTE M-mode depicting systolic anterior motion, (**b**) TTE parasternal long axis view measurements with asymmetric septal hypertrophy, (**c**) TTE early systole-no systolic anterior motion, (**d**) TTE mid systole systolic anterior motion plus LVOT obstruction, (**e**) Resting gradient of 80 mmHg across the LVOT depicted by spectral Doppler, (**f**) Moderate mitral regurgitation secondary to systolic anterior motion of mitral valve

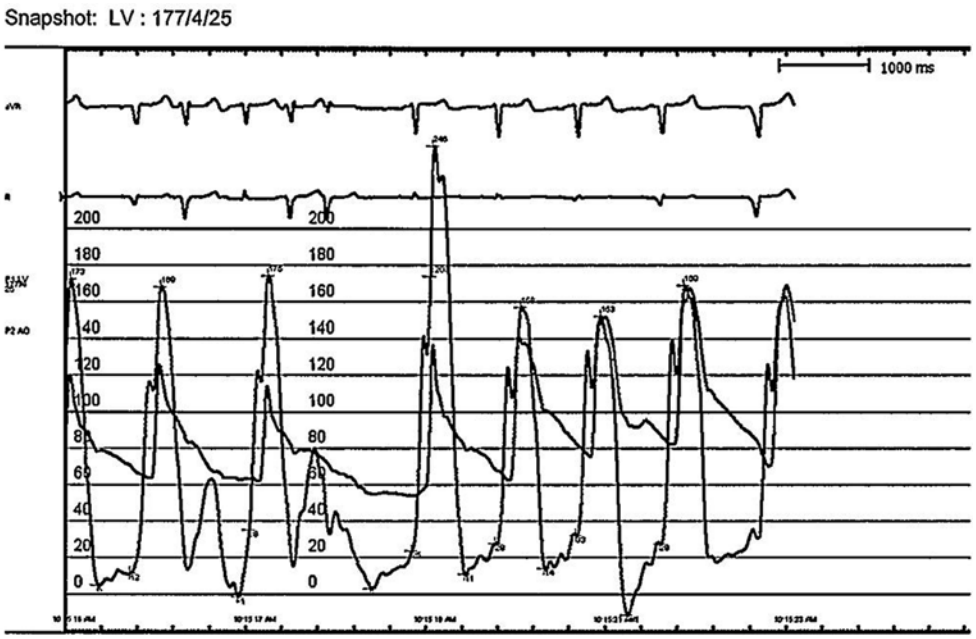

Fig. 24.6 Case 2: Cardiac catheterization depicting provocable LVOT gradient

hypertension with normal pulmonary vascular resistance and normal cardiac output. She was noted to have obstructive physiology with 0–20 mmHg resting gradient provocable to approximately 80 mmHg despite her medical regimen. Following these results, a decision was made to discuss invasive options.

Clinical Decision Making—Patient selection for myectomy vs. alcohol ablation

In order to refer a patient to either invasive strategy, as reflected in the ACCF/AHA guidelines [1] it is recommended that a core set of pre-requisites should be fulfilled: (1) Symptoms attributable to LVOT obstruction should be refractory to optimal pharmacologic therapy, which typically means two classes of medications titrated to side effects. (2) It must be demonstrated that the obstruction is caused by apposition of the mitral valve with the hypertrophied septum (and not attributable to systolic cavity obliteration or severe diastolic dysfunction). (3) A maximal instantaneous gradient of at least 50 mmHg at rest or with physiologic provocation is necessary. When these criteria are met, invasive options can be considered. Surgical myectomy is preferred in patients of younger age, greater septal thickness, esp. >30 mm, and concomitant anatomic cardiac disease independently requiring surgical correction (e.g., intrinsic mitral valve disease) or coronary artery disease requiring coronary artery bypass grafting. Midventricular obstruction, or obstruction due to abnormal papillary muscles or membranes, should also be treated surgically. Patients more appropriate for alcohol septal ablation include those who are older or at advanced age or with significant comorbidities that selectively increase surgical risk. In addition, patients with a pre-existent pacemaker or ICD may elect to proceed with alcohol septal ablation. Importantly, while every anatomy is potentially treatable by surgery, only select anatomy is ideal for alcohol septal ablation. This includes basal septal hypertrophy, lack of intrinsic mitral pathology, and an adequate septal perforator to the target myocardium. In addition, patient's with pre-existent LBBB may best be served by myectomy, whereas those with pre-existent RBBB may be best served by alcohol septal ablation; this approach reduces the risk of complete heart block and pacemaker requirement post-procedure. Finally, when both procedures seem equally safe and efficacious in a given patient, the principle of patient autonomy dictates that a patient may decide in favor of one or the other procedure after a balanced and thorough discussion, including appropriate consultations. It is recommended, however, that surgeons and interventionalists should have performed at least 20 such procedures to be deemed experienced.

The patient was strongly recommended to undergo surgical myectomy, and received surgical consultation for the procedure. However, the patient chose alcohol septal ablation. Though myectomy is typically preferred in patients of this age, there were several reasons the patient was a reasonable candidate for alcohol ablation. The patient did not have

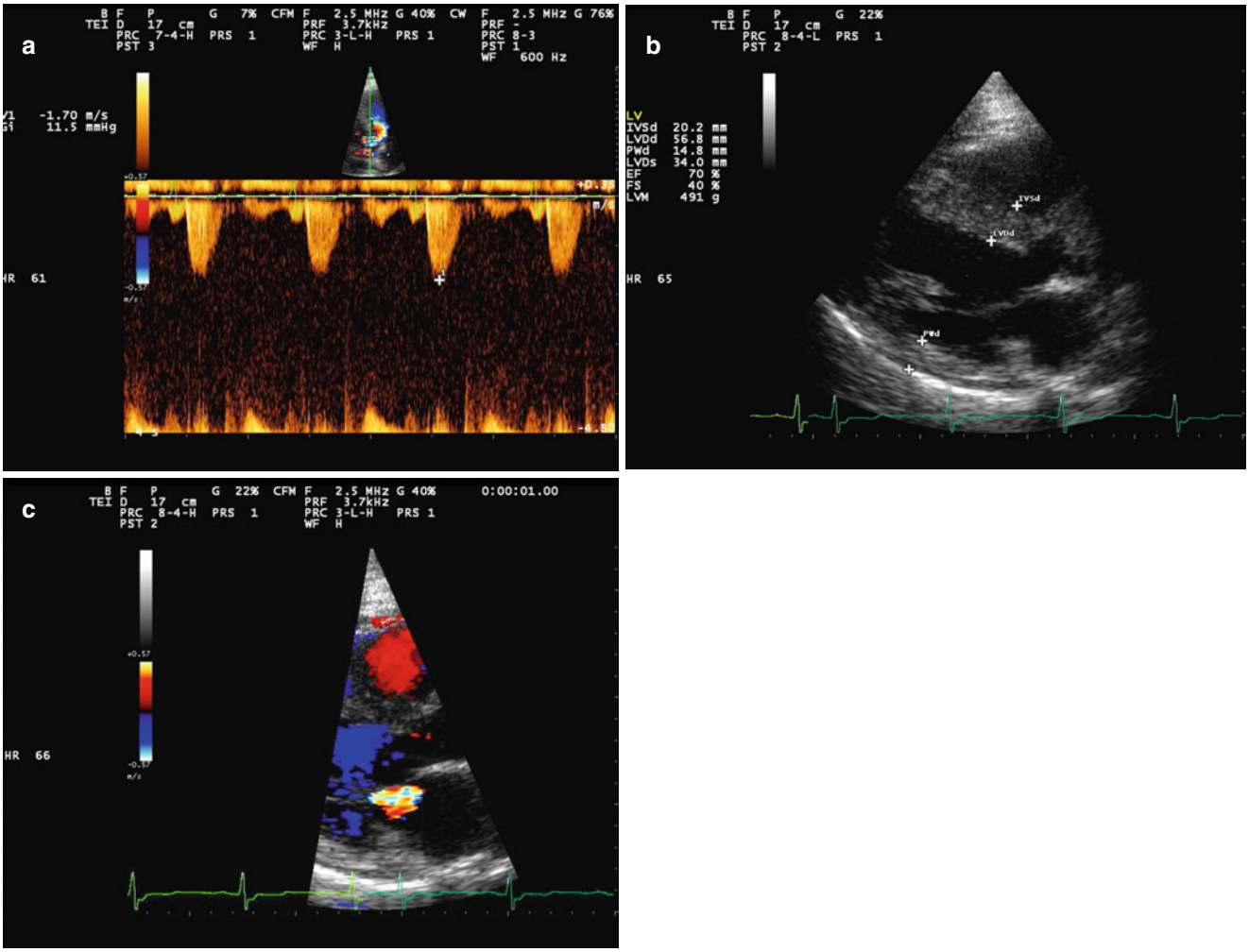

Fig. 24.7 Case 2: TTE 1 month post alcohol septal ablation. (**a**) Reduced LVOT outflow gradient on spectral Doppler, (**b**) parasternal long axis view: basal septum reduced in size compared with baseline measurements pre-procedure, (**c**) reduction in mitral regurgitation

familial support or a record of compliance that would indicate she would tolerate open-heart surgery, besides airway management issues due to morbid obesity. She was a single mother of two children, without insurance, who did not want to take the risk of prolonged recovery, including the inability to carry her children post-surgery. Ultimately after a thorough discussion, the patient opted for an alcohol ablation. A month later, alcohol septal ablation was performed using standard technique.

On outpatient follow up 1 month later, the two dimensional echocardiogram (Fig. 24.7) revealed improved septal wall hypertrophy (basal septum = 2 cm) with mild systolic anterior motion of the mitral valve causing minimal left ventricular outflow tract obstruction with a peak gradient of 12 mmHg and mild mitral regurgitation. There was no pulmonary hypertension. At this time, the patient's symptoms were New York Heart Association Class II and her medical regimen, which included beta-blocker and Disopyramide, was continued. She was also advised to seek genetic screening for herself and the rest of her family. On subsequent visits the Disopyramide sustained release was increased to 200 mg b.i.d. due to persistent New York Heart Association Class II symptoms and a year after her ablation her symptoms significantly resolved to Class I. The physician and patient discussed genetic testing. At this point, 18 months post ablation, an echocardiogram (Fig. 24.8) on followup revealed excellent remodeling of her left ventricular septum with a thickness of 1.4 cm at the base, resolution of the systolic anterior motion of the mitral valve, and a left ventricular outflow tract gradient of 15 mmHg which increased to 16 mmHg on provocation with the Valsalva maneuver. Her left ventricular ejection fraction was 55 %, with grade I diastolic dysfunction. Given her favorable outcome and improvement in symptoms, the Disopyramide extended-release was reduced in half with consideration to terminate it in future.

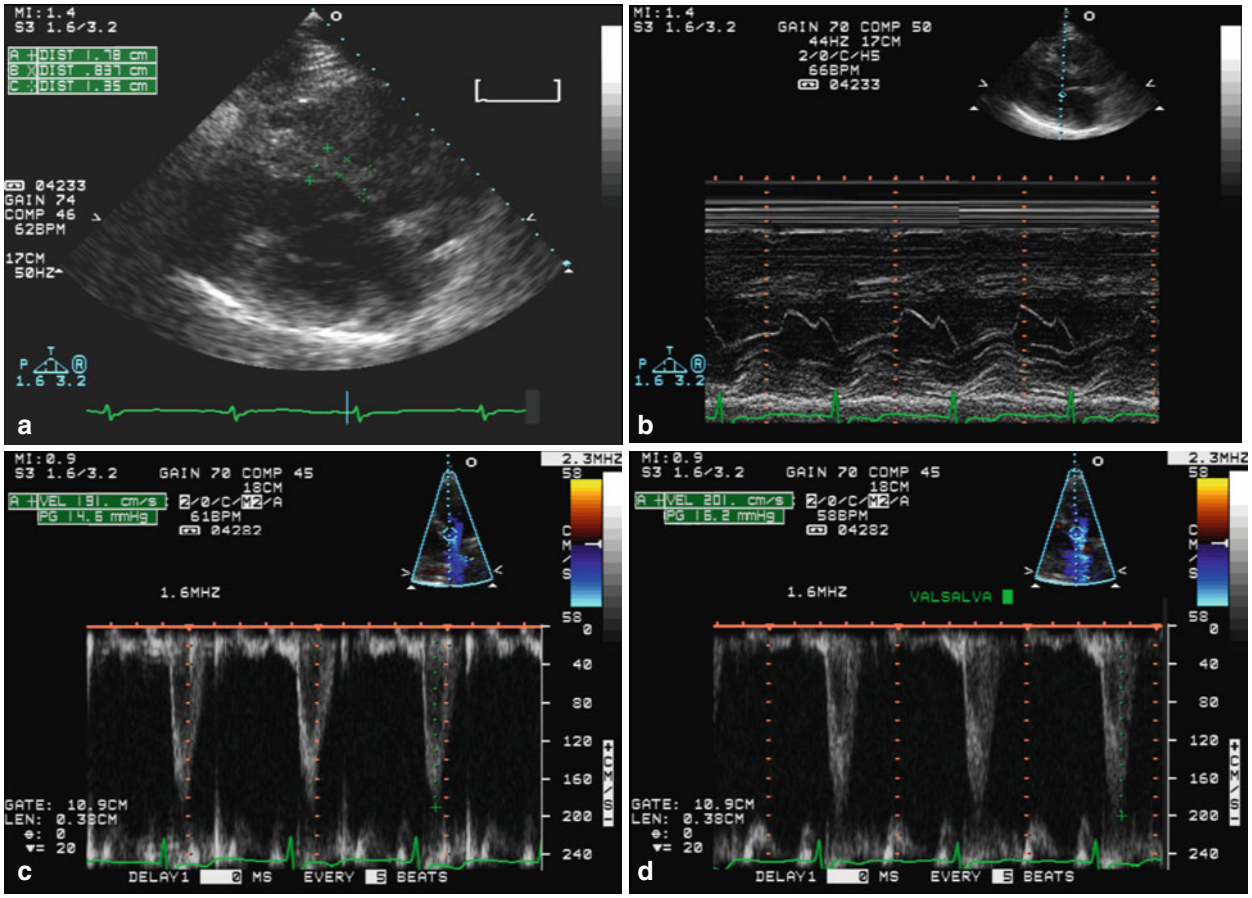

Fig. 24.8 Case 2: TTE 18 month post procedure. (**a**) Remodelling of LV septum 18 month post alcohol septal ablation, (**b**) absence of systolic anterior motion on M-mode echocardiogram (compare with Fig. 24.5a), (**c**) 14 mmHg peak LVOT gradient on spectral Doppler with no significant change on Valsalva maneuver (16 mmHg) in (**d**)

Clinical Pearl—What is the response of the left ventricle to invasive therapy?

The time course to improvement differs between alcohol septal ablation and surgical myectomy. After myectomy, obstruction is removed immediately, and over the ensuing months remodeling occurs that improves diastolic function. However, due to the recovery period from open heart surgery, the patient may not feel significant benefit for several months. After alcohol septal ablation, in contrast, there is little recovery needed for the body as a whole. However, the initial alcohol infusion creates a localized infarction that reduces outflow obstruction. Over time, this area scars and thins, further widening the outflow tract diameter and simulating surgical myectomy. This results in similar improvements in diastolic dysfunction, and remodeling of the hypertrophy and septal and distant sites. Consequently, the full effect of alcohol septal ablation may take 6–10 months, with continued remodeling after both procedures noted over several years. In both instances, there is a mild decrease in ejection fraction, although systolic function remains normal. Accordingly, patience is necessary and waiting at least 6 months is required in order to make a determination of success or failure.

Family screening by two-dimensional echocardiograms revealed that one of her children had a muscular ventricular septal defect, which was conservatively managed while her 14-year-old sibling was found to have left ventricular hypertrophy thought to be secondary to Hypertrophic Cardiomyopathy and was advised to avoid competitive athletics.

Clinical Pearl—When to screen relatives, including children, for HCM

It is the responsibility of the patient and the physician to make sure immediate family members are screened by genetic testing and/or imaging (e.g., transthoracic echocardiogram). Adults should be screened by echocardiogram every 5 years, while children should be screened every 12–18 months. If found, HCM should be managed at an HCM center and careful counseling regarding symptoms, risk of sudden death and other lifestyle discussions should take place. Particular issues concerning children and young adults (sex, drugs, sports) need to be discussed in detail, so that they and the parent understand the risks of their disease. Importantly, many families may be screened outside of an HCM center. In such instances, it is wise to tell the patient and family members that their physician should specifically look for any signs or symptoms of HCM. If any doubt, the images can be transferred to an HCM center for further evaluation.

Two years after ablation, the patient returned with an episode of chest pain and left arm and shoulder pain and reported lightheadedness similar to previous episodes. The electrocardiogram revealed no changes while an echocardiogram now showed complete resolution of gradient, both at rest and with provocation. At this time, the AV delay of the ICD was increased to allow for her native AV nodal conduction, in case this was contributing to symptoms. She also reported continued weight gain, breast discharge, and subsequently was found to have prolactin level derangements and visual disturbances referable to pituitary adenoma. The patient is undergoing endocrine treatment, and is now asymptomatic.

Clinical Decision Making—When to consider other diseases?

Patients with HCM may develop other diseases, or may have accompanying morbidities, such as obesity, that may partly explain symptoms. In the current patient, she had symptoms from severe outflow tract obstruction and HCM early on, including cardiac arrest, followed by symptoms related to worsening obesity and development of endocrine derangements later on after obstructive physiology was resolved, medications withdrawn and hypertrophy reduced. Accordingly, treatment of her HCM initially improved symptoms, with objective improvements by serial echocardiograms. Recurrence or worsening of symptoms in such patients may be due to new diseases or alternate etiologies, including coronary disease, lung disease or obesity and endocrine derangements, as in our patient, and must not be ignored. The clue in this patient was that her anatomy and physiology did not support a recurrence of symptoms; therefore, an alternate etiology had to be found.

Case 3: A 43 Year Old Woman with Long Standing Non-obstructive HCM and Advanced Heart Failure

Ms. LL is a 43-year old female with history of hypertrophic cardiomyopathy (HCM), obesity and sleep apnea. Her history with HCM began at age 18 when a first cousin died suddenly and was found to have HCM by autopsy. Subsequently her family was screened and she and 2 of her brothers were found to have the HCM phenotype with asymmetric septal hypertrophy but no outflow tract obstruction, though she was asymptomatic at the time. Over the next several years, her 2 brothers died, both at relatively early age, 41 and 38, from sudden cardiac death. Her 200 member family was studied at the National Institutes of Health, Maryland, USA [13], and the V95A alpha-tropomyosin mutation was identified in all 15 affected members.

Clinical Pearl

As described by the study of Mrs. L's family [13], the V95A mutation is associated with low penetrance (53 %), mild hypertrophy, but poor prognosis. The mean maximum LV wall thickness was 16.66 mm in the 15 affected members of her family, with wide distribution, and electrocardiograms that did not fit the classic criteria for hypertrophy. Cardiomyopathy as well as symptomatic bradycardia and cardiac arrest have been noted in a large number of patients with this mutation. The most common cause of death is sudden cardiac death and may occur at rest, and with mild or no LVH. Genetic counseling and preventative measures are essential when treating a patient with V95A mutation, as the phenotype is quite mild and poor outcomes can occur in patients with little or no signs or symptoms of the disease.

By the time she was 27 years old, she began to experience symptoms of progressive decline in exercise tolerance, as well as orthopnea and occasional paroxysmal nocturnal dyspnea. She was enrolled in several investigational studies at the NIH including studies of losartan and terfenadine,

though she reported minimal improvement in her functional status with either agent.

Clinical Decision Making—What is pharmacologic management in non-obstructive HCM?

Symptoms of dyspnea and angina should be managed with beta-blockers and/or verapamil. Some experts recommend calcium channel blockers as first line agents in such patients. While Disopyramide is advocated by some in obstructive HCM, there is a paucity of data in non-obstructive patients and thus it is generally avoided. Congestion is often a factor in non-obstructive disease, due to diastolic dysfunction and chronically reduced cardiac output. Patients with edema should be initiated on diuretics, starting with low potency agents and progressing to loop diuretics without and then with additional agents. Patients should be monitored for symptomatic bradycardia and hypotension when titrating medications, and potassium should be supplemented. The usefulness of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers is not well established, and these drugs should be used with extreme caution in patients with outflow tract obstruction. Ongoing research is evaluating spironolactone and novel sodium channel blockers, although results are pending. As mentioned above, diuretics may be added to patients with symptomatic volume overload, though they should also be titrated cautiously to avoid hypovolemia [1].

At age 36, after being symptomatic for several years, she underwent ICD implantation following an episode of syncope.

Cinical Decision Making—What are indications for ICD in this patient?

Patients with HCM have an increased risk of sudden cardiac death. However, some patients have low risk while others are at high risk; SCD risk stratification aims at identifying those at high risk in whom the benefits of ICD outweigh the lifetime risks. In addition, younger patients, presumably with more dangerous genetic mutations and more severe hypertrophy, have higher rates of SCD whereas older patients generally have a more benign course. Based on the current guidelines, this patient should undergo risk stratification at initial consultation and then yearly or as signs and symptoms change for (a) personal history of ventricular arrhythmias or SCD, (b) family history of sudden cardiac death in a person <50 years with known HCM, (c) unexplained recurrent syncope, (d) NSVT, (e) LV wall thickness greater that 30 mm. Given Mrs. L's strong family history of sudden cardiac death (11 out of 13 deceased family members), and her episode of unexplained syncope, an ICD is appropriate. Indeed, based on recent guidelines it would have been appropriate for her to have had an ICD placed after the first episode of SCD in a first-degree family member. Accordingly, the syncope, while prompting further discussion and eventual placement of the ICD, was not the first indication for ICD placement.

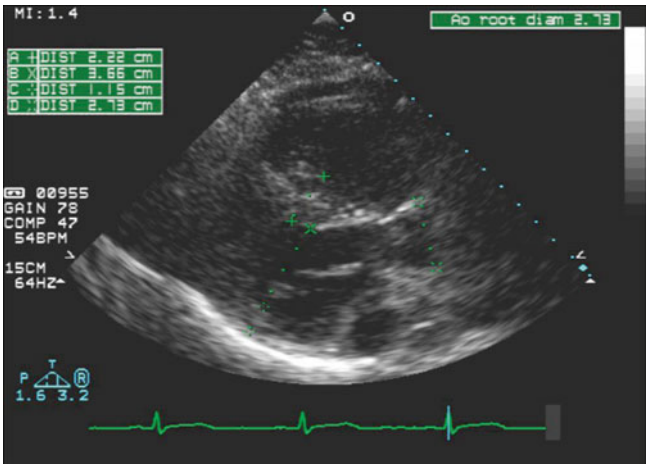

Fig. 24.9 Case 3: TTE on initial evaluation depicting basal septal hypertrophy in parasternal long axis view

The patient subsequently initiated care at the HCM Center (Figs. 24.9 and 24.10 depict the initial echocardiographic findings). Over the next few years, the patient started to decompensate, with progressive symptoms including palpitations and fatigue. She had a catheterization at age 39 which revealed a mean right atrial pressure of 11 mmHg, right ventricular pressure 45/16 mmHg, pulmonary capillary wedge pressure of 22 mmHg and aortic pressure 109/62 mmHg with left ventricular pressure of 110/35 mmHg (no outflow tract gradient). Fick Cardiac Output was 4.05 L/min and Fick Cardiac Index was 2.05 L/min/m^2.

Clinical Pearl—Assessment of hemodynamics

Based on the patient's right heart catheterization, she had elevated RA filling pressure, with mildly elevated pulmonary pressures and elevated left-sided filling pressures, indicating impaired LV function. There was no transpulmonary gradient and thus no overt intrinsic lung disease.

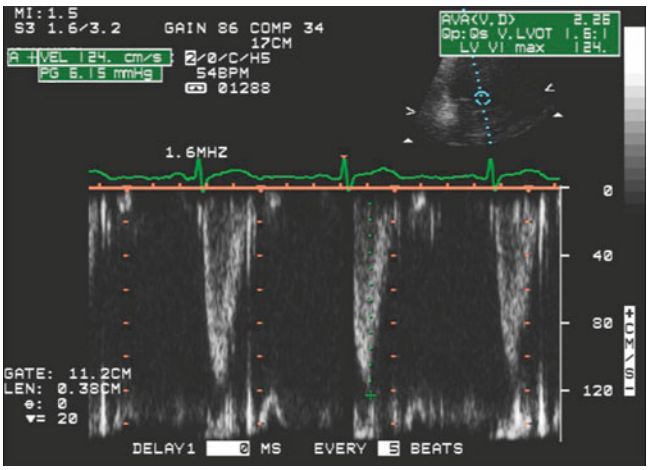

Fig. 24.10 Case 3: TTE on initial evaluation depicting lack of significant LVOT gradient in 3-chamber view

Her LV to aorta systolic pressure gradient was minimal, indicating no obstruction to LV outflow either at rest or on provocation. Based on the lack of obstruction and the elevated LV diastolic pressure, LV diastolic dysfunction was the most likely etiology of her symptoms. Patients with severe diastolic dysfunction will typically show reduced cardiac output and index both at baseline and on exertion. Exercise hemodynamics can be helpful in elucidating diastolic dysfunction, reduced output and index, and any affects of cardiac disease on the pulmonary vasculature, which may compound symptoms. Most patients with significant diastolic dysfunction present as severe fatigue followed by worsening congestion.

Numerous studies have found that while patients with HCM may have preserved or even hypercontractile LV function, they develop diastolic dysfunction early on in the disease process. Diastolic dysfunction is most likely the cause of exercise intolerance and angina in this subset of patients. Due to the massive asymmetric hypertrophy in HCM, the LV completely empties by end-systole, and in some cases, near cavity obliteration occurs, resulting in impaired suction to promote LV filling. Prolonged relaxation, myocardial fibrosis as well as impaired LV filling due to diminished suction all play a role in diastolic dysfunction [14]. In some patients, progressive LV dilation may result. Initial LV chamber enlargement occurs to allow initiation and further progression of diastolic filling, and may depend directly and indirectly on active forces [15]. Also, as progressive fibrin deposition ensues, the LV walls become stiffer and in turn, require higher pressures for diastolic filling. In such instances, diuretics typically improve symptoms.

She was enrolled in a clinical trial looking at spironolactone versus placebo in the HCM population. An echocardiogram during this time showed an ejection fraction of 70 % with no obstruction, and asymmetric septal hypertrophy with an interventricular septal thickness of 23 mm. Stress testing was also performed using the modified Naughton protocol, with a resting blood pressure of 100/65 mmHg and resting heart rate of 61 bpm. She was able to exercise for 10 min and 34 s, reaching a maximum heart rate of 135 bpm and peak METs 5.6, and had no hypotension or arrhythmia with exercise. The exercise study was terminated due to chest pain. Cardiopulmonary exercise testing was also performed with a peak VO2 of 17.6 ml/kg/min, VE/VCO2 30, and anaerobic threshold was reached at VO2 of 17 ml/kg/min, which is 53 % of her age-predicted-maximum and is inconsistent with her advanced symptoms of heart failure.

Clinical Decision Making—When to perform exercise testing, including VO2?

In patients without resting gradients greater than or equal to 50 mmHg, exercise stress testing is reasonable (IIb indication) to determine functional status as well as for SCD risk stratification [1, 16]. Concomitant echocardiogram may be used to document obstructive or non-obstructive physiology. When a patient has significant exercise impairment, such as this patient, cardiopulmonary exercise testing is also useful to determine the patient's true exercise capacity and help differentiate cardiac from pulmonary components. The peak VO2, which is the peak oxygen consumption, in conjunction with the respiratory exchange ratio helps discern whether the patient's disease process correlates with the level of impairment, or whether there is a non-cardiac reason for impairment, such as de-conditioning. The peak VO2 is also used to determine if the patient is impaired enough to require cardiac replacement therapy, such as heart transplantation, the only available invasive therapy aside from pacemaker placement for patients with profound diastolic dysfunction and severe symptoms [17].

Following termination of the clinical trial of spironolactone, her symptoms had persisted despite no outflow tract obstruction (Figs. 24.11 and 24.12 depict followup echocardiographic findings), and she was advised to seek evaluation for cardiac replacement therapy. At the time that she was referred for advanced therapies she was on a medication regimen of verapamil 240 mg daily, furosemide 40 mg daily and had NYHA class III-IIIb symptoms, including one-block exercise tolerance and inability to

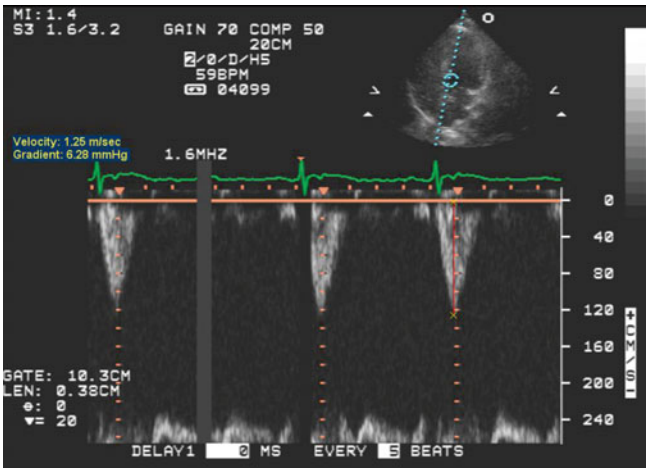

Fig. 24.11 Case 3: Follow-up TTE depicting lack of any significant resting LVOT gradients despite severe HCM related symptoms

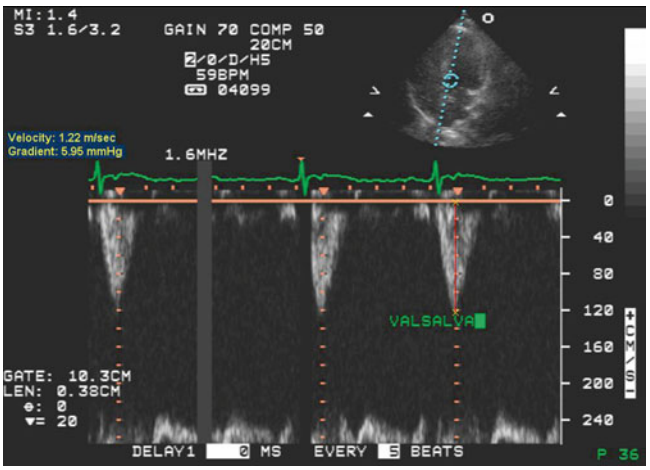

Fig. 24.12 Case 3: Follow-up TTE revealing lack of any significant LVOT gradient with Valsalva maneuver despite severe HCM related symptoms

climb a flight of stairs. Her blood pressure was 124/76 mmHg and resting heart rate was 62 bpm and regular, and she had no murmur on cardiac auscultation. Over the next several months, the patient had progressive symptoms of exertional dizziness and dyspnea on exertion. The patient was restarted on spironolactone (outside of the trial) with little change to her functional status. A repeat cardiopulmonary exercise test was performed which showed decline in her functional status with a peak VO2 of 11 ml/kg/min, which was more consistent with her class IIIB symptoms. Due to worsening symptoms, a right heart catheterization was repeated which revealed right atrial pressure of 11 mmHg, right ventricular pressure of 39/12 mmHg, pulmonary artery pressure of 36/18 (mean = 24) mmHg, mean pulmonary capillary wedge pressure of 20 mmHg and a pulmonary artery saturation of 70.3 %, resulting in a Fick Cardiac output of 4.59 L/min, transpulmonary gradient of 4 mmHg and a pulmonary vascular resistance of 0.87 Wood Units. After arm exercise, her transpulmonary gradient increased to 10 mmHg, with a drop in cardiac output to 3.9 L/min, cardiac index 1.8 L/min/m^2 and a pulmonary vascular resistance of 2.6 Wood Units. These results indicate severe diastolic dysfunction and a secondary minor lung component.

Clinical Decision Making—When to consider heart transplant?

In patients with advanced heart failure symptoms with non-obstructive HCM or restrictive physiology who are refractory to medical therapy, heart transplantation should be considered. This may also be an option in burnt-out systolic heart failure patients with HCM. Accordingly, heart transplantation referral is not contingent on a reduced ejection fraction, though patients with preserved ejection fraction rarely are impaired enough to require transplantation. Once a patient is deemed eligible for heart transplantation, it becomes imperative that the patient's hemodynamics be maintained to ensure preservation of end-organ function. Thus it is important that the patient has timely referral to a heart transplantation cardiologist. In addition to symptoms and hemodynamic criteria, cardiopulmonary exercise testing can be used to determine the extent that the patient's functional status is impaired and is an important factor in determining if a patient is a candidate for heart transplantation. Traditionally a VO2 of less than 12 ml/kg/min is accepted for patients receiving beta-blocker therapy and a VO2 of less than 14 ml/kg/min is used for patients who are beta-blocker intolerant [17].

The patient was listed for heart transplantation and continued to have symptoms of dyspnea and dizziness on exertion leaving her primarily homebound. Her ICD failed to reveal any significant arrhythmia, and her resting blood pressure ranged from 96/60 mmHg sitting to 85/60 mmHg standing. Her diuretics required titration due to delicate fluid balance. In addition to diuresis, the patient was able to lose 50 lbs, which resulted in improved exercise tolerance, though she continued to be limited by dyspnea. Physical exam now revealed a short systolic murmur 2/6 at the left sternal border that did not increase with Valsalva. Repeat cardiopulmonary exercise testing showed a peak VO2 of 14.2 ml/kg/min and respiratory exchange ratio (RER) of 0.97, which represents 67 % of her age-predicted-maximum.

Clinical Pearls—How to manage patients on the heart transplant list

Following patients with HCM prior to transplantation can be challenging, particularly as their cardiac output begins to drop. In this patient, weight loss was a key to symptom management, as the decreased weight resulted in an improved exercise tolerance and down-titration of diuretics. In addition, it increased her chances of obtaining a donor heart. However, despite improved exercise capacity, her peak VO2 remained 14, which is still an indication for heart transplantation, and thus the patient continued to wait. In such cases, the options for advanced therapies remain quite limited, given the small ventricular size and ventricular stiffness that contributes to the overall low-output clinical state.

Inotropes have a limited benefit and may actually cause harm in patients with a restrictive cardiomyopathy. The low cardiac output in these cases is due to the non-distensible, stiff ventricle that is unable to stretch to increase stroke volume [18, 19]. As a result, inotropes may exacerbate heart failure and may also result in ventricular arrhythmias. Mechanical support, such as a ventricular assist device would also not be suitable due to the small ventricular cavity size and preserved ejection fraction.

In most cases, patients are able to wait for heart transplant with close monitoring by a cardiologist and frequent titrations of their oral medication regimen and careful diuresis. However, in cases where the patient's functional capacity becomes extremely limited, the patient may require hospitalization with day-by-day medical optimization. In these cases, the transplant committee may provide an exception for upgrading the patient's transplant status, since the traditional criteria of intractable arrhythmias or inotrope dependence may not be met. In the extreme cases, patients may ultimately develop "burnt-out" HCM, in which cases, their ventricle dilates and therapy is then modified to treat the dilated cardiomyopathy with inotropes and mechanical support.

Finally, at age 43, almost 2 years after being listed for heart transplantation, the patient underwent successful orthotopic heart transplantation and was ultimately discharged home. Although she has had some of the typical post-transplantation complications, she has not had significant rejection episodes and is currently noting improved symptom status.

Clinical Pearl—Management of patients with diastolic dysfunction

Most patients with non-obstructive HCM have minimal to no symptoms. This is because the lack of obstruction also makes progressive hypertrophy and worsening diastolic dysfunction less likely, and cardiac output is not usually as affected. In addition, there is usually no accompanying mitral regurgitation. However, a subset of patients may either develop obstruction later in life or progress to severe diastolic dysfunction requiring transplantation, as in the current case. This is in part also due to reduced cavity size available for LV filling, especially in patients with severe apical HCM and cavity obliteration. Management of these severely symptomatic patients is extremely difficult given the absence of good medical therapy and standard invasive options. Pacemakers to optimize AV delay, and medications to improve congestion and relaxation are the mainstay of therapy until transplantation is required. In such patients, active involvement by family, physicians and others is required to get the patient ready for transplantation and through the system to obtain a heart. In addition, a proactive stance, including VO2 testing and exercise invasive hemodynamics, as well as serial right heart catheterizations, may be needed to arrive at the diagnosis of severe diastolic dysfunction. Once confirmed, multiple transplant waiting lists might be required, as hearts are more readily available to patients with ischemic or dilated cardiomyopathy.

Case 4: Congestive Heart Failure in an Elderly Woman with Longstanding HCM

Ms. BP is an 82-year-old woman with known longstanding history of hypertrophic obstructive cardiomyopathy, in addition to hypertension and one episode of atrial fibrillation. She had been managed conservatively for her arrhythmia, without anticoagulation, due to risk of falls. She had also been labeled to have chronic obstructive lung disease despite being a non-smoker. She was referred to our cardiology service during a hospital admission for congestive heart failure in the setting of atrial fibrillation, at which time she had significant dyspnea and lower extremity swelling. Two-dimensional echocardiography (Fig. 24.13a–c) revealed an ejection fraction of 60–65 %, severe mitral regurgitation with systolic anterior motion of the mitral valve and asymmetric septal hypertrophy

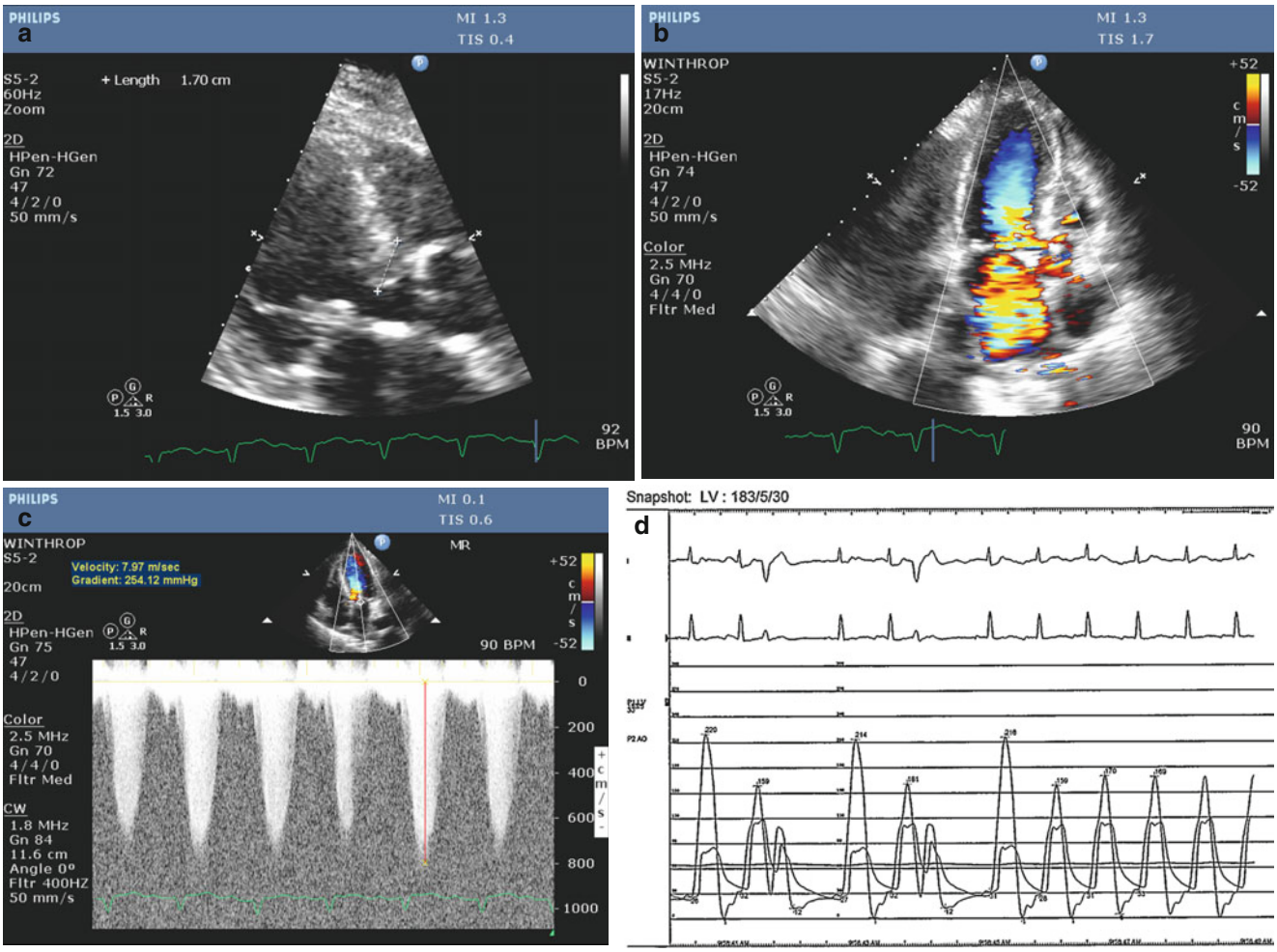

Fig. 24.13 Case 4: Measurements on presentation. (**a**) TTE parasternal long axis view depicting asymmetric septal hypertrophy, (**b**) TTE 3 chamber view depicting severe mitral regurgitation, (**c**) spectral Doppler on TTE consistent with severe mitral regurgitation, (**d**) hemodynamic data on cardiac catheterization revealing significant resting and provoked LVOT gradients

with a septum measuring 17 mm. Accordingly, she was evaluated by the HCM center and treated with beta-blockers and diuretics.

Clinical Decision Making—What is the role of diuretics in HCM?

It is important to avoid use of high dose diuretics in patients with obstructive HCM for other concomitant conditions like hypertension. Diuretics (similar to alcohol intake and dehydration from reduced oral fluid intake) can reduce preload and thus exacerbate dynamic LVOT obstruction, especially in patients with pre-existing resting or provocable LVOT gradients [1], in effect leading to worsening of symptoms.

However ACCF/AHA guidelines support addition of diuretics to symptomatic patients when congestion (volume overload) is present. This may be the case in non-obstructive forms, but also is common with long-standing obstructive disease. However, in the latter, care must be taken to avoid over-diuresis which might precipitate worsening obstructive symptoms. Accordingly, invasive hemodynamics to document extent of congestion and choose type and dose of diuretic may be needed. In such patients, hydrochlorothiazide or combination of triamterene with hydrochlorothiazide may be less potent choices in patients with mild degrees of congestion, whereas loop diuretics together with metolazone may be required in severe cases.

After adequate diuresis the HCM service decided to do a right and left heart catheterization as an outpatient. At this time, she was in normal sinus rhythm. Cardiac catheterization (Fig. 24.13d) revealed severe resting and provocable obstructive physiology with resting gradient of greater than 40–50 mmHg and provocable gradient greater than 100 mmHg. There was mild noncritical disease in the coronaries. There was also moderate pulmonary hypertension and moderately elevated right and left filling pressures despite diuretic therapy. PVR was only mildly elevated, confirming that the primary problem was HCM and not COPD.

Clinical Decision Making—When to perform cardiac catheterization in HCM patients

Patients with HCM should undergo cardiac catheterization to assess for epicardial coronary stenosis, define coronary anatomy including septal perforators and assess hemodynamics. In addition, catheterization can aid in determining the relative contributions of pulmonary and cardiac disease to heart failure, including the assessment of filling pressures. This is particularly relevant in a patient with obstructive physiology and congestion, in whom diuretics have been employed, as overshooting or undershooting the dose can result in continued or even new symptoms. Cardiac catheterization is an ACCF/AHA Class I recommendation in patients with HCM with chest discomfort who have an intermediate to high likelihood of CAD when the identification of concomitant CAD will change management strategies. In addition, catheterization should be performed before surgical myectomy or alcohol septal ablation [1]. In addition, cardiac catheterization is reasonable for patients with severe symptoms on optimal medical therapies, in order to fully understand cardiopulmonary function, evidence of heart failure (including cardiac output and volume status), pulmonary contribution, and assess whether severe obstructive physiology is present. Meticulous hemodynamics are required in order to fully elucidate underlying physiology.

Diuresis was continued and Disopyramide twice daily was added to the above therapy both for improvement in obstructive physiology and prevention of recurrent atrial fibrillation. Despite these additions and a short-term stay in cardiac rehab, she remained in New York Heart Association class III symptoms and began losing weight consistent with cardiac cachexia. Following this, her treatment strategy was re-evaluated and a recommendation for permanent pacemaker implantation was made.

Clinical Decision Making—Why was a permanent pacemaker recommended for this patient?

Given her elderly and frail status, she did not appear to be a good candidate for invasive septal reduction therapy. Surgical myectomy would be too high risk, and it was not clear whether resolution of gradient at this late stage would be enough to reverse the course of disease. In such patients who are already on first and second line pharmacotherapy, implantation of a permanent pacemaker may be reasonable. Pacemakers with RV leads paced at the apex using a short AV delay may alleviate obstructive physiology [20] in a subset of patients, particularly the elderly (as observed in patients ≥65 years in the M-PATHY trial) [21], and also may allow higher doses of beta-blockers. Given lack of history of sudden cardiac death in the patient, history of ventricular tachycardia or non-sustained ventricular tachycardia, recent unexplained syncope or left ventricular hypertrophy >30 mm, she was not at high risk for sudden cardiac death. Therefore, an implantable cardioverter defibrillator was not implanted.

On followup after pacemaker placement she continued to have New York Heart Association Class III symptoms, however, despite augmented beta-blocker dosage. A review of systems revealed absence of other cardiac complaints besides significant shortness of breath, including palpitations, dizziness, syncope or lower extremity swelling. She was a nonsmoker and was complaint with her medications, which included Aspirin 81 mg q.d., Furosemide 40 mg q.d., Disopyramide sustained release 150 mg b.i.d., Metoprolol Succinate 25 mg b.i.d., and Spironolactone 25 mg q.d. Physical exam in the out-patient office was significant for blood pressure 92/52 mmHg, heart rate 80/min, absence of jugular venous distension, presence of regular rate and rhythm, grade 3/6 systolic ejection murmur at the left sternal border which increased with Valsalva maneuver, and absence of rales on lung exam or edema in lower extremities. An echocardiogram revealed asymmetric septal hypertrophy 1.5 cm with significant outflow tract obstruction and moderate mitral regurgitation that appeared to be due to systolic anterior motion of the mitral valve, while there was no significant aortic stenosis. Alcohol septal ablation was discussed.

Clinical Decision Making—When to recommend alcohol septal ablation in HCM patients and what are the risks?

Alcohol septal ablation was contemplated for this patient for multiple reasons. First, she had refractory symptoms after maximal medical therapy, including

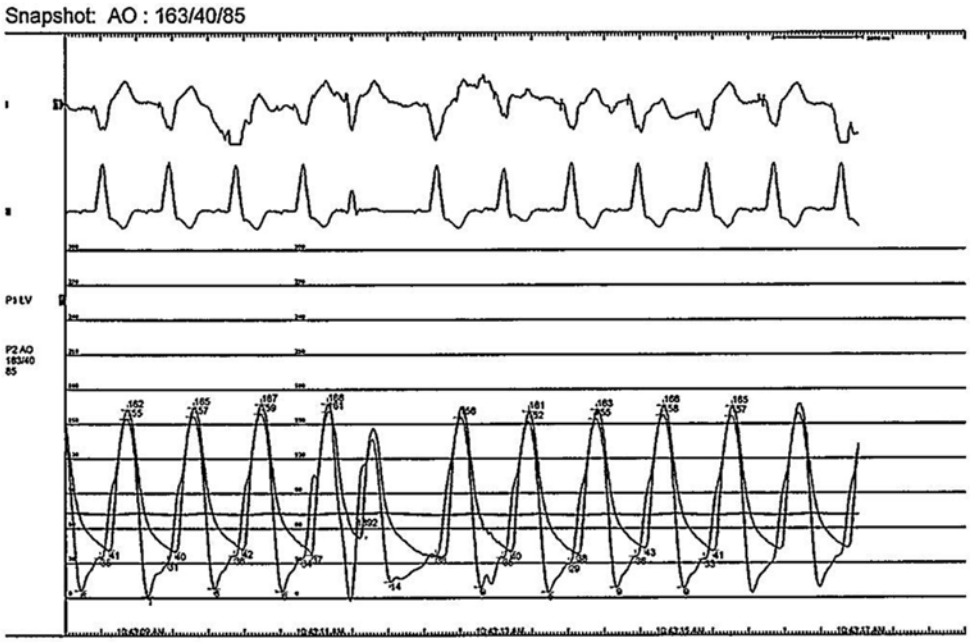

Fig. 24.14 Case 4: No significant resting or provocable gradient post alcohol septal ablation on cardiac catheterization

(in this case) pacemaker placement. Second, she was a poor surgical candidate due to her advanced age and frail status. Third, her septum was measured to be greater than 15 mm in thickness and there was severe obstructive physiology due to systolic anterior motion of the mitral valve, and thus the morphology was amenable to alcohol septal ablation. And fourth, her anatomy indicated a high chance of success, with focal septal bulge, an appropriate septal perforator and a lack of intrinsic mitral regurgitation. An in-depth discussion was held involving the patient and family informing them of potential complications including high-grade heart block becoming completely dependent on a permanent pacemaker of 8.9 % [22], approximately 1 % risk of sustained ventricular tachyarrhythmias during hospitalization, and in-hospital mortality rate up to 1 % [23]. In this patient, with a pacemaker implanted, the risks are reduced. However, given the septal thickness is borderline at 1.5 cm, the risk of creating a VSD was discussed, and estimated at roughly 1 %. After explanation of all risk and benefits, decision was made to proceed with the alcohol ablation, although it was recognized that it would be very difficult to determine what percent of her symptoms the procedure would alleviate given her overall functional status and comorbidities, and longstanding disease. In effect, the therapy was felt to be palliative in an effort to improve quality of life.

Alcohol septal ablation was performed using standard technique via the 1st septal perforator. The provocable gradient reduced from 160 mmHg prior to ablation to 0 mmHg post ablation (Fig. 24.14). The procedure was marked by complete AV nodal block during which she required 100 % pacing from her permanent pacemaker. The rest of the hospital course was unremarkable. She was discharged on day 3 and followed up as an outpatient 3 weeks later and reported significant improvement, now at NYHA class I. Followup echocardiograms did not reveal any left ventricular outflow-tract obstruction (Fig. 24.15). By 6 months of followup dyspnea was completely resolved and she reported being able to dance at her granddaughter's wedding "all night". Her appetite returned and she had gained 10 lb within 3 months, with no evidence of congestion. The permanent pacemaker interrogation did not reveal any further atrial fibrillation episodes. Her medical regimen was re-visited and her beta-blocker dosage was slightly decreased, Disopyramide was stopped 2 months post ablation, and Spironolactone was switched to Hydrochlorothiazide 25 mg q.d. at 6 months. At the most recent office visit, consideration was given to start an angiotensin receptor blocker in the future for better blood pressure control in this patient with resolution of obstructive physiology. The patient and family were extremely grateful that we had taken a chance on someone that most would have considered end-stage.

Clinical Pearl

Patients with long-standing HOCM physiology may deteriorate from both a physical and functional status, including frailty and cachexia from chronic heart

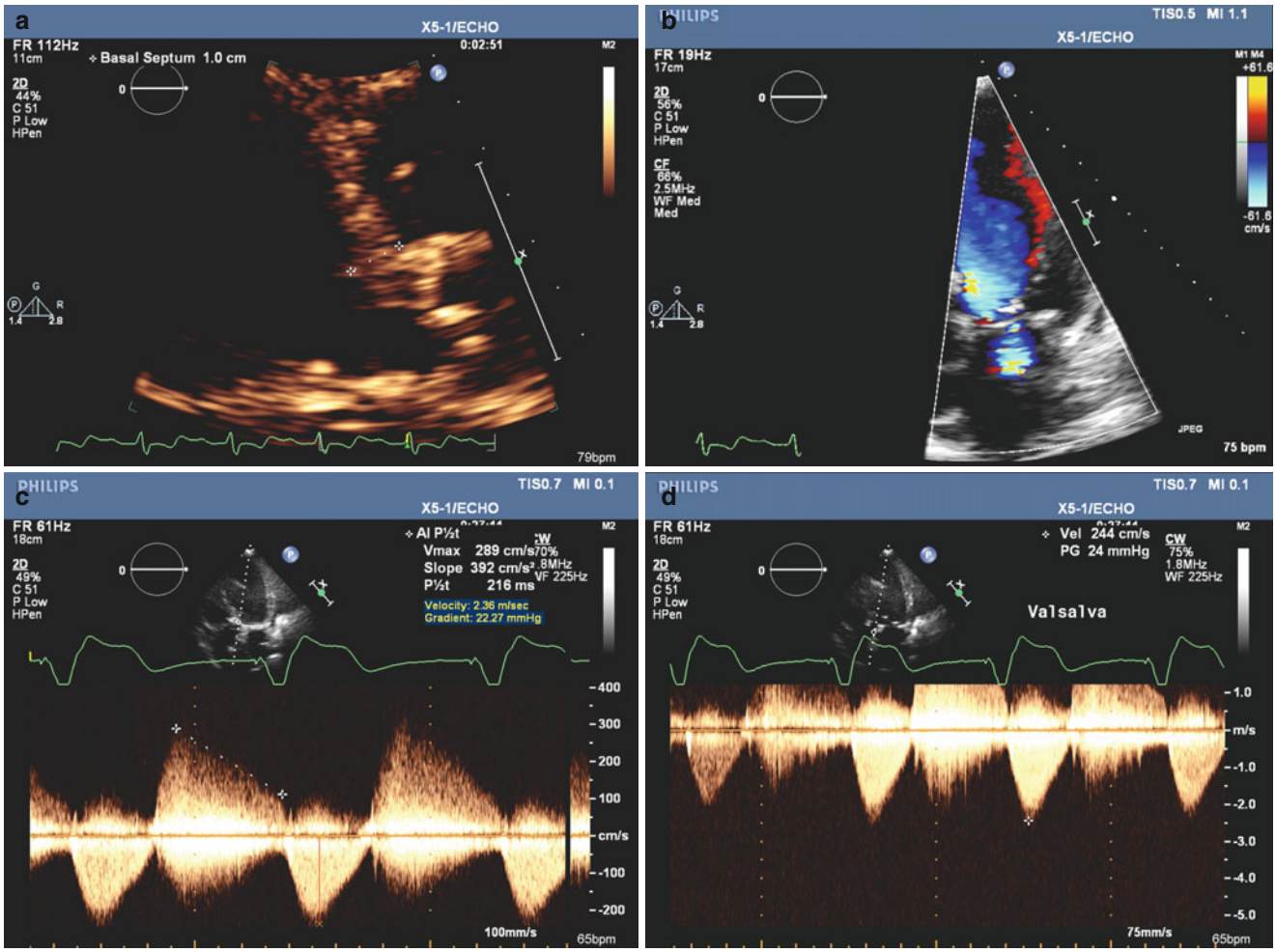

Fig. 24.15 Case 4: Post-ablation TTE images. (**a**) reduction in basal septal thickness on PLAVX view (1 cm), (**b**) mild mitral regurgitation reduced from severe mitral regurgitation pre-ablation, (**c**, **d**) reduced LVOT gradient post ablation, not worsened with Valsalva maneuver

failure symptoms. Such patients may see significant improvement in overall status with aggressive HCM therapy including medications, pacemakers and invasive therapies. In older patients such as these, alcohol septal ablation is a particularly palatable option as the risks are lower than surgery, and the patient may be willing to take this risk in order to see whether the HOCM physiology is the largest contributor to their overall debility. Patients with a prior permanent pacemaker have overall low risk with alcohol septal ablation, and may only need to be monitored for 3 days in the hospital post-procedure, barring other unforeseen complications.

Case 5: A 52 Year Old Woman with Non-obstructive HCM and SCD

Patient R.C. presented to the Hypertrophic Cardiomyopathy Center at the age of 52 in January of 2008. She had originally been diagnosed with HCM in 2006 when she had an episode of sudden cardiac death. This event was preceded by lightheadedness and she was found to have ventricular tachycardia in the ambulance. An echocardiogram revealed severe asymmetric septal hypertrophy and HCM, without obstructive physiology. She noted that at the time of the initial diagnosis she was not told this condition was hereditary. She had also not undergone structured risk stratification for SCD prevention.

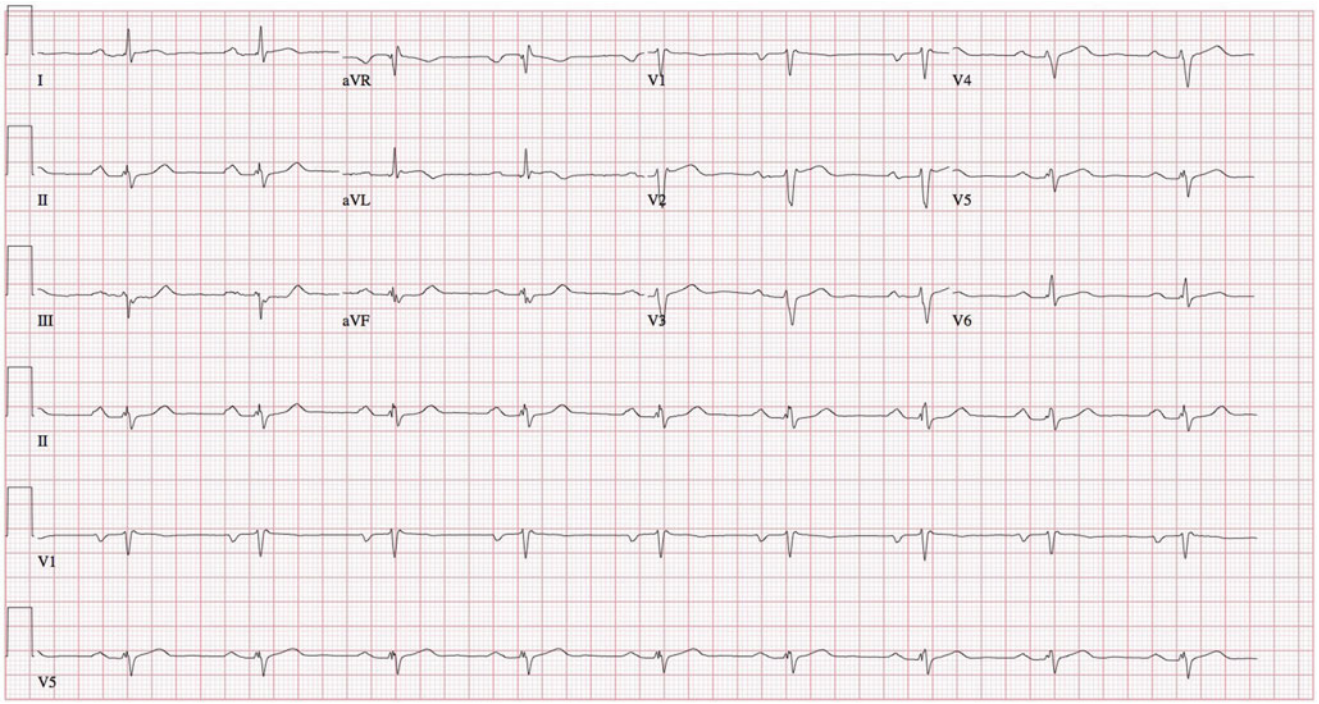

Fig. 24.16 Case 5: Initial 12 lead electrocardiogram depicting an incomplete right bundle branch block

Clinical Pearl—Genetic basis of HCM

HCM is caused by an autosomal dominant mutation in genes that encode sarcomere proteins or sarcomere-associated proteins [1]. Informing patients of the genetic basis of HCM is crucial as HCM mutations have high penetration >95 % and an affected parent has 50 % chance to transmit the mutation to the child, thus warranting genetic counseling and screening of the patient and all first degree relatives, who accordingly have roughly a 50 % risk of sharing the disease causing mutation [24]. This patient has one son, who was a teenager involved in high-risk sports at the time of her initial presentation and diagnosis, and therefore he should have been screened for HCM morphology or symptoms. If diagnosed with HCM, he would have been advised against competitive athletics and an ICD would have been implanted. Sporadic cases are rare, measuring roughly 5 % at most of patients with HCM.

Besides HCM, she reported a history of dyslipidemia and asthma and was an ex-smoker (7 pack-years) who had quit tobacco 25 years ago. She reported her father was alive with a history of acute MI at age 72 and her mother was alive and well.

Patient denied previous symptoms, including specifically no dyspnea, edema, palpitations, chest pain or syncope. Workup during the hospitalization included an electrocardiogram which revealed a right bundle branch block (Fig. 24.16), an echocardiogram (Fig. 24.17a, b), which was significant for severe asymmetric septal wall hypertrophy, an ejection fraction of 60–65 %, grade 1 diastolic dysfunction, a mildly dilated left atrium and mild mitral valvular regurgitation. There was no provocable gradient on the Valsalva maneuver, and no exacerbation of MR. A diagnostic cardiac catheterization revealed normal coronary anatomy and a hyperkinetic ventricle (Fig. 24.17c, d). Following this an implantable cardioverter defibrillator was placed. No electrophysiology testing was performed.

Clinical Pearl—When to do electrophysiology testing for risk stratification?

Electrophysiology studies (EPS) for risk stratification are not recommended by ACCF/AHA clinical guidelines [1] due to the poor sensitivity and specificity. Accordingly, inducibility of VT at EPS is not an indication for ICD placement. Instead, the decision to

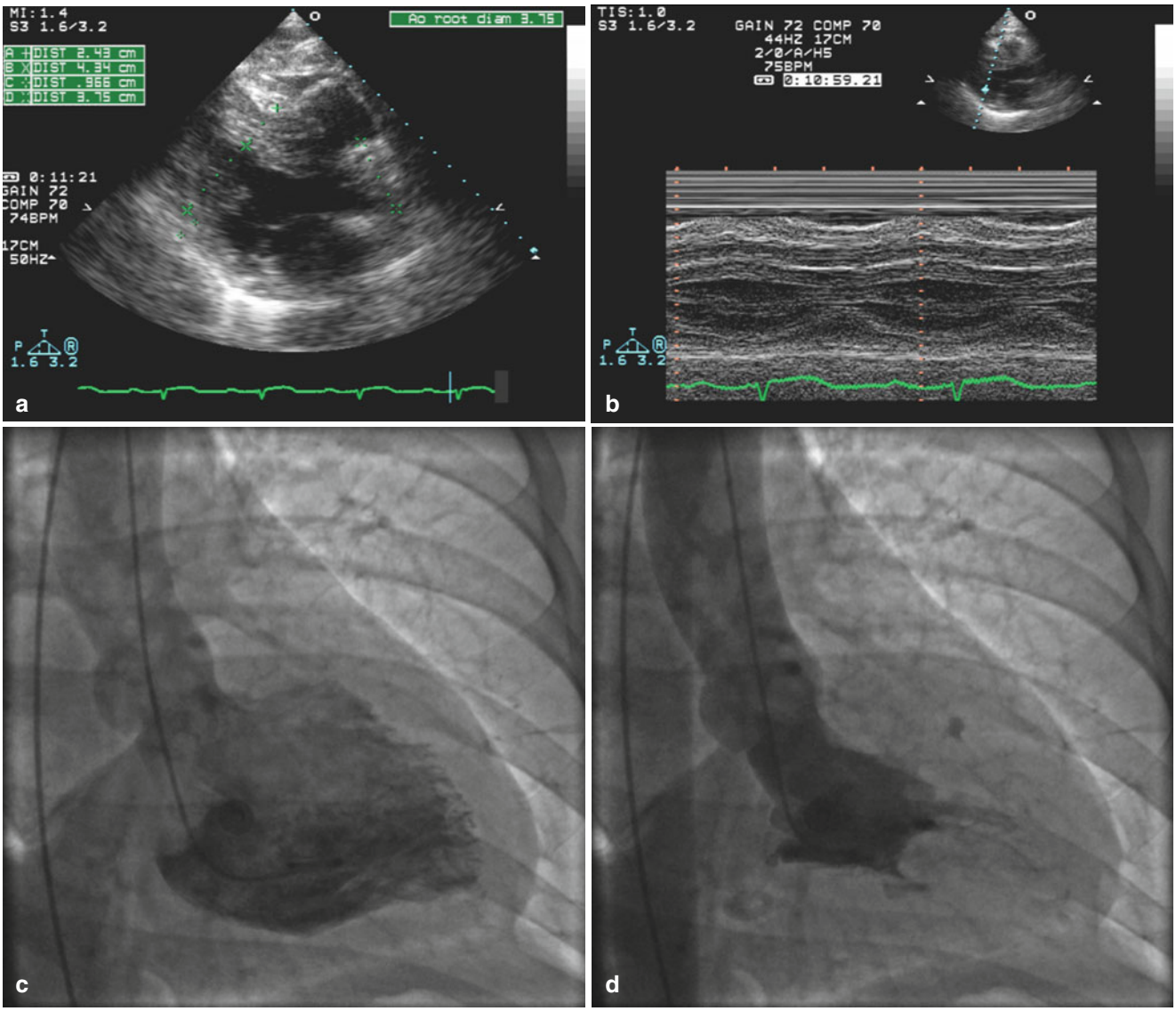

Fig. 24.17 Case 5: Baseline measurements. (**a**) TTE in parasternal long axis view depicting asymmetric septal hypertrophy (2.4 cm), (**b**) M-mode TTE depicting complete obliteration of LV cavity in systole, (**c**, **d**) cardiac catheterization depicting hyperkinetic ejection fraction secondary to severe septal hypertrophy

place an ICD is based on clinical algorithms of elevated risk. EPS may be utilized to check device thresholds, especially with addition of new anti-arrhythmic medications, or for ablation or treatment of arrhythmias by catheter ablation. In addition, EPS may be helpful in patients with heart block or high degree block after surgical myectomy or alcohol septal ablation, in whom permanent pacemaker placement is being considered.

The patient did well for the next 2 years and denied symptoms. At presentation to the HCM clinic a repeat two-dimensional echocardiogram showed similar findings as above significant for marked septal wall hypertrophy without systolic anterior motion of the mitral valve. Review of medications revealed she was taking Atorvastatin 10 mg q.d., Verapamil extended release 360 mg q.d., Aspirin 81 mg q.d., Montelukast 10 mg q.d. and Tamoxifen 10 mg once daily.

Clinical Decision Making—Choosing Verapamil vs. Beta-blocker

Verapamil therapy is recommended for the treatment of symptoms (angina or dyspnea) in patients with obstructive or nonobstructive HCM who do not respond to beta-blocking drugs or who have side effects or contraindications to beta-blocking drugs [1]. Our patient had a history of reactive upper airway disease and was using bronchodilator therapy, hence verapamil therapy was instituted from the beginning. In addition, some clinicians prefer calcium-channel blockers in patients with non-obstructive HCM, due to theoretic potential to better improve diastolic function. However, diltiazem is poorly studied and therefore the preferred calcium blocker is verapamil. Care should be taken to avoid high dose verapamil in patients with obstructive physiology, as verapamil may have a profound effect on afterload and result in worsening of obstructive physiology, hypotension, syncope and death in some patients. Accordingly, some clinicians prefer to not increase verapamil to doses over 240 mg daily.

She was categorized as New York Heart Association Class I heart failure based on lack of any symptoms and she was advised to continue her current medication regimen. Exercise testing revealed good exercise tolerance without arrhythmia or hypotension. At this point various options were available if symptoms developed, including decreasing the AV delay in order to improve diastolic filling, changing medications to b.i.d., and adding metoprolol succinate. No changes were made at the next 6 month follow-up as she continued to be doing well on her medical regimen. She was advised against competitive athletics, and instructed on appropriate exercise to maintain ideal weight. By the next visit, she continued to do well but her genetic testing confirmed a positive mutation consistent with hypertrophic cardiomyopathy and she was advised to have her son tested.

Roughly 2 years later, ICD interrogation revealed a short episode of atrial flutter, even though she did not report any significant palpitations. Anticoagulation was discussed, but given the opportunity to interrogate her ICD more frequently for monitoring of recurrence, the patient elected to not initiate warfarin. Five months after the previous visit she presented to the HCM center outpatient office after receiving an inappropriate ICD shock—her ICD lead was found to be on a recent manufacturer recall and was replaced.

Clinical Pearl—ICD complications in HCM patients

ICD lead implants in relatively young HCM patients are not benign as the younger patients may live many years and the collective morbidity for ICD complications including lead malfunctions, perforations, dislodgement, pocket site complications, generator malfunctions/changes is not inconsequential as is demonstrated by this case. In addition, HCM patients with ICDs may suffer from T wave oversensing [25] due to high amplitude T waves leading to spurious ICD detection and unnecessary therapy, which can reduce the quality of life of these patients [26]. In one multicenter study these extraneous shocks were observed more frequently in patients <30 years old who met the criteria for the highest clinical risk stratification; however by extrapolation it was determined 1 in 4 patients experienced an appropriate ICD shock over the initial 5 years post ICD implantation, thus making ICDs a reliable way to reduce mortality in high risk patients [27]. The vast majority of patients with >1 risk marker however will not experience SCD. In the same study, the number of risk factors did not correlate with the rate of subsequent appropriate ICD discharges among the presumably high-risk patients selected for ICD placement. Lead fracture is another major complication in HCM patients and may be more common due to hyperdynamic LV and RV function, and the more vigorous activities that younger individuals participate in.

In addition to lead malfunction, the ICD interrogation in our patient also revealed several episodes of atrial fibrillation, subsequent to which her Aspirin was stopped and Warfarin started with a goal to keep the International Normalized Ratio 2–3 for cardioembolic stroke prevention, given her CHADS2-VASc score of 2. On follow-up a month later she had gained 7 lb now weighing 216 lb. She had paroxysmal atrial fibrillation but still no obstructive physiology on the echocardiogram. In July of 2010 the patient presented to the emergency room with another ICD shock following an episode of rapid atrial fibrillation. At this point her Verapamil was increased to b.i.d. dosing and she was discharged home.

The next year was unremarkable. In June of 2011, however, an ICD check revealed 4 episodes of atrial fibrillation and 5 beats of Non-sustained ventricular tachycardia. She reported feeling well. She had lost some weight (weighing now 205 lb). In December of 2011 the patient came in for an ICD check, which revealed 6 beats of NSVT but no episodes

of AF. She had started Dabigatran 150 mg b.i.d. instead of warfarin, and Metoprolol Succinate 25 mg q.d. was added to her regimen. A followup echocardiogram 6 months later was unchanged.

Clinical Decision Making—Anticoagulants in HCM with AF

Patients with HCM are at increased risk of atrial fibrillation related strokes, perhaps more than the general population. Stroke is the third leading cause of death in HCM patients after SCD and progressive heart failure. It is important to discuss anticoagulation with the patients. Choices include Warfarin and the newer oral anticoagulants like Pradaxa, although the latter have not been studied specifically in the HCM population. Our patient did have mild diastolic dysfunction with mildly dilated left atrium in absence of any significant mitral regurgitation. She also was hesitant in the beginning to initiate warfarin. A frequent reason cited by patients is the need to closely monitor INR levels by invasive blood testing. Given her paroxysmal atrial fibrillation and CHADS2-VASc score of 2 she would have been a reasonable candidate for the newer oral anticoagulants like Dabigatran, Rivaroxaban or Apixiban. However, patients should be counseled about the lack of data for these agents in the HCM population. In addition, it is not clear that the CHADS2 and CHADS2-VASc scores are validated in HCM; therefore, patients may be reasonably anticoagulated with any episodes of atrial fibrillation, regardless of the presence or absence of modifying risk factors for thromboembolism.

At 3.5 years after initial presentation she continued to do well overall symptomatically but an ICD check demonstrated several episodes of NSVT with the longest one with 27 beats at a heart rate of 166 bpm, terminating spontaneously. There were no further episodes of AF. Remarkably, the addition of low dose metoprolol resulted in cessation of all AF. Her electrocardiogram now showed sinus rhythm with right bundle branch block, left anterior fascicular block and first-degree atrioventricular delay. An echocardiogram revealed stable non-obstructive HCM with a septal thickness of 2.4 cm (Fig. 24.17a, b). Her weight, electrocardiogram and medications were unchanged and she was referred for an exercise stress test to evaluate her exercise tolerance.

Clinical Decision Making—Why and which HCM patients to refer for exercise stress testing?

Exercise treadmill is useful to determine functional capacity and response to therapy in patients with HCM, besides risk stratifying for sudden cardiac death [1] (if abnormal blood pressure response or ventricular arrhythmia is found—see chapter on risk stratification for SCD). In patients with HCM who do not have a resting peak instantaneous gradient of greater than or equal to 50 mmHg, ACCF/AHA guidelines suggest exercise echocardiography is reasonable for the detection and quantification of exercise-induced dynamic LVOT obstruction [1]. Both of these conditions were met in our patient, although once an ICD is already in place, patients who are asymptomatic likely can forego annual exercise treadmill tests solely for risk stratification.

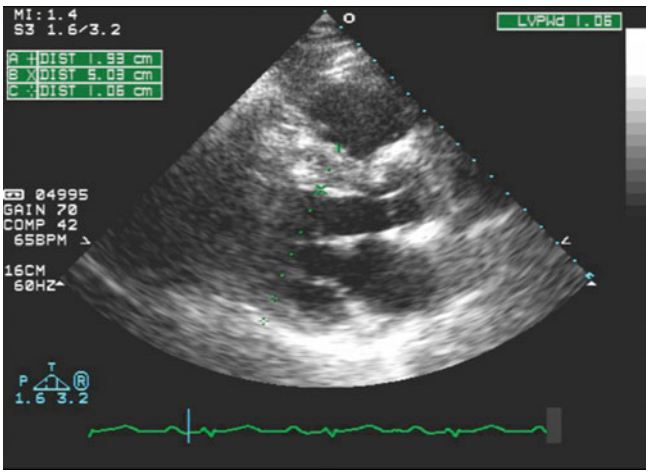

Fig. 24.18 Case 5: TTE parasternal long axis view, 5 years follow-up, on medical therapy. Mild regression in septal hypertrophy (1.9 cm) compared to baseline measurements (see Fig. 24.17a)

At the stress test she demonstrated a good exercise capacity of 9:31 min of the Bruce exercise protocol, and achieved 10.45 Metabolic Equivalents (METS) with a peak heart rate of 130 bpm which was 79 % of her age predicted maximal heart rate (while on calcium-channel blockers and beta-blockers). Stress electrocardiogram revealed only sinus tachycardia without stress-induced obstructive physiology, confirming non-obstructive HCM.

On her last follow up she had NYHA Class II symptoms, but no changes to her medical regimen were made. A repeat echocardiogram (Figs. 24.18 and 24.19) revealed no progression of septal hypertrophy and absence of any significant resting or provocable gradient. Over the years, genetic tests became available for her family and her mother, brother and son are all positive for the same HCM mutation. Her son was found to also have the phenotype, and therefore underwent ICD implantation based on the fact that our patient, his mother, had suffered SCD due to HCM.

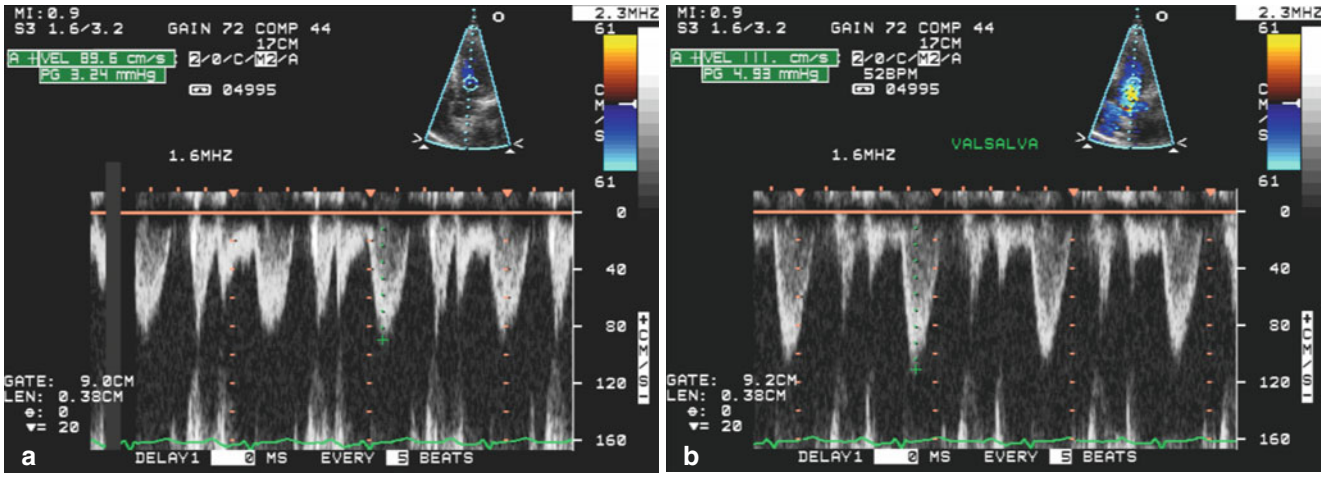

Fig. 24.19 Case 5: TTE parasternal long axis view, 5 years follow-up, on medical therapy. (**a**) resting LVOT gradient = 3 mmHg, (**b**) LVOT gradient at Valsalva maneuver = 5 mmHg

Clinical Pearl—How to use genetic testing

Genetic testing is now increasingly utilized in HCM patients. The main power of genetic testing is in tracing the gene's passage through the family, and in both confirming and excluding the presence of this genetic disease. In this case, the mother of our patient was found to be the individual who transmitted the gene to RC, and therefore it is the maternal side of the family that should be further tested and, most importantly, informed. In addition, the son was found to be positive for the gene. In all cases of gene positivity, imaging including echocardiogram and sometimes MRI are required to ascertain whether gene-positivity is accompanied by phenotype-positivity, as it is presently believed that it is the presence of the phenotype that confers risk of SCD [28]. There is no data available regarding rate of SCD in genotype-positive and phenotype-negative individuals with HCM [29]. By consensus opinion, therefore, these genotype-positive and phenotype-negative patients may be managed conservatively, and they are not typically excluded from competitive sports. However, any phenotypic abnormality that might be consistent with HCM would prompt the full battery of annual testing and visits, and exclusion from competitive sports. This includes, in most cases, the presence of any maximal thickness >1.5 cm, or other abnormalities that are highly suggestive of clinical disease (i.e. significant LGE on cardiac MRI typical of HCM, significant asymmetric hypertrophy or the presence of outflow tract obstruction).

Case 6: Exertional Dyspnea in a 61 Year Old Male with Severe LVOT Obstruction

Mr. AH presented to the HCM center in late 2007 as a 61 year old male with known history of hypertension, dyslipidemia, peptic ulcer disease, gastro-esophageal reflux disorder and hypertrophic cardiomyopathy. HCM was first diagnosed 9 months prior to referral to our center by his primary cardiologist when he had started experiencing exertional dyspnea on walking one block, in addition to frequent lightheadedness on exertion, consistent with NYHA Class III symptoms. He had been managed with atorvastatin for dyslipidemia and atenolol for hypertension that was later switched to amlodipine with little relief of his symptoms. A two dimensional echocardiogram several years earlier was interpreted as "normal". This was followed by a cardiac catheterization in January 2007, which was reported as "normal coronary anatomy".

He denied tobacco or alcohol use. His family history was significant for death of his mother at age 67 from "heart failure" and his brother had died at age 37 of an unknown cause. Physical examination revealed blood pressure 112/70 and a regular heart rate at 90 bpm. Cardiovascular exam revealed a grade 3/6 systolic ejection murmur at the left sternal border and a hyperdynamic left ventricle. Chest exam was clear to auscultation bilaterally and the rest of his exam was unremarkable. Notably, there was no edema.

His electrocardiogram in the office revealed normal sinus rhythm with left ventricular hypertrophy and repolarization abnormality (Fig. 24.20). On this initial visit, due to likely obstructive physiology based on his examination and his significant heart failure symptoms, the amlodipine was discontinued and beta-blocker therapy initiated

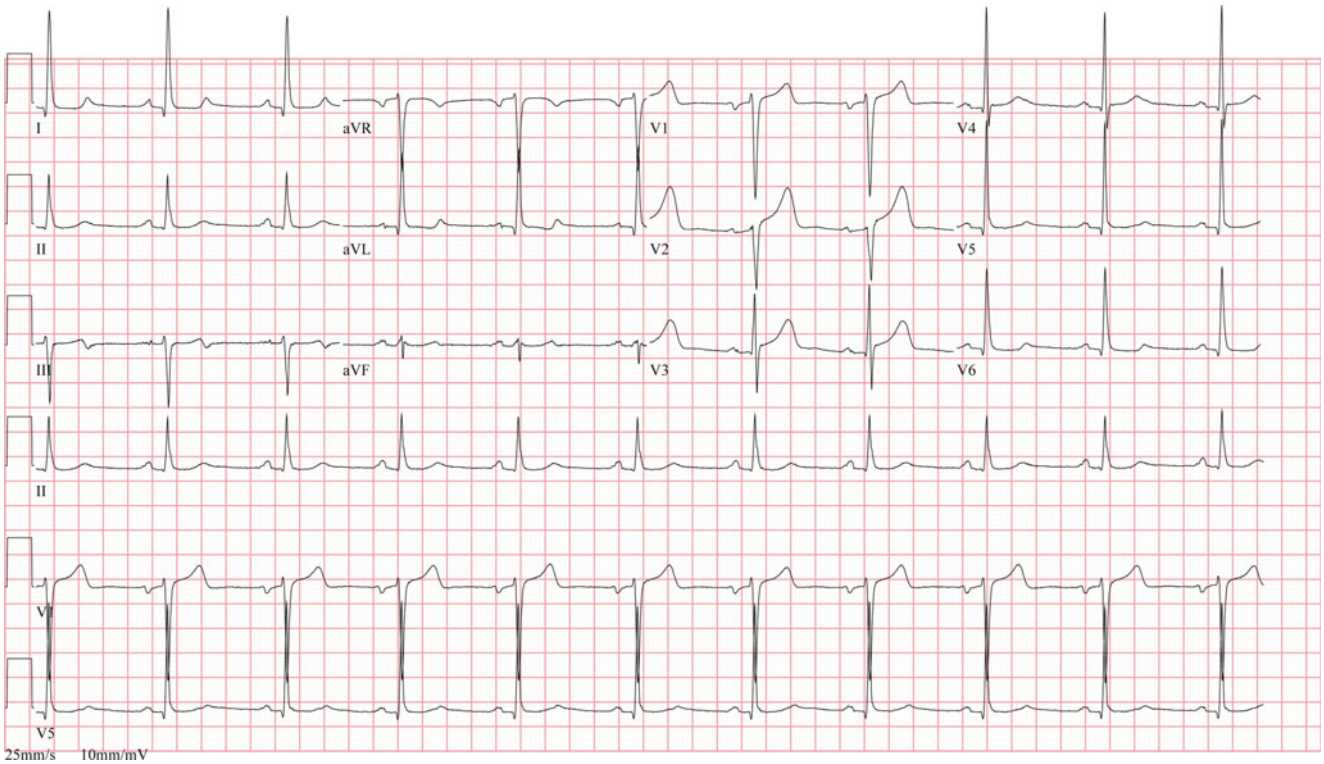

Fig. 24.20 Case 6: 12 lead electrocardiogram depicting left ventricular hypertrophy and repolarization abnormality

with metoprolol succinate 25 mg b.i.d. In addition a 24-h ambulatory electrocardiogram monitor was placed for assessing risk for sudden cardiac death and possible consideration for implantable cardioverter defibrillator given his significant family history. He was also advised life style modification measures including avoiding alcohol, dehydration, competitive athletic activities and ensuring aggressive oral fluid hydration.

Clinical Pearls—Approach to the initial visit

Patients with HCM and presumed obstructive physiology should undergo a comprehensive echocardiogram to diagnosis HCM, presence or absence of obstructive physiology and the maximal thickness. If there is doubt, a cardiac MRI is often useful. Once diagnosed, patients should be counseled on their initial visit on multiple areas. First, a description of HCM must be given in detail, including the variety of symptoms that may be present. Patients with systolic ejection murmurs indicative of obstructive physiology should be told to avoid any medications that could reduce the afterload or preload or increase contractility. They should be educated on situations that could lead to dehydration and advised to avoid alcohol, caffeine or other stimulants. Phosphodiesterase inhibitors for erectile dysfunction are contraindicated, as are nitrates. They should be told to run any new medications by their cardiologist directly, as many anti-hypertensives are relatively contraindicated due to their primary afterload reducing effects or their tendency to cause reflex tachycardia, both of which can worsen obstruction. Accordingly, during the initial visit, medications are usually adjusted or eliminated.

Patients should avoid any athletic activities that can cause a sudden increase in left ventricular outflow tract gradient or arrhythmia like sprinting, tennis, basketball, lifting free weights, or soccer [30]. In addition to discussing lifestyle modification as above, risk of sudden cardiac death should be discussed, including the annual screening that is required. Finally, the family inheritance pattern and genetic testing aspects should be discussed. In general, the first visit concentrates on understanding the patient's symptoms, physiology and adjusting medications, while educating regarding lifestyle modification and compliance. Subsequent visits can focus on the issues surrounding genetic testing and risk of SCD. However, as in the present case, initiating the SCD risk stratification protocol, for example with Holter monitoring, may be reasonable. Other tests such as exercise treadmill testing for risk stratification might be better timed after appropriate beta-blockade has been initiated.

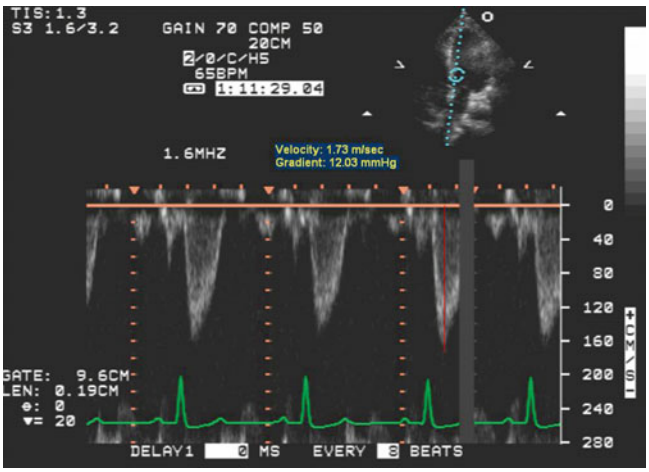

Fig. 24.21 Case 6: Initial TTE, spectral Doppler revealing 12 mmHg resting LVOT gradient

An echocardiogram was performed and revealed systolic anterior motion of the mitral valve with mild to moderate mitral regurgitation, a normal left ventricular systolic function, echogenic contact region at the SAM septal contact point, and asymmetric septal hypertrophy with basal septum 2.2 and 1.7 cm left ventricular posterior wall. The resting left ventricular outflow tract gradient was 12 (Fig. 24.21) mmHg and with Valsalva maneuver it increased to 26 mmHg. The ambulatory electrocardiogram recorder had revealed normal sinus rhythm besides sinus bradycardia and 7 couplets but no non-sustained ventricular tachycardia or atrial arrhythmia. The betablocker dose was doubled due to continued NYHA Class III symptoms, and a decision was made to perform an exercise treadmill test both to continue his risk stratification and to assess his exercise tolerance on medication.

Clinical Decision Making—Why would an exercise treadmill test (ETT) be helpful in this patient?

Besides helping determine exercise tolerance, which can confirm or refute a patient's subjective assessment, an ETT would help risk stratify this patient. Although he has a family member who died at a young age, HCM was not known in this person, and therefore the family history alone cannot be used to justify ICD implantation. Thus, any indication for ICD placement would be based on the confluence of other risk factors, as in all patients with HCM. Given his maximal septal thickness is 2.2 cm (less than the 3.0 cm cut-off point), and absence of NSVT, SCD or VT, an abnormal blood pressure response during the ETT would help assign risk [31, 32]. Patients with a 20 mmHg drop in systolic blood pressure or less than 20 mmHg rise in this pressure during the ETT are considered at increased risk of sudden cardiac death and may warrant ICD placement as a Class IIb in the 2011 ACCF/AHA guidelines [1]. An exercise stress echocardiogram may also be considered in patients with resting gradients less than 50 mmHg to determine if there is a significant exercise-induced gradient or an increase in the mitral regurgitation [1]. Finally, exercise tolerance can help determine whether to increase medications or maintain the current dose; in general, NYHA Class I to II patients typically can be maintained on medications while higher degrees of debilitation often require escalation of medications or contemplation of invasive therapies once medications have been exhausted or limited by side effects.

The patient continued to have NYHA Class III symptoms despite augmented medical therapy. Options included increasing medications further or proceeding to invasive therapies. After a thorough and balanced discussion, including surgical and interventional consultation, the patient requested a minimally-invasive approach and thus an alcohol septal ablation was performed. During the cardiac catheterization, no resting gradient was present, but a peak gradient of 300 mmHg was found and this reduced to 120 mmHg after the ablation. The first septal artery was diminutive and deemed not suitable for septal ablation, so the procedure was performed via an anomalous septal artery arising from the right coronary artery (Fig. 24.22). Echocardiographic guidance was utilized for the ablation. Peak creatinine phosphokinase level of 900 International Units/Litre followed by post procedure placement of a dual chamber implantable cardioverter defibrillator electively for complete heart block, due to the significant family history of sudden cardiac death, a large provocable gradient and monomorphic non-sustained ventricular tachycardia >48 h post procedure (Class 2b indication). A week post-procedure, the patient reported feeling "100 %" better in the office and had New York Heart Association Class I symptoms. He was able to engage in low-level exercises and walk several city blocks without any symptoms. No changes to his medical regimen were made at this time.

Clinical Decision Making—When to conclude an alcohol septal ablation procedure?

Historically, alcohol septal ablation was deemed successful when a >50 % reduction in resting and peak gradient was achieved, as in this patient. More recently,

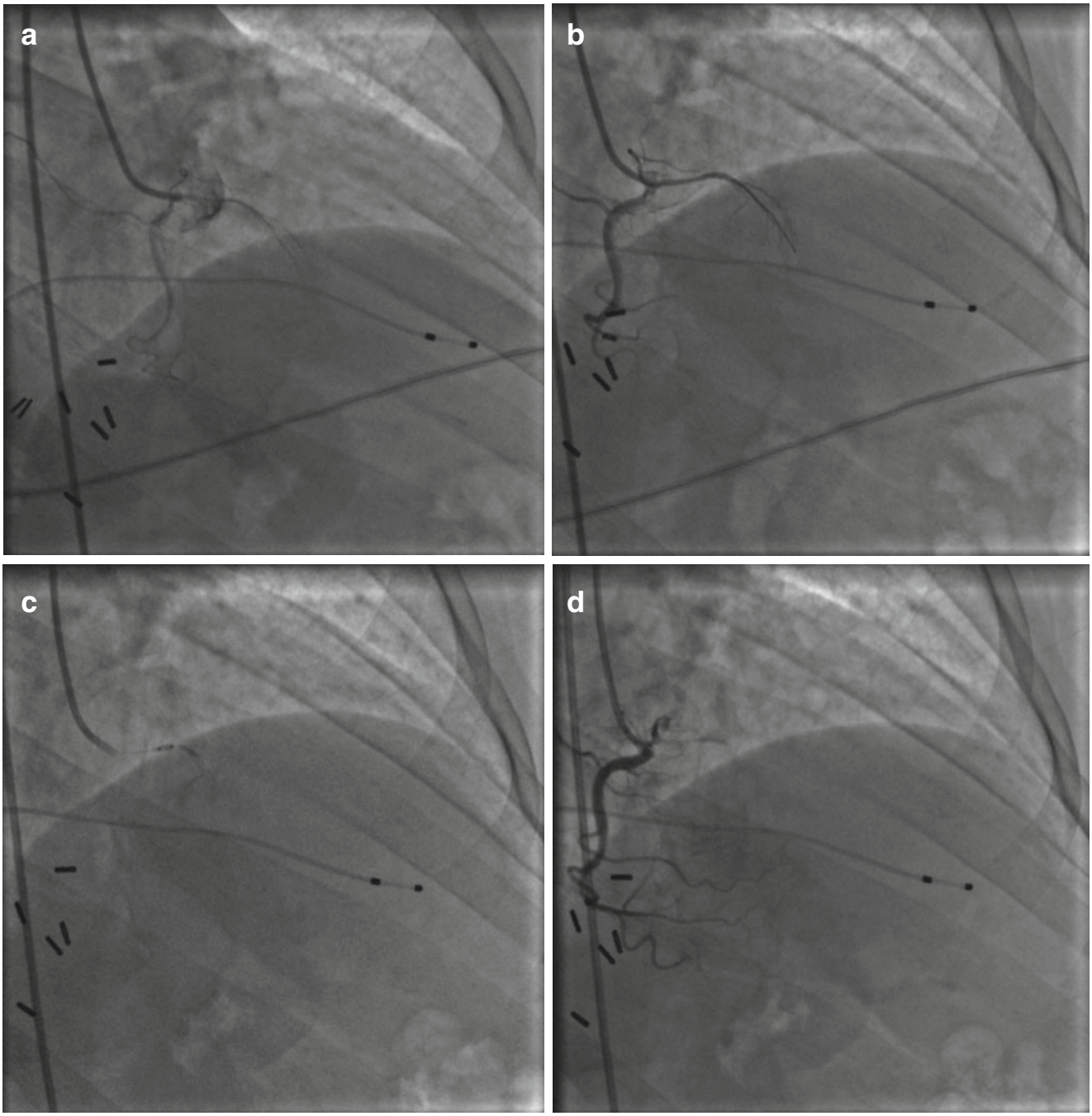

Fig. 24.22 Case 6: Initial alcohol septal ablation via first basal septal perforator originating from the right coronary ostium. (**a**) Engaging the septal perforator with a Judkins Right guiding catheter, (**b**) wire inserted into the septal perforator, (**c**) balloon inflated and ethanol injected into the branch, (**d**) post ablation obliterated perforator branch

many experts have advocated for continuing to ablate additional septal perforators (if present) in order to leave a residual resting gradient of <10 mmHg (which mirrors surgical results) and a >50 % reduction in peak gradient. Our patient met this criteria, as there was no resting gradient after the procedure. While this more stringent goal may increase the risk of complete heart block requiring pacemaker placement, a more effective and durable result may be obtained. This remains a point of controversy, however, within the field. In the current patient, a decision was made to conclude the procedure, and follow the patient clinically.

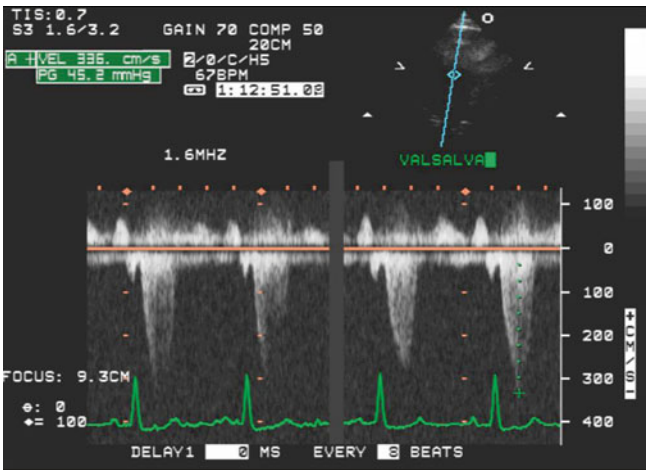

Fig. 24.23 Case 6: Symptoms persisted after initial ablation leading to a TTE study. Spectral Doppler revealed persisted LVOT provocable gradient on the Valsalva maneuver

The patient was seen again in the office 1 month post ablation and was only reporting some fatigue with exertion. ICD interrogation did not reveal any ventricular tachycardia or atrial fibrillation, and he was less than 1 % of the time atrial and ventricular paced. By this time, the patient's ICD lead had been recalled by the manufacturer, but had no signs of fracture and therefore it was not extracted.

Three months post ablation, the patient was again seen in the office, this time complaining of intermittent lightheadedness, dizziness, palpitations and shortness of breath with minimal exertion, reporting occasional dizziness at rest besides a 10-lb weight gain. An echocardiogram (Fig. 24.23) at this time revealed a resting gradient of 19 mmHg and a provoked gradient of 45 mmHg while the basal septum measured 1.8 cm (down from 2.2 cm). An echo 3 months ago had revealed the resting gradient to be 11 mmHg and the provoked gradient to be 18 mmHg. At this point the patient was conservatively managed and seen frequently as an outpatient and symptoms monitored, given ongoing expected remodeling from the ablation that might continue to improve over time. However, at 8 months post-ablation, due to continued New York Heart Association Class III symptoms, a repeat echocardiogram revealed a gradient of 100 mmHg with systolic anterior motion of the mitral valve causing LVOT obstruction and mild mitral regurgitation. A right and left heart cardiac catheterization was repeated and while no resting gradient was again noted, a provoked gradient of 180 mmHg was discovered and the first septal perforator had increased in size. This was thought to be due to the demand arising from the first ablation and a second alcohol septal ablation was therefore planned.

Clinical Decision Making—How frequently is a second alcohol ablation needed?

Studies report 2.7–12.8 % incidence of repeat alcohol septal ablations and 1.1–2.8 % incidence of referral to septal reduction surgery, after an initial alcohol septal ablation [22, 23, 33], as patients may have refractory symptoms due to severe hypertrophy, inability to adequately ablate the entirety of the obstructive area, or recurrence of obstruction due to collateral vessels as in our patient. Patients should therefore be told that a second invasive therapy may be required in a small subset of patients. In order to improve the initial efficacy, it is now thought that resting gradient should be reduced to less than 10 mmHg and peak gradient at least 50 % reduced, if not more; in this manner, there appears to be little risk of recurrence. However, care must be taken to not infuse too much alcohol and instead focus on targeting the exact area of septal contact by contrast echo guidance, so as to improve efficacy while maintaining safety. In fact in the Multicenter North American Registry, higher volume of injected alcohol was associated with higher mortality as was more the number of arteries injected with ethanol [22]. Patients should also be considered for septal myectomy after an initial failed alcohol ablation. However, although successful, surgical myectomy in this setting has a high incidence of permanent pacemaker (10–20 %). In the case of our patient, due to the focal nature of the septal bulge contributing to his symptoms, the more proximal LVOT obstruction that appeared to align with the now available first septal perforator and the presence of an ICD already in place, a repeat alcohol septal ablation was chosen. Importantly, the patient continued to have septal thickness sufficient to justify ablation (>1.5 cm). This may not always be the case, and when significant thinning is present a surgical myectomy may be safer as the surgeon can take care to avoid resection near the thinned septum.

The second ablation (Fig. 24.24) was done via the first septal perforator and resulted in disappearance of the provocable LVOT gradient with Valsalva and Brockenbrough maneuver completely. The patient was seen frequently as an outpatient after this ablation and has had complete resolution of his symptoms with no residual dyspnea on exertional or dizziness. Echocardiograms show no LVOT obstruction either at rest or with provocation, and absence of SAM.

Five years later, the patient remained in NYHA Class 1 and was asymptomatic without lightheadedness or dyspnea. An interrogation revealed lead noise and the ICD lead was revised for lead fracture. At 6 years followup, he continued to do well

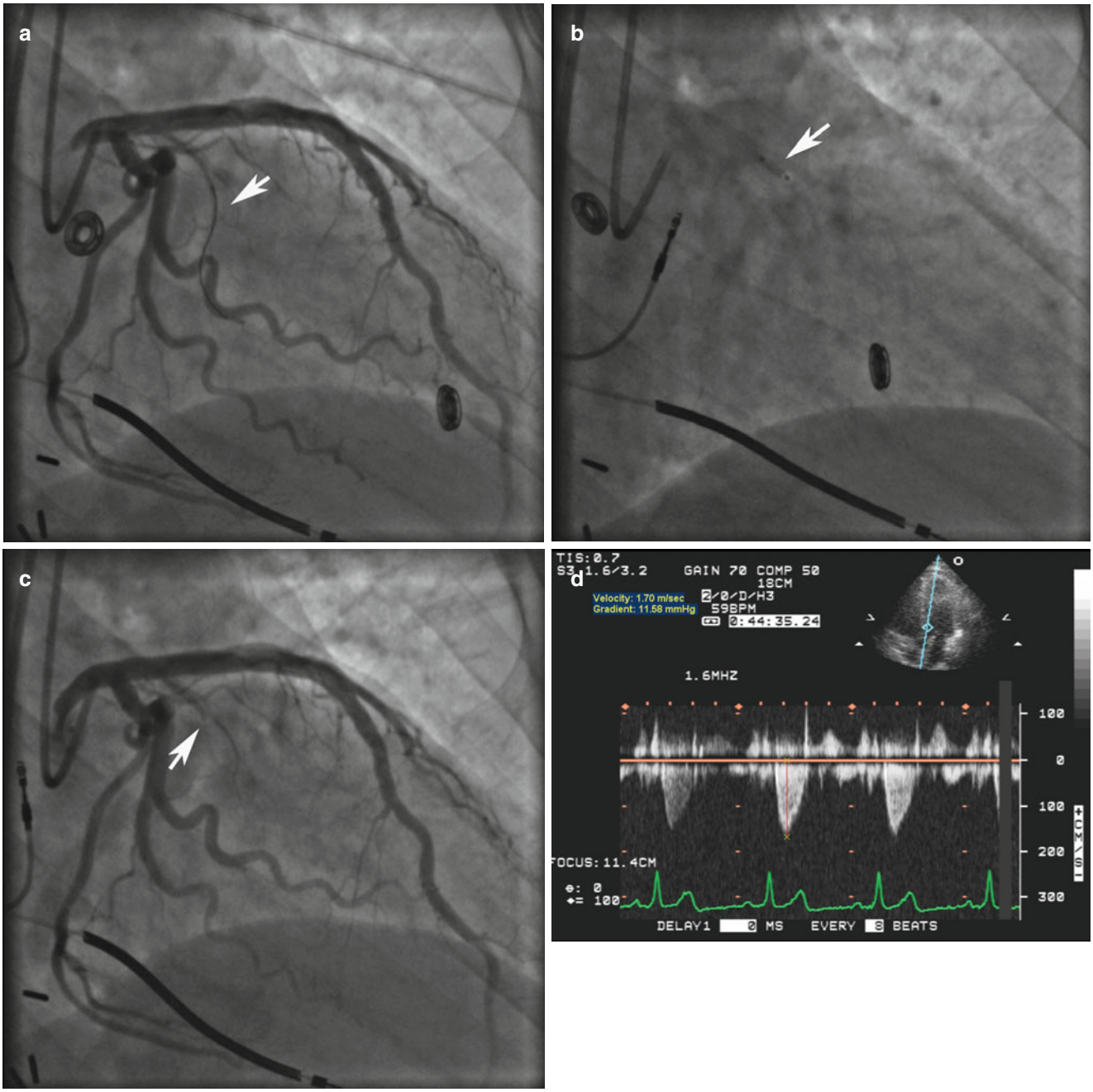

Fig. 24.24 Case 6: Repeat alcohol septal ablation. (**a**) basal septal perforator from the LAD (*arrow*) engaged with a wire, (**b**) balloon (*arrow*) inflated in the branch and alcohol injected distal to the balloon, (**c**) ablated perforator branch (*arrow*), (**d**) TTE spectral Doppler post ablation revealing reduced resting gradient across the LVOT (12 mmHg). Arrow head points toward

from the cardiac perspective. His echocardiogram revealed no LVOT obstruction or systolic anterior motion of mitral valve and he had mild to moderate mitral regurgitation.

Clinical Pearls—ICD lead complications in HCM patients are not inconsequential

HCM patients with ICD implants may lead long productive lives and these patients may outlast the life span of any given device system. While ICDs have been shown to be effective at aborting SCD in patients with HCM, the benefits and risks of an ICD implantation should be carefully considered and preferred only in patients with high risk for sudden cardiac death. This is especially the case for the very young, in whom multiple revisions may be required over their

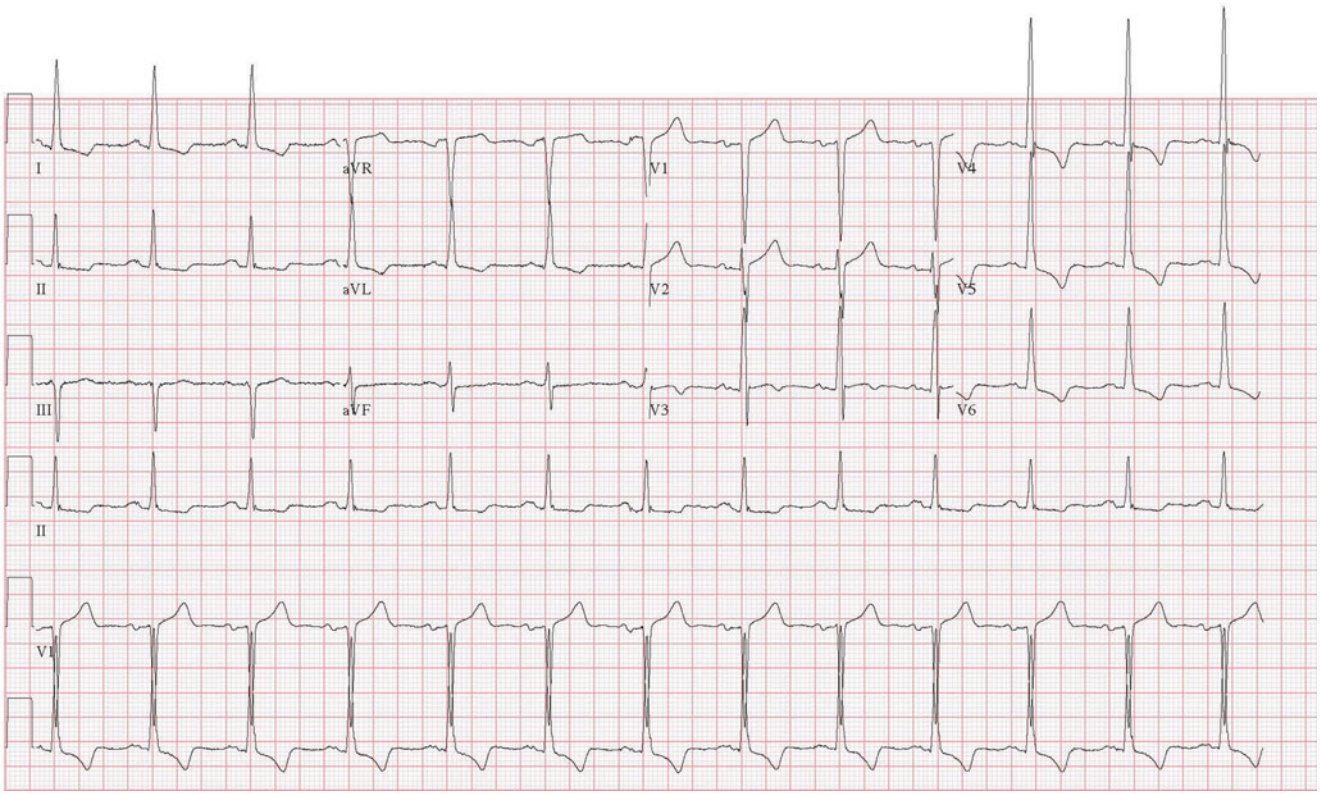

Fig. 24.25 Case 7: 12 lead electrocardiogram depicting left bundle branch block

lifetime. In addition, HCM patients are prone to T wave oversensing, and other lead malfunctions due to the hypertrophied heart with hyperdynamic contraction. Conversely, the risk of SCD is such that patients may benefit from ICD implantation many years afterwards, and the risk stratification protocol is not perfect. Thus the decision to implant an ICD should be individualized in patients considering both the potential benefits and the potential long-term morbidity of living with these devices.

Case 7: A 57 Year Old Man with Dyspnea on Exertion and Chest Heaviness

A 57 year old Caucasian male presented to our HCM center with a diagnosis of HCM, dyslipidemia and mitral valve prolapse. HCM had been diagnosed after a year of progressive dyspnea on exertion associated with chest heaviness. There were no reports of palpitations, lightheadedness, or syncope. At the time of his initial evaluation, he was unable to perform light housework or climb one flight of stairs, consistent with NYHA Class III. An electrocardiogram revealed a left bundle branch block (Fig. 24.25) while an echocardiogram demonstrated preserved left ventricular systolic function with asymmetric basal septal wall hypertrophy measuring 1.9 cm, a posterior wall thickness measuring 1.3 cm, and a left ventricular outflow tract obstruction with a resting gradient of 65 mmHg augmenting to 140 mmHg with provocation. Systolic anterior motion (SAM) of the anterior mitral valve leaflet was present associated with moderate eccentric mitral regurgitation. Turbulence in the outflow tract, which is associated with obstructive physiology, appeared to be both at the area of septal hypertrophy, but also somewhat higher in the outflow tract right below the aortic valve, raising concern for sub-aortic membrane. Following a normal 24-h ambulatory electrocardiogram monitor study and an exercise treadmill test showing no evidence of ischemia or ectopy, the patient was referred for cardiac catheterization to further assess the gradient and the etiology of symptoms, including dyspnea and chest pain.

Clinical Decision Making—When is cardiac catheterization recommended for HCM patients?
Coronary angiography is an ACCF/AHA Class I recommendation in HCM patients with chest discomfort who may have an intermediate to high likelihood of coronary artery disease (CAD) when the identification

of concomitant CAD will change approaches to management [1]. While chest discomfort is a common complaint in patients with HCM it is important to assess whether symptoms are due to HCM itself or instead related to epicardial obstructive CAD, as CAD as a comorbid disease entity signifies a higher risk for adverse outcomes [34]. Such patients are candidates for revascularization. Ischemia however in HCM can also be secondary to severe hypertrophy itself or due to microvascular dysfunction. In addition, coronary angiography is essential to delineate the coronary anatomy and this can be an important factor in considering management options for septal reduction therapy in highly symptomatic patients. For example, the presence of multi-vessel disease or left main disease may prompt surgical septal myectomy instead of alcohol septal ablation.

In addition to coronary angiography, hemodynamic evaluation with cardiac catheterization can aid in the determination of right and left heart filling pressures, contribution of pulmonary disease, presence or absence of resting or provocable outflow tract obstruction, as well as evidence for diastolic dysfunction. In patients with significant heart failure, angina, pre-syncope or syncope, a comprehensive cardiac catheterization can therefore aid in determining and prioritizing etiologies, and organizing treatment scheme. For example, patients with congestive heart failure or dyspnea may benefit from augmented diuretics, whereas patients with normal filling pressures and pulmonary circulation, but severe obstruction may benefit from augmented beta-blockers, initiation of disopyramide or contemplation of invasive septal reduction therapies. Exercise hemodynamics may also be of benefit in elucidating diastolic dysfunction, or sub-clinical pulmonary disease as contributions to patient symptoms.

Cardiac catheterization can also aid in determining the components of subvalvular versus valvular obstruction in patients with HOCM and valvular aortic stenosis; in such patients, standard transthoracic echocardiography is often not definitive. The relative contributions of valvular and sub-valvular obstruction can be quantified, and actual valve area calculated based on the isolated valvular gradient and Fick-equation derived cardiac output.

The patient underwent diagnostic cardiac catheterization revealing normal coronary arteries, a hyperkinetic left ventricle, and a sub-aortic valvular gradient of 30 mmHg, which increased to >50 mmHg with Brockenbrough maneuver. There was no valvular gradient. Filling pressures and pulmonary pressures, including pulmonary vascular resistance, were normal. A transesophageal echocardiography (TEE) was recommended for further evaluation of the left ventricular outflow tract obstruction given the presence of a subvalvular gradient during hemodynamic assessment and equivocal etiology (two area of turbulence in the outflow tract, concerning for concomitant muscular and membrane components).

Clinical Decision Making—When is a TEE recommended for patients with HCM?

ACCF/AHA guidelines [1] indicate that TEE (1) can aid clinical decision making when imaging from TTE is inconclusive, (2) can guide surgical planning by helping delineate hypertrophied septum that needs to be removed surgically, (3) can be useful to study any structural abnormalities of the mitral valve apparatus in patients with mitral regurgitation, (4) can be used to help decide feasibility of alcohol septal ablation, (5) can identify the presence of a subaortic membrane causing fixed obstruction with or without coexisting dynamic obstruction, and (6) can be useful in patients with atrial fibrillation contemplating DCCV or anti-arrhythmic therapy, in order to exclude left atrial appendage thrombus.

In the evaluation of mitral regurgitation, central or anterior jets indicate an intrinsic abnormality of the mitral valve, whereas posterior jets timed with SAM are indicative of mitral regurgitation related to HOCM physiology. The latter would be expected to resolve with isolated surgical myectomy or alcohol septal ablation. It is pertinent to point out that HCM patients with a subaortic membrane who are undergoing invasive management for drug-refractory symptoms, the treatment of choice is surgical myectomy, during which the membrane can be resected.

The TEE (Fig. 24.26) confirmed the systolic anterior motion of the anterior mitral valve leaflet with left ventricular outflow tract obstruction and posteriorly directed MR. However, a subvalvular membrane was also identified (Fig. 24.27). At this point, the patient continued to experience severe drug-refractory symptoms despite combination therapy with optimal doses of Metoprolol Succinate and Verapamil. A decision was therefore made to proceed with septal reduction therapy and membrane excision.

Clinical Decision Making—How to appropriately select HCM patients requiring septal reduction therapy to either surgical myectomy vs. alcohol septal ablation

ACCF/AHA guidelines [1] recommend that septal reduction therapy should be performed only by experienced operators—20 cumulative procedures for an individual operator or 50 cumulative procedures for an

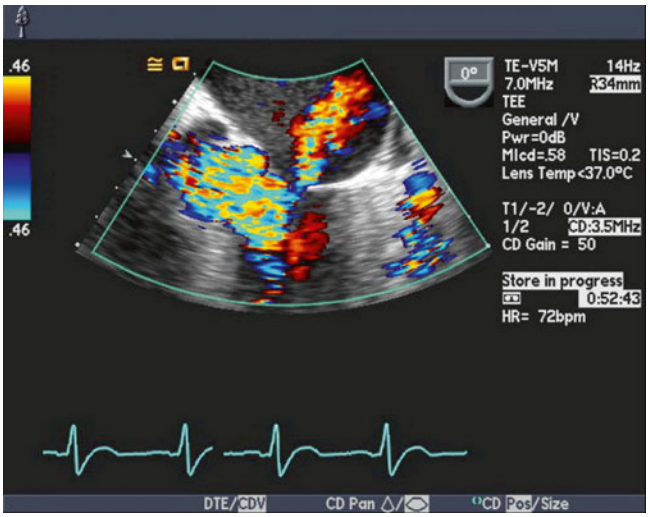

Fig. 24.26 Case 7: TTE depicting moderate mitral regurgitation secondary to systolic anterior motion with a mosaic pattern visualized from turbulent flow in the LVOT secondary to the systolic anterior motion and the subaortic membrane resulting in elevated LVOT gradients (see text for details)

individual operator working in a dedicated HCM center in the context of a comprehensive clinical HCM program (Class I recommendation). This treatment should be restricted to patients with evidence of LVOT obstruction and severe drug-refractory symptoms who meet strict anatomic and hemodynamic criteria.

Currently surgical septal myectomy is the first consideration for patients who require invasive therapy due to its long track record and safety data, as long as it can be performed in an experienced center (Class IIa indication). When comorbidities exist, including advanced age, that increase the risks of surgery, alcohol septal ablation is useful as an alternative (Class IIa indication). Finally, when both options are available, the principle of patient autonomy dictates that a patient should be able to choose between the two procedures after a balanced and thorough discussion (Class IIb indication).

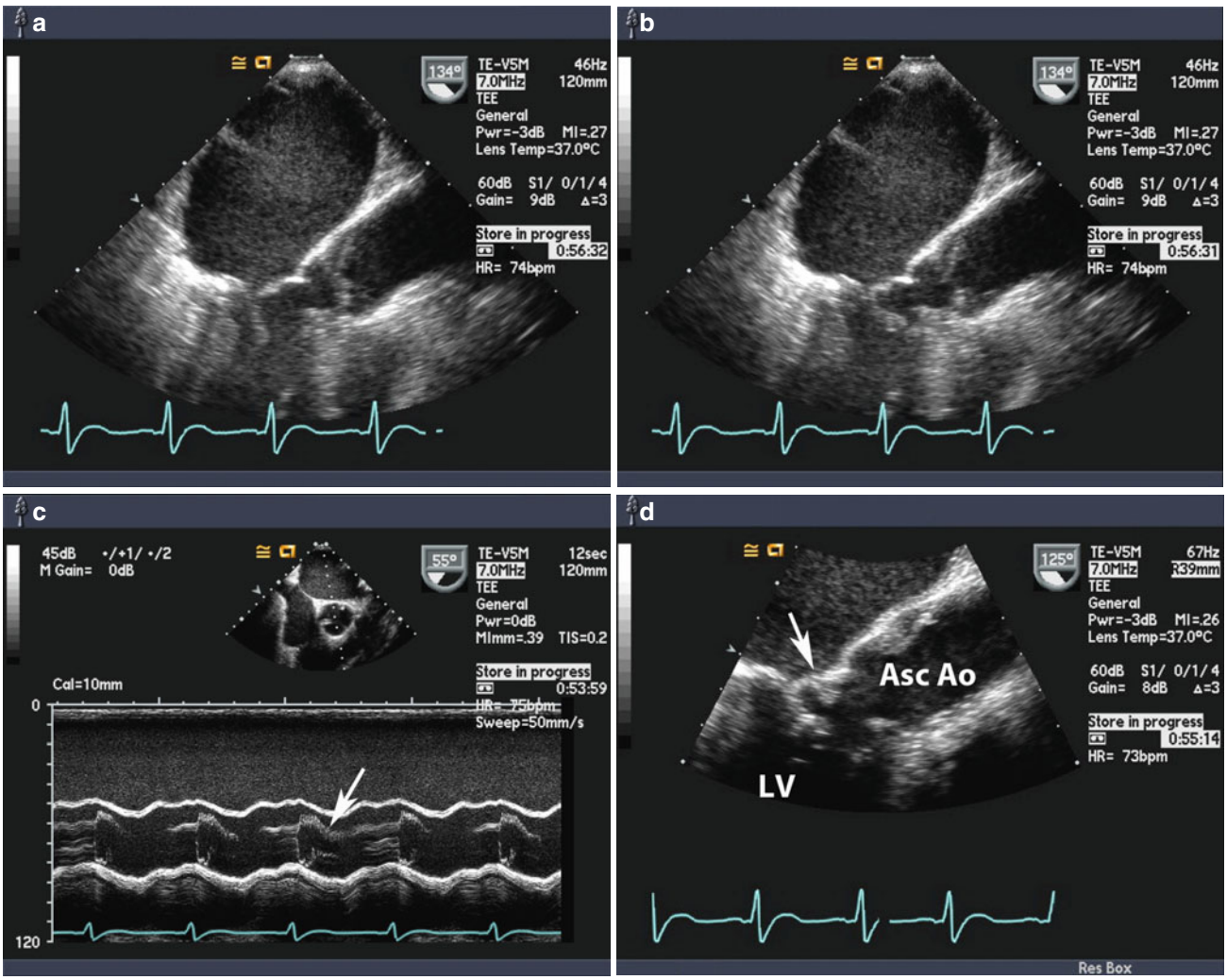

Fig. 24.27 Case 7: TEE depicting systolic anterior motion of mitral valve (**a**–**b**), (**c**) M-mode finding suggesting sub-aortic valve membrane (*white arrow head*) and (**d**) the systolic anterior motion is confirmed (*white arrow head*) on the long axis view of the left ventricle

Factors favoring surgical septal myectomy include younger age (<30–40), greater septal thickness (>3.0 cm), and concomitant surgical cardiac disease (e.g., structural heart disease requiring surgery or CAD requiring coronary artery bypass grafting). Pre-existent LBBB also favors surgery. Factors that favor alcohol septal ablation include older age, significant comorbidity that increases surgical risk and the patient's strong preference to avoid open-heart surgery after a careful discussion with the patient. Pre-existent RBBB favors alcohol septal ablation.

In the present case, the sub-aortic membrane is an absolute contraindication to alcohol septal ablation, and thus surgical myectomy was required. In general, patients with unusual sub-valvular anatomy, including re-do myectomy, prior alcohol septal ablation, and membranes, as well as abnormal papillary muscles or mitral valvular contributors, should be treated by surgeons at HCM centers with a large surgical experience.

Given the patient's age, persistent NYHA Class III symptoms with coexisting dynamic LVOT obstruction and presence of a subvalvular aortic membrane, the patient was referred for surgery. A successful circumferential excision of the fibrous ridge/membrane along with septal myectomy was performed without complications. Consequently, the patient's symptoms improved, and he now remains in NYHA Class I functional status 5 years later. He continues to be evaluated annually for SCD risk stratification and family counseling and tracking.

Clinical Pearl—When to suspect a membrane?

The vast majority of patients with sub-valvular outflow tract obstruction have SAM and obstruction due to mitral leaflet contact with the septum. Such obstruction is dynamic and based on preload, afterload and contractility. Turbulence in the outflow tract on the parasternal long axis view is seen at the point of septal/SAM contact. In patients with a membrane, the obstruction may be fixed (as opposed to dynamic), associated with aortic regurgitation, and the turbulence will be at a distinct or separate location compared to SAM. These raise suspicion of a membrane, and prompt TEE or other imaging to rule out its presence, such as cardiac MRI. As such, the clinician must have a heightened sense of awareness in order to pick up a membrane. Failure to do so might result in inadvertent alcohol septal ablation, which would fail to eliminate the gradient.

Conclusions

HCM patients present in many different ways, and the course of their disease may result in a myriad of phenotypes. These include presentations early and late in life, during pregnancy or as a result of family screening. These also include a vast array of arrhythmias from SCD to atrial fibrillation. As patients are brought in, they are evaluated in a comprehensive manner to include optimal imaging to make the diagnosis and understand the physiology, medication titration to control symptoms, initial and annual testing to understand their risk of SCD, and ongoing discussions with their families to protect their loved ones. Moreover, as patients age, they may develop new diseases that need to be treated, or may have their disease progress to the point of needing new therapies, including pacemakers, ICDs, or septal reduction treatment. Conversely, they may experience long periods of stability, during which routine visits simply confirm stability of symptoms and minimal risk factors for SCD.

The preceding cases were chosen as a representative cohort to elucidate long-term management and all of these factors that are seen in the context of an HCM program, and how they were handled at least at one Center. While practice patterns may differ, the goal was to give the reader an understanding of the nuances of care, both diagnostic and therapeutic, that are required when caring for this challenging yet rewarding patient population. It also gives the reader an understanding of how to integrate all the preceding chapters into the practical management of the patient with HCM.

References

1. Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2011;58:e212–60.
2. Maron MS, Appelbaum E, Harrigan CJ, et al. Clinical profile and significance of delayed enhancement in hypertrophic cardiomyopathy. Circ Heart Fail. 2008;1:184–91.
3. Choudhury L, Mahrholdt H, Wagner A, et al. Myocardial scarring in asymptomatic or mildly symptomatic patients with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2002;40:2156–64.
4. Talreja DR, Nishimura RA, Edwards WD, et al. Alcohol septal ablation versus surgical septal myectomy: comparison of effects on atrioventricular conduction tissue. J Am Coll Cardiol. 2004;44:2329–32.
5. Spirito P, Autore C, Rapezzi C, et al. Syncope and risk of sudden death in hypertrophic cardiomyopathy. Circulation. 2009;119:1703–10.
6. Zipes DP, Wellens HJ. Sudden cardiac death. Circulation. 1998;98:2334–51.

7. Elliott PM, Poloniecki J, Dickie S, et al. Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. J Am Coll Cardiol. 2000;36:2212–8.
8. Ackerman MJ. Genetic testing for risk stratification in hypertrophic cardiomyopathy and long QT syndrome: fact or fiction? Curr Opin Cardiol. 2005;20:175–81.
9. Noseworthy PA, Newton-Cheh C. Genetic determinants of sudden cardiac death. Circulation. 2008;118:1854–63.
10. Van Tintelen JP, Pieper PG, Van Spaendonck-Zwarts KY, Van Den Berg MP. Pregnancy, cardiomyopathies, and genetics. Cardiovasc Res. 2014;101:571–8.
11. Avila WS, Rossi EG, Ramires JA, et al. Pregnancy in patients with heart disease: experience with 1,000 cases. Clin Cardiol. 2003;26:135–42.
12. Autore C, Conte MR, Piccininno M, et al. Risk associated with pregnancy in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2002;40:1864–9.
13. Karibe A, Tobacman LS, Strand J, et al. Hypertrophic cardiomyopathy caused by a novel alpha-tropomyosin mutation (V95A) is associated with mild cardiac phenotype, abnormal calcium binding to troponin, abnormal myosin cycling, and poor prognosis. Circulation. 2001;103:65–71.
14. Geske JB, Sorajja P, Nishimura RA, Ommen SR. Evaluation of left ventricular filling pressures by Doppler echocardiography in patients with hypertrophic cardiomyopathy: correlation with direct left atrial pressure measurement at cardiac catheterization. Circulation. 2007;116:2702–8.
15. Pasipoularides A. LV twisting and untwisting in HCM: ejection begets filling. Diastolic functional aspects of HCM. Am Heart J. 2011;162:798–810.
16. Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011;124:e783–831.
17. Mehra MR, Kobashigawa J, Starling R, et al. Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates–2006. J Heart Lung Transplant. 2006;25:1024–42.
18. Fifer MA, Vlahakes GJ. Management of symptoms in hypertrophic cardiomyopathy. Circulation. 2008;117:429–39.
19. Sanderson JE, Gibson DG, Brown DJ, Goodwin JF. Left ventricular filling in hypertrophic cardiomyopathy. An angiographic study. Br Heart J. 1977;39:661–70.
20. Nishimura RA, Trusty JM, Hayes DL, et al. Dual-chamber pacing for hypertrophic cardiomyopathy: a randomized, double-blind, crossover trial. J Am Coll Cardiol. 1997;29:435–41.
21. Maron BJ, Nishimura RA, McKenna WJ, Rakowski H, Josephson ME, Kieval RS. Assessment of permanent dual-chamber pacing as a treatment for drug-refractory symptomatic patients with obstructive hypertrophic cardiomyopathy. A randomized, double-blind, crossover study (M-PATHY). Circulation. 1999;99:2927–33.
22. Nagueh SF, Groves BM, Schwartz L, et al. Alcohol septal ablation for the treatment of hypertrophic obstructive cardiomyopathy a Multicenter North American Registry. J Am Coll Cardiol. 2011;58:2322–8.
23. Veselka J, Krejčí J, Tomašov P, Zemánek D. Long-term survival after alcohol septal ablation for hypertrophic obstructive cardiomyopathy: a comparison with general population. Eur Heart J. 2014:eht495.
24. Charitakis K, Basson CT. Can genetic testing improve our aim in hypertrophic cardiomyopathy? Circ Res. 2010;106:1446–8.
25. Kapa S, Curwin JH, Coyne RF, Winters SL. Inappropriate defibrillator shocks from depolarization—repolarization mismatch in a patient with hypertrophy cardiomyopathy. Pacing Clin Electrophysiol. 2007;30:1408–11.
26. Koneru JN, Swerdlow CD, Wood MA, Ellenbogen KA. Minimizing inappropriate or "unnecessary" implantable cardioverter-defibrillator shocks: appropriate programming. Circ Arrhythm Electrophysiol. 2011;4:778–90.
27. Maron BJ, Spirito P, Shen WK, et al. Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy. JAMA. 2007;298:405–12.
28. Sylvester J, Seidenberg P, Silvis M. The dilemma of genotype positive-phenotype negative hypertrophic cardiomyopathy. Curr Sports Med Rep. 2014;13:94–9. doi:10.1249/JSR.0000000000000037.
29. Sylvester J, Seidenberg P, Silvis M. The dilemma of genotype positive-phenotype negative hypertrophic cardiomyopathy. Curr Sports Med Rep. 2014;13:94–9.
30. Maron BJ, Chaitman BR, Ackerman MJ, et al. Recommendations for physical activity and recreational sports participation for young patients with genetic cardiovascular diseases. Circulation. 2004;109:2807–16.
31. Sadoul N, Prasad K, Elliott PM, Bannerjee S, Frenneaux MP, McKenna WJ. Prospective prognostic assessment of blood pressure response during exercise in patients with hypertrophic cardiomyopathy. Circulation. 1997;96:2987–91.
32. Olivotto I, Maron BJ, Montereggi A, Mazzuoli F, Dolara A, Cecchi F. Prognostic value of systemic blood pressure response during exercise in a community-based patient population with hypertrophic cardiomyopathy. J Am Coll Cardiol. 1999;33:2044–51.
33. Alam M, Dokainish H, Lakkis NM. Hypertrophic obstructive cardiomyopathy-alcohol septal ablation vs. myectomy: a meta-analysis. Eur Heart J. 2009;30:1080–7.
34. Sorajja P, Ommen SR, Nishimura RA, Gersh BJ, Berger PB, Tajik AJ. Adverse prognosis of patients with hypertrophic cardiomyopathy who have epicardial coronary artery disease. Circulation. 2003;108:2342–8.