Applied Respiratory Physiology

with special reference to anaesthesia

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Hypnos and the Flame
(original photograph courtesy of Dr. John W. Severinghaus)

FOREWORD

A FLAME FOR HYPNOS

The lighted candle respires and we call it flame. The body respires and we call it life. Neither flame nor life are substance, but process. The flame is as different from the wick and wax as life from the body, as gravitation from the falling apple, or love from a hormone. Newton taught science to have faith in processes as well as substances—to compute, predict and depend upon an irrational attraction. Caught up in enlightenment, man began to regard himself as a part of nature, a subject for investigation. The web of self-knowledge, woven so slowly between process and substance, still weaves physiology, the process, and anatomy, the substance, into the whole cloth of clinical medicine. Within this multihued fabric, the warp fibres of process shine most clearly in the newest patterns, among which must be numbered anaesthesiology. The tailors who wove the sciences into the clinical practice of anaesthetics are men of our time such as Ralph Waters and Chauncey Leake who knit together respiratory physiology and pharmacology to cloak the first medical school Department of Anesthesiology, at Wisconsin, scarcely 45 years ago. Both of them still delight in watching the fashion parade they set in motion. Their partnership lasted only five years, but anaesthesiology and respiratory physiology remain as intimately interwoven as any pair of clinical and basic sciences. In this volume stands the evidence: references to more than 100 anaesthetists who have substantially contributed to respiratory physiology and John Francis Nunn's superb text which, for the first time, comprehensively binds the two together.

Man's interest in his own reaction to his environment constituted a further leap of the intellect. From substance to process to self-examination, and then full circle to the processes of interaction. 1969 may be considered the centenary of environmental or applied physiology. One hundred years ago Paul Bert, in a series of lectures to the Academie de Science in Paris, proposed to investigate the role of the low partial pressure of oxygen upon the distress experienced at high altitudes. Applying Dalton's law of partial pressures to physiology for the first time, he thus launched his monumental research of the barometric pressure, surely the cornerstone of applied physiology. The demands of military aviation during World War II generated a quantum jump of interest in applied physiology, exemplified by the founding 21 years ago of the *Journal of Applied Physiology*. This youngster, having just come of age, provides well over 100 references in Nunn's text, many of them written by anaesthetists. Anaesthesia may justly claim its birthright share of *Applied Respiratory Physiology*. Three years hence will be celebrated the bicentenary of N_2O, noting that Joseph Priestley reported N_2O two years before O_2!

And what of the god of sleep, patron of anaesthesia? The centuries themselves number more than 21 since Hypnos wrapped his cloak of sleep over Hellas. Now before Hypnos, the artisan, is set the respiring flame—that he may, by knowing the process, better the art.

San Francisco JOHN W. SEVERINGHAUS

PREFACE

Clinicians in many branches of medicine find that their work demands an extensive knowledge of respiratory physiology. This applies particularly to anaesthetists working in the operating theatre or in the intensive care unit. It is unfortunately common experience that respiratory physiology learned in the pre-clinical years proves to be an incomplete preparation for the clinical field. Indeed, the emphasis of the pre-clinical course seems, in many cases, to be out of tune with the practical problems to be faced after qualification and specialization. Much that is taught does not apply to man in the clinical environment while, on the other hand, a great many physiological problems highly relevant to the survival of patients find no place in the curriculum. It is to be hoped that new approaches to the teaching of medicine may overcome this dichotomy and that, in particular, much will be gained from the integration of physiology with clinical teaching.

This book is designed to bridge the gap between pure respiratory physiology and the treatment of patients. It is neither a primer of respiratory physiology, nor is it a practical manual for use in the wards and operating theatres. It has two aims. Firstly, I have tried to explain those aspects of respiratory physiology which seem most relevant to patient care, particularly in the field of anaesthesia. Secondly, I have brought together in review those studies which seem to me to be most relevant to clinical work. Inevitably there has been a preference for studies of man and particular stress has been laid on those functions in which man appears to differ from laboratory animals. There is an unashamed emphasis on anaesthesia because I am an anaesthetist. However, the work in this specialty spreads freely into the territory of our neighbours.

References have been a problem. It is clearly impracticable to quote every work which deserves mention. In general I have cited the most informative and the most accessible works, but this rule has been broken on numerous occasions when the distinction of prior discovery calls for recognition. Reviews are freely cited since a book of this length can include only a fraction of the relevant material. I must apologize to the writers of multi-author papers. No one likes to be cited as a colleague, but considerations of space have precluded naming more than three authors for any paper.

Chapters are designed to be read separately and this has required some repetition. There are also frequent cross-references between the chapters. The principles of methods of measurement are considered together at the end of each chapter or section.

In spite of optimistic hopes, the book has taken six years to write. Its form, however, has evolved over the last twelve years from a series of lectures and tutorials given at the Royal College of Surgeons, the Royal Postgraduate

Medical School, the University of Leeds and in numerous institutions in Europe and the United States which I have been privileged to visit. Blackboard sketches have gradually taken the form of the figures which appear in this book.

The greater part of this book is distilled from the work of teachers and colleagues. Professor W. Melville Arnott and Professor K. W. Donald introduced me to the study of clinical respiratory physiology and I worked under the late Professor Ronald Woolmer for a further six years. My debt to them is very great. I have also had the good fortune to work in close contact with many gifted colleagues who have not hesitated to share the fruits of their experience. The list of references will indicate how much I have learned from Dr. John Severinghaus, Professor Moran Campbell, Dr. John Butler and Dr. John West. For my own studies, I acknowledge with gratitude the part played by a long series of research fellows and assistants. Some fifteen are cited herein and they come from eleven different countries. Figures 2, 3, 6, 11 and 15, which are clearly not my blackboard sketches, were drawn by Mr. H. Grayshon Lumby. I have had unstinted help from librarians, Miss M. P. Russell, Mr. W. R. LeFanu and Miss E. M. Reed. Numerous colleagues have given invaluable help in reading and criticising the manuscript.

Finally I must thank my wife who has not only borne the inevitable preoccupation of a husband writing a book but has also carried the burden of the paper work and prepared the manuscript.

J.F.N.

CHAPTER 1

PHYSICAL AND STRUCTURAL FEATURES OF GAS EXCHANGE

No vital processes appear to be involved in the exchange of gases at the alveolar-capillary membrane. Oxygen, carbon dioxide and the anaesthetic gases pass from one medium to another in response to partial pressure gradients according to the laws of physics and not as a result of active secretion. Furthermore, much of the ventilation and perfusion of the lung can only be understood in terms of the physical processes concerned. It will therefore be clear that much of this book is concerned with physics, and it seems best to start with a brief review of those aspects which are most relevant to the behaviour of gases in the respiratory system. This is followed by an account of the structural aspects of the lungs, which is the only valid starting point for a consideration of function.

Physical quantities and units of measurement are perennial sources of confusion in respiratory physiology. Apart from any inherent difficulty, we suffer from an unnecessary duplication of units, particularly those of pressure. Appendices A and B are intended to resolve some of these difficulties but they need not be read by those readers who have already obtained a grasp of the subject.

THE GAS LAWS

Certain physical attributes of gases are customarily presented under the general heading of the gas laws. These are of fundamental importance in respiratory physiology.

Boyle's law describes the inverse relationship between the volume and absolute pressure of a perfect gas at constant temperature:

$$PV = K \qquad \ldots(1)$$

where P represents pressure and V represents volume. At temperatures near their boiling point, gases deviate from Boyle's law. At room temperature, the deviation is negligible for oxygen and nitrogen and is of little practical importance for carbon dioxide or nitrous oxide. Anaesthetic vapours show substantial deviations.

Charles' law describes the direct relationship between the volume and absolute temperature of a perfect gas at constant pressure:

$$V = KT \qquad \ldots(2)$$

where T represents the absolute temperature. There are appreciable deviations

at temperatures immediately above the boiling point of gases. Equations (1) and (2) may be combined as follows:

$$PV = RT \qquad \ldots(3)$$

where R is the universal gas constant, which is the same for all perfect gases and has the value of 8·1314 times 10^7 ergs/degree absolute/mole. From this it may be derived that the mole volume of all perfect gases is 22·4 litres at S.T.P.D. Carbon dioxide and nitrous oxide deviate from the behaviour of perfect gases to the extent of having mole volumes of 22·2 litres at S.T.P.D.

Van der Waals' equation is an attempt to improve the accuracy of equation (3) in the case of non-perfect gases. It makes allowance for the finite space occupied by gas molecules and the forces which exist between them. The Van der Waals equation includes two additional constants:

$$(P + a/V^2)(V - b) = RT \qquad \ldots(4)$$

where a corrects for the attraction between molecules and b corrects for the volume occupied by molecules. This expression is of particular interest to anaesthetists since the constants for anaesthetic gases are related to their anaesthetic potency (Wulf and Featherstone, 1957).

Adiabatic heating.—A great deal of respiratory physiology can fortunately be understood without much knowledge of thermodynamics. However, a recurrent problem is the heating which occurs when a gas is compressed. This effect is sufficiently large to be a readily detectable source of error in such techniques as the body plethysmograph (page 5), and the use of a large rigid container as a simulator for the paralysed thorax.

Henry's law describes the solution of gases in liquids with which they do not react. It does not apply to vapours which, in the liquid state, are infinitely miscible with the solvent (e.g. ether in olive oil) (Nunn, 1960b). The general principle of Henry's law is simple enough. The number of molecules of gas dissolving in the solvent is directly proportional to the partial pressure of the gas at the surface of the liquid, and the constant of proportionality is an expression of the solubility of the gas in the liquid. This is a constant for a particular gas and a particular liquid at a particular temperature but falls with rising temperature.

For many people, confusion arises from the multiplicity of units which are used. For example, when considering oxygen dissolved in blood, it is customary to consider the amount of gas dissolved in units of vols. per cent (ml. of gas (S.T.P.D.) per 100 ml. blood) and the pressure in mm Hg. Solubility is then expressed as: vols. per cent/mm Hg, the value for oxygen in blood at 37°C being 0·003. However, for carbon dioxide in blood, we tend to use units of mEq./l. of carbon dioxide per mm Hg. The units are then: mEq./l./mm Hg, the value for carbon dioxide in blood at 37°C being 0·03. Both vols. per cent and mEq./l. are valid measurements of the quantity (mass or number of molecules) of the gas in solution and are interchangeable with the appropriate conversion factor.

Physicists are more inclined to express solubility in terms of the *Bunsen*

coefficient. For this, the amount of gas in solution is expressed in terms of volume of gas (S.T.P.D.) per unit volume of solvent (i.e. one-hundredth of the amount expressed as vols. per cent) and the pressure is expressed in atmospheres.

Biologists, on the other hand, prefer to use a related term—the *Ostwald coefficient.* This is the volume of gas dissolved expressed as its volume under the conditions of temperature and pressure at which solution took place. It might be thought that this would vary with the pressure in the gas phase, but this is not so. If the pressure is doubled, according to Henry's law, twice as many molecules of gas dissolve. However, according to Boyle's law, they would occupy half the volume at double the pressure. Therefore, if Henry's and Boyle's laws are obeyed, the Ostwald coefficient will be independent of changes in pressure at which solution occurs. It will differ from the Bunsen coefficient only because the gas volume is expressed as the volume it would occupy at the temperature of the experiment rather than at 0°C. Conversion is thus in accord with Charles' law and the two coefficients will be identical at 0°C. This should not be confused with the fact that, like the Bunsen coefficient, the Ostwald coefficient falls with rising temperature.

The partition coefficient is the ratio of the number of molecules of gas in one phase to the number of molecules of gas in another phase when equilibrium between the two has been attained. If one phase is gas and another a liquid, the liquid/gas partition coefficient will be identical to the Ostwald coefficient. Partition coefficients are also used to describe partitioning between two media (e.g. oil/water, brain/blood, etc.).

Graham's law of diffusion governs the influence of molecular weight on the diffusion of a gas through a gas mixture. Diffusion rates through orifices or through porous plates are inversely proportional to the square root of the molecular weight. This factor is only of importance in the gaseous part of the pathway between ambient air and the tissues, and is of limited importance in the whole process of 'diffusion' as understood by the respiratory physiologist.

Dalton's law of partial pressure states that, in a mixture of gases, each gas exerts the pressure which it would exert if it occupied the volume alone. This pressure is known as the partial pressure (or tension) and the sum of the partial pressures equals the total pressure of the mixture. Thus, in a mixture of 5 per cent CO_2 in oxygen at a total pressure of 760 mm Hg, the carbon dioxide exerts a partial pressure of $5/100 \times 760 = 38$ mm Hg. In general terms:

$$P_{CO_2} = F_{CO_2} \times P_B*$$

(Note that fractional concentration is expressed as a fraction and not as a percentage: per cent concentration $= F \times 100$.)

In the alveolar gas at sea level, there is about 6·7 per cent water vapour, which exerts a partial pressure of 47 mm Hg. The available pressure for other gases is therefore $(P_B - 47)$, an expression which recurs frequently in the following pages.

Tension is synonymous with partial pressure and is applied particularly to gases dissolved in a liquid such as blood. Molecules of gases dissolved in liquids have a tendency to escape, but net loss may be prevented by exposing the liquid

* Abbreviations and symbols are listed in Appendix C.

to a gas mixture in which the tension of the gas exactly balances the escape tendency. The two phases are then said to be in equilibrium and the tension of the gas in the liquid is considered equal to that of the tension of the gas in the gas mixture with which it is in equilibrium. Thus a blood P_{CO_2} of 40 mm Hg means that there would be no net exchange of carbon dioxide if the blood were exposed to a gas mixture which had a P_{CO_2} of 40 mm Hg. Directly or indirectly this forms the basis of all methods of measurement of blood P_{CO_2} and P_{O_2} (pages 323 and 380).

It is not the intention to discourse on physics any more than is necessary for the understanding of what follows in the rest of this book. Physics as applied to respiratory physiology and anaesthesia is a vast and absorbing field of study. Those whose knowledge of physics is rusty will benefit from a perusal of *Physics for the Anaesthetist* (MacIntosh, Mushin and Epstein, 1958) and *Physics Applied to Anaesthesia* (Hill, 1967), which will also serve as an introduction to more advanced reading such as *The Physics of Gases*, by Radford (1964).

LUNG VOLUMES AND CAPACITIES

The lung volume is considered in relation to three volumes which are relatively fixed for a particular patient under particular conditions.

(1) *Total lung capacity* (T.L.C.), which is the volume of gas in the lungs at the end of a maximal inspiration.

(2) *Functional residual capacity* (F.R.C.), which is the volume of gas in the lungs at the end of a normal expiration. In the unconscious patient, the F.R.C. is defined as the volume of gas in the lungs when there is no inspiratory or

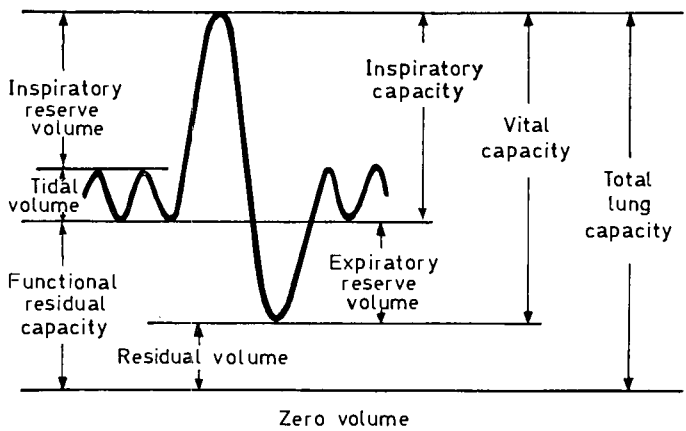


Figure 1. Static lung volumes. The 'spirometer curve' indicates the lung volumes which can be measured by simple spirometry. These are the tidal volume, inspiratory reserve volume, expiratory reserve volume, inspiratory capacity and vital capacity. The residual volume cannot be measured by observation of a simple spirometer trace and it is therefore impossible to measure the functional residual capacity or the total lung capacity without further elaboration of methods. Dynamic measurements of maximal breathing capacity and forced expiratory volume are discussed at the end of Chapter 4

expiratory muscle tone and when the alveolar pressure equals the ambient pressure.

(3) *Residual volume* (R.V.), which is the volume of gas in the lungs at the end of a maximal expiration.

Within this framework, there is no difficulty in defining inspiratory and expiratory reserve volumes, tidal volume, vital capacity and inspiratory capacity. This is best shown diagrammatically (*Figure 1*).

The total lung capacity is reached when the force developed by the inspiratory muscles is exactly balanced by the resistance of the tissues to expansion. This and the inspiratory capacity may be limited either by weakness of contraction of inspiratory muscles or by diminished mobility of the lungs, chest wall or diaphragm.

There has been doubt about the precise factors governing the residual volume but it is clearly determined by the balance between the force exerted by the expiratory muscles and the resistance to decrease in volume of lungs, chest wall and diaphragm.

The functional residual capacity is dependent upon the balance of elastic forces and is considered in detail in Chapter 3. It is altered by changes in posture, alveolar pressure (relative to ambient) and development in tone of either inspiratory or expiratory muscles. It is also altered by changes in abdominal pressure (e.g. due to pregnancy) or by changes in elasticity of lungs or chest wall. Thus destruction of lung tissue in emphysema causes loss of elastic recoil and increase in functional residual capacity.

Principles of Measurement of Lung Volumes

Tidal volume, vital capacity, inspiratory capacity, inspiratory reserve volume and expiratory reserve volume can all be measured by simple spirometry without the necessity of using a spirometer designed for high frequency response or low inertia. Of these measurements, only the tidal volume has any significance in the unconscious patient.

Total lung volume, functional residual capacity and residual volume all contain a fraction (the residual volume) which cannot be measured by simple spirometry. However, if one is measured, the others can be easily derived since the volumes which relate them can be measured by simple spirometry. Measurement of F.R.C. can be made by one of three techniques. The first method is to wash the nitrogen out of the lungs by several minutes of oxygen breathing with measurement of the total quantity of nitrogen eliminated. Thus if 4 litres of nitrogen are eliminated and the initial alveolar nitrogen concentration was 80 per cent, it follows that the initial volume of the lung was 5 litres. The second method uses the wash-in of a tracer gas such as helium. If 50 ml. of helium is introduced into the lungs and the helium concentration is then found to be 1 per cent, it follows that the volume of the lung is 5 litres. These methods are discussed in greater detail in *The Lung*, by Comroe and his colleagues (1962). They may be conveniently combined with tests of distribution of inspired gas.

The third method of measurement of functional residual capacity uses the body plethysmograph making use of Boyle's law (DuBois and his colleagues,

1956). The subject is confined within a gas-tight box so that changes in the volume of his body may be readily determined as a change in either the gas volume or pressure within the box. He then adjusts his lung volume to F.R.C., purses his lips around a tube leading to a manometer and attempts to breathe against the occluded airway. This is rather like a Valsalva or Müller manœuvre except that occlusion is not at the glottis but within the external breathing apparatus at a point distal to the manometer. Changes in alveolar pressure are recorded during the obstructed breathing together with the changes in lung volume which result from the pressure changes. The lung volume changes are measured as changes in whole body volume which are considered to be the same as lung volume changes under these conditions. These data permit calculation of the lung volume and the method is both accurate and convenient for those fortunate enough to have access to a body plethysmograph. Clearly there are difficulties in the application of this technique to anaesthetized patients.

At the time of writing, there has been little interest in measurement of pulmonary gas volumes (other than tidal volume) during anaesthesia. In part this is due to the difficulty of the technique in an unconscious patient. However, the measurement offers important confirmatory evidence of the presence of atelectasis, and lung volumes have been measured during anaesthesia for this purpose by Déry and his colleagues (1965).

RELATION OF PULMONARY STRUCTURE TO FUNCTION

This section is not intended as an exposition of lung structure but is rather an account of those structural features which are directly relevant to an understanding of function. During recent years there has been a regrettable tendency for pulmonary structure and function to be pursued as separate subjects. It is now generally realized that a full understanding of function is not possible without a morphological background.

An excellent introduction to pulmonary structure in relation to function has been written by Staub (1963b). This leads to the reviews of Krahl (1964) and Weibel (1964). Source books are *The Lung* (Miller, 1947), *The Human Lung* (von Hayek, 1960), *The Pulmonary Circulation* (Harris and Heath, 1962) and *Morphometry of the Human Lung* (Weibel, 1963). The Ciba Foundation held a symposium on *Pulmonary Structure and Function*, published under the editorship of de Reuck and O'Connor in 1962.

The Air Passages

Simplified accounts of lung function distinguish sharply between conducting air passages and areas in which gas exchange takes place. In fact, no such sharp demarcation occurs and the air passages gradually change their character showing a transition from the trachea to the alveoli, with the role of conduction gradually giving way to the role of gas exchange. *Table 1* traces the essential structural features progressively down the respiratory tract. The different levels are indicated as generations, with the trachea as the first, the main bronchi as the second, and so on down to the alveolar sacs as the twenty-third. It may be assumed that the passages of each generation bifurcate so that the number of

passages in any one generation is twice that in the previous generation. In fact, there are many situations in which clear-cut bifurcation does not occur and trifurcation or lateral branching may be seen. Nevertheless, consideration of air passages in generations *as if* bifurcation occurred at each generation is very helpful and the numbers of air passages at each generation so calculated do, in fact, accord very closely with the numbers actually observed in the lungs.

Table 1 gives only the mean values for the number of generations down to each level. Thus, for example, it shows the transition from terminal bronchi to bronchioles occurring after the eleventh generation. In fact the transition may occur anywhere between the ninth and fourteenth generations.

Trachea

The trachea has a mean diameter of 1·8 cm. and length of 11 cm. It is supported by U-shaped cartilages which are joined posteriorly by smooth muscle bands. In spite of the cartilaginous support, the trachea is fairly easy to occlude by external pressure. For part of its length, the trachea is not subjected to intrathoracic pressure changes but it is subject to pressures arising in the neck as, for example, due to haematoma formation after thyroidectomy. The mucosa is columnar ciliated epithelium containing numerous mucus-secreting goblet cells. The cilia beat in a co-ordinated manner causing an upward stream of mucus and foreign bodies.

Main, Lobar and Segmental Bronchi (first to fourth generations)

The trachea bifurcates asymmetrically, with the right bronchus being wider than the left and leaving the long axis of the trachea at a smaller angle. It is thus more likely to receive foreign bodies, extra long endotracheal tubes, etc. Main, lobar and segmental bronchi have firm cartilaginous support in their walls, U-shaped in the main bronchi but in the form of irregular shaped and helical plates lower down. Where the cartilage is in the form of irregular plates, the bronchial muscle takes the form of helical bands which form a geodesic network extending down to the lowest limits of the air passages. The bronchial epithelium is similar to that in the trachea although the height of the cells gradually diminishes in the more peripheral passages until it becomes cuboidal in the bronchioles. Bronchi in this group are sufficiently regular in pattern to be named.

Bronchi of the first to fourth generations are subjected to the full effect of changes in intrathoracic pressure and will collapse when the intrathoracic pressure exceeds the intraluminar pressure by about 50 cm H_2O. This occurs in the larger bronchi during a forced expiration since the greater part of the alveolar-to-mouth pressure difference is taken up in the segmental bronchi under these circumstances. Therefore the intraluminar pressure within the larger bronchi remains well below the intrathoracic pressure, particularly in patients with emphysema (Macklem, Fraser and Bates, 1963; Macklem and Wilson, 1965). Collapse of the larger bronchi limits the peak expiratory flow rate in the normal subject and gives rise to the brassy note of a 'voluntary wheeze' produced in this way.

Small Bronchi (fifth to eleventh generations)

The small bronchi extend through about seven generations with their

Table 1

Structural characteristics of the air passages (after Weibel, 1963)

	Generation (mean)	*Number*	*Mean diameter (mm.)*	*Area supplied*	*Cartilage*	*Muscle*	*Nutrition*	*Emplacement*	*Epithelium*
Trachea	0	1	18	Both lungs	U-shaped	Links open end of cartilage	From the bronchial circulation	Within connective tissue sheath alongside arterial vessels	Columnar ciliated
Main bronchi	1	2	13	Individual lungs					
Lobar bronchi	2 ↓ 3	4 ↓ 8	7 ↓ 5	Lobes	Irregular shaped and helical plates	Helical bands			
Segmental bronchi	4	16	4	Segments					
Small bronchi	5 ↓ 11	32 ↓ 2,000	3 ↓ 1	Secondary lobules					
Bronchioles Terminal bronchioles	12 ↓ 16	4,000 ↓ 65,000	1 ↓ 0·5		Absent	Strong helical muscle bands		Embedded directly in the lung parenchyma	Cuboidal
Respiratory bronchioles	17 ↓ 19	130,000 ↓ 500,000	0·5	Primary lobules		Muscle bands between alveoli	From the pulmonary circulation		Cuboidal to flat between the alveoli
Alveolar ducts	20 ↓ 22	1,000,000 ↓ 4,000,000	0·3	Alveoli		Thin bands in alveolar septa		Forms the lung parenchyma	Alveolar epithelium
Alveolar sacs	23	8,000,000	0·3						

diameter progressively falling from 3·5 to 1 mm. Since their number approximately doubles with each generation, the *total* cross-sectional area increases markedly with each generation to a value (at the eleventh generation) of about seven times the total cross-sectional area at the level of the lobar bronchi.

Down to the level of the smallest true bronchi, air passages lie with pulmonary vessels in a sheath which may be distended by oedema fluid. They are not directly attached to the lung parenchyma and thus are not subjected to direct traction. They are nevertheless subject to intrathoracic pressure and if the extramural pressure is substantially above the intraluminar pressure, collapse will occur. It now seems likely that this does not occur to any great extent in the small bronchi since the resistance to air flow between alveoli and small bronchi is now known to be less than had formerly been deduced from study of post-mortem lungs which had been fixed without inflation. It is now believed that during a forced expiration, the intraluminar pressure in the small bronchi rapidly rises to more than 80 per cent of the alveolar pressure. This pressure is sufficient to withstand the collapsing tendency of the high extramural intrathoracic pressure.

Secondary lobule.—The area of lung supplied by a small bronchus immediately before transformation to a bronchiole is sometimes referred to as a secondary lobule, each of which has a volume of about 2 ml. and is defined by connective tissue septa.

Bronchioles (twelfth to sixteenth generations)

An important change occurs at about the eleventh generation where the diameter is of the order of 1 mm. Cartilage disappears from the wall of the air passages at this level, and structural rigidity ceases to be the principal factor in maintaining patency. Fortunately, at this level the air passages leave their fibrous sheath and come to be embedded directly in the lung parenchyma. Elastic recoil of the alveolar septa is then able to hold the air passages open like the guy ropes of a bell tent. The calibre of airways below the eleventh generation is, therefore, mainly influenced by lung volume, since the forces acting to hold their lumina open are stronger at high lung volume. The calibre of the bronchioles is, however, less influenced by intrathoracic pressure than is the case in the bronchi.

In succeeding generations, the number of bronchioles increases far more rapidly than the calibre diminishes. Therefore the *total* cross-sectional area increases until, in the terminal bronchioles, it is about 90 times the area at the level of the large bronchi. It is therefore hardly surprising that the resistance to flow offered by the smaller air passages (less than 2 mm. diam.) is only about one-tenth of total flow resistance (Macklem and Mead, 1967). Formerly, precisely the opposite was thought to be true, and it was believed that the major fraction of the total resistance was in the narrower vessels. This belief was in part due to earlier studies (e.g. Rohrer, 1915) which seriously underestimated the calibre of the smaller air passages. This error arose from failure to inflate the excised lung to its normal volume before fixation.

Bronchioles have strong helical muscular bands and a cuboidal epithelium. Contraction of the muscle bands is able to wrinkle the mucosa into longitudinal

folds which may cause a very substantial decrease in calibre. In some studies the contraction may have been a post-mortem artefact.

Down to the terminal bronchiole the air passages derive their nutrition from the bronchial circulation and are, therefore, liable to be influenced by changes in systemic arterial blood gas levels. From this point onwards, the small air passages rely upon the pulmonary circulation for their nutrition.

Respiratory Bronchioles (seventeenth to nineteenth generations)

Down to the end of the bronchioles, the function of the air passages is solely conduction and humidification. At the next generation (first order respiratory bronchiole) gas exchange occurs to a small extent and this function increases progressively through the three generations of respiratory bronchioles until, in the first order alveolar duct (twentieth generation), the entire surface is

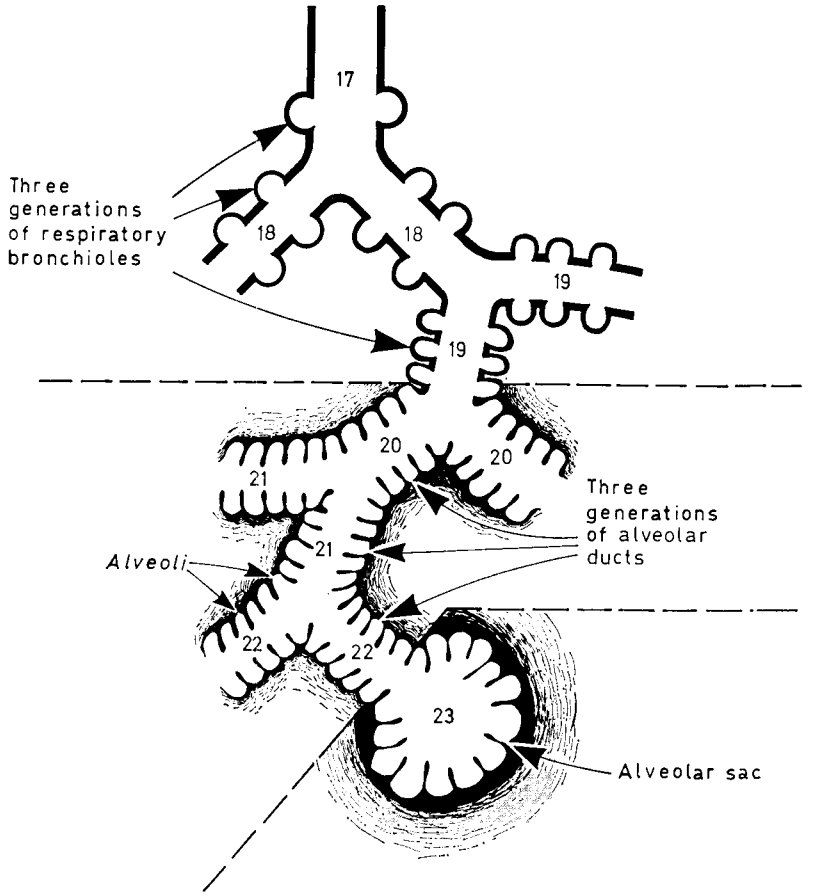


Figure 2. Diagrammatic representation of the terminal air passages of a primary lobule or functional unit. Successive generations are numbered and correspond to Table 1. The strict bifurcation at each generation affords an adequate model for explanation of function, but the actual structure is less regular. Different authors have variously defined the primary lobules as the area of lung supplied by the first, second or third generation of respiratory bronchiole

devoted to gas exchange. The respiratory bronchioles may thus be regarded as a transitional zone between bronchioles and alveolar duct with progressive changes in structure according to the change from conduction to gas exchange. The epithelium is cuboidal between the mouths of the mural alveoli but becomes progressively flatter until it finally gives way entirely to alveolar epithelium in the alveolar ducts. Like the bronchioles, the respiratory bronchioles are embedded in lung parenchyma and rely upon tissue traction for maintenance of their lumen. There is a well marked muscle layer and the muscle forms bands which loop over the opening of the alveolar ducts and the mouths of the mural alveoli. There is no significant change in the calibre of advancing generations of respiratory bronchioles and the total cross-sectional area at this level is of the order of hundreds of square centimetres.

Table 2

Distribution of alveoli in a primary lobule (after Weibel, 1963)

	Generation (as in Table 1)	*Number of alveoli per unit (mean)*	*Number of units per generation (mean)*	*Number of alveoli per generation (mean)*
Respiratory bronchioles				
1st order	17	5	1	5
2nd order	18	8	2	16
3rd order	19	12	4	48
Alveolar ducts				
1st order	20	20	8	160
2nd order	21	20	16	320
3rd order	22	20	32	640
Alveolar sacs	23	17	64	1,088
Total number of alveoli in primary lobule				2,277

Diameter of primary lobule at F.R.C., 3·5 mm.; volume of primary lobule at F.R.C., 23 µl.; number of primary lobules in average lung, 130,000; total number of alveoli in average lung, 300,000,000; diameter of alveolus at F.R.C., 0·2 mm.

Primary lobule or functional unit.—There is some disagreement about the extent of the primary lobule. Currently the majority view is that the primary lobule is the area supplied by a first order respiratory bronchiole (*Figure 2*). According to this definition, there are about 130,000 primary lobules, each with a diameter of about 3·5 mm. and containing about 2,000 alveoli (*Table 2*). They probably correspond to the areas of lung which are seen to pop open at thoracotomy during expansion of collapsed lung by inflation.

Alveolar Ducts (twentieth to twenty-second generations)

Alveolar ducts arise from the terminal respiratory bronchiole from which they differ by having no mucosa at all. The walls are in fact composed entirely of alveoli (about 20 in number) which open widely onto the lumen of the alveolar duct and are separated only by their septa. *Figure 2* shows the alveolar duct system as two successive bifurcations. Miller (1947) presents a somewhat different arrangement with terminal respiratory bronchioles trifurcating into a single generation of alveolar ducts from each of which arise three passages

which he terms atria. In fact, Miller's atria are structurally and functionally indistinguishable from alveolar ducts and there seems little point in introducing a separate category. The differences between the model system in *Figure 2* and the reconstructions of Miller are of anatomical interest but need not concern us from the functional standpoint.

The alveolar septa form a series of rings across the length of the alveolar duct. These contain smooth muscle and are capable of contraction causing considerable narrowing of the lumen of the duct. About half of the total number of alveoli arise from ducts and some 35 per cent of the alveolar gas resides in the alveolar ducts and the alveoli which arise directly from them.

Alveolar Sacs (twenty-third generation)

The last generation of the air passages are designated alveolar sacs although they are functionally identical to alveolar ducts except for the fact that they are blind. Staub (1963b) does not consider that they merit any distinction from alveolar ducts. About 17 alveoli arise from each alveolar sac, and this accounts for about half the total number of alveoli.

Alveoli

The size of the alveoli is proportional to the lung volume and therefore in histological specimens depends critically upon the manner of fixation of the lung. At functional residual capacity the average alveolar diameter in man is 0·2 mm., astonishingly close to the estimate of 1/100 inch made by Stephen Hales in 1731. However, it has now become clear that the size is not uniform throughout the lungs but is largest in the uppermost part of the lung and smallest in the most dependent parts (Glazier and his colleagues, 1967). This is a gravitational phenomenon and is increased at high G (during centrifugation, for example). It derives from the fact that the lung is an elastic body with a specific gravity of about 0·3 and its centre of gravity migrates in a downward direction in whatever position the lung is held. This phenomenon has most important implications in the mechanics of breathing, regional distribution of ventilation (page 199), distribution of ventilation/perfusion ratios (page 234), and in the development of pulmonary collapse (page 236).

Alveolar walls which separate two adjacent alveoli consist of two layers of alveolar epithelium on separate basement membranes, which enclose the capillary vascular network, elastic and collagen fibres, bands of smooth muscles and nerves. Apart from the mouths of the alveoli, the panels which comprise the walls are approximately flat and in a state of tension due partly to the elastic fibres but more to the surface tension acting at the air/fluid interface. There was formerly considerable doubt as to whether alveolar epithelium existed. This has now been resolved by the electron microscope which reveals a continuous sheet of epithelium containing nuclei which bulge into the lumen of the alveoli (*Figure 3*).

It seems likely that the alveolar septa in man have small fenestrations (pores of Kohn) lying between branches of the capillary network. The pores do not only connect alveoli of the same primary lobule, since communication can be demonstrated between the air spaces supplied by fairly large bronchi (Liebow, 1962). Direct communications have also been found between small bronchioles and neighbouring alveoli (Lambert, 1955).

The alveolar epithelium is covered with a very thin film of alveolar lining fluid which forms an interface with the alveolar gas. Surface tension at the interface tends to make the alveolar septa contract and this constitutes a major fraction of the lung 'elasticity'. The surface tension is, however, modified in a most important manner by a lipoprotein secreted by the alveolar epithelium, and this is discussed in Chapter 3 (page 59).

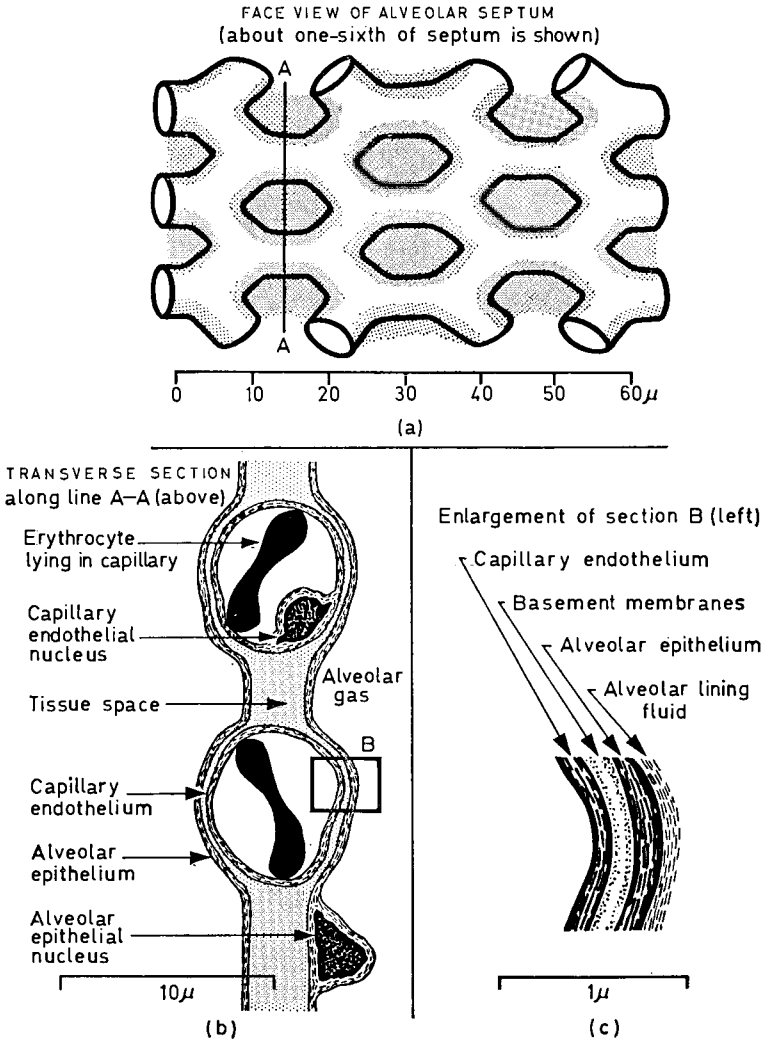


Figure 3. (a) represents a face view of an alveolar septum (of which about one-sixth is shown). The capillary network is dense, with the spaces between the capillaries being rather less than the diameter of the capillaries. (b) shows a section (A—A) through two capillaries, demonstrating the very thin membrane through which gas exchange takes place. This is shown in an enlarged view in (c)

The Pulmonary Vasculature

The Pulmonary Arteries

Although the pulmonary circulation carries roughly the same flow as the systemic circulation, the arterial pressure and the vascular resistance are only one-sixth as great. The media of the pulmonary arteries is about half as thick as in systemic arteries of corresponding size. It consists predominantly of elastic tissue in the larger vessels but in the smaller vessels the media is mainly muscular, the transition being in vessels of about 1 mm. diameter. Pulmonary arteries lie close to the corresponding air passages in connective tissue sheaths.

Pulmonary Arterioles

The transition to arterioles occurs at a diameter of 100 microns. These vessels differ radically from the corresponding systemic vessels in being devoid of muscular tissue, consisting of merely a thin media of elastic tissue separated from the blood by the endothelium. The structure is, in fact, very similar to that of a pulmonary venule. Pulmonary arterioles lie close to the corresponding alveolar ducts. The general proximity of arterial blood vessels and gas-conducting tubes means that each is subjected to the same pressure changes and they are also conveniently located for the rather feeble homeostatic mechanisms which provide some compensation for regional inequalities of either ventilation or perfusion.

Pulmonary Capillaries

Pulmonary capillaries tend to arise abruptly from much larger vessels, the pulmonary metarterioles (Staub, 1963b). This helps to avoid plugging of the vasculature by emboli which is important since the lungs have a filtration function analogous to that of the oil filter in an internal combustion engine. The capillaries form a dense network over the walls of one or more alveoli and the spaces between the capillaries are of the same order as the diameter of the capillaries themselves (*Figure 3*). The actual area of the interalveolar septum occupied by functioning capillaries is about 75 per cent of total but the precise figure varies, particularly in response to the effect of gravity, vascularity being greater in the dependent parts of the lung. This is the basis of the regional scatter of ventilation/perfusion ratios which is of considerable functional importance (page 234). The vessels are extremely thin-walled with an endothelium of less than 0·1 micron except where it is expanded to enclose the nuclei. It is generally believed that expansion of the alveoli leads to a reduction of the total cross-sectional area of the capillary bed, and an increased resistance to blood flow. It appears likely that the capillary network may pass continuously from one septum on to a second and possibly a third before draining into a venule. This must clearly have a bearing on the concept of 'capillary transit time'.

Pulmonary Venules and Veins

Pulmonary capillary blood is collected into venules which are structurally almost identical to the arterioles. In fact, the pulmonary circulation of the excised lung may be run in reverse, and Duke (1954) has obtained satisfactory

gas exchange with an isolated lung of cat perfused from the pulmonary veins. The pulmonary veins do not run alongside the pulmonary arteries but lie some distance away, tending towards the septa separating the segments of the lung.

Bronchial Circulation

Down to the terminal bronchioles, the air passages and the accompanying blood vessels receive their nutrition from the bronchial vessels which arise from the systemic circulation. Part of the bronchial circulation returns to the systemic venous system but part mingles with the pulmonary venous drainage. This constitutes a shunt and is further discussed in Chapter 8 (page 211).

Bronchopulmonary Arterial Anastomoses

It is well known that in pulmonary arterial stenosis, blood flows through a pre-capillary anastomosis from the bronchial circulation to reach the pulmonary capillaries. It is less certain whether this occurs in normal lungs (page 211).

Pulmonary Arteriovenous Anastomoses

There seems little doubt that, when the pulmonary arterial pressure of the dog is raised by massive pulmonary embolization, pulmonary arterial blood is able to reach the pulmonary veins without apparently having traversed a capillary bed. The nature of the communication and whether it occurs in man is discussed in Chapter 9 (page 240), since it offers a possible explanation of some abnormalities of respiratory function which are consistently found during anaesthesia.

This chapter has reviewed the physical behaviour of gases so far as it is relevant to respiratory physiology. It has also described the subdivisions of the lung volume and the micro-anatomy of the air passages and alveoli. In the case of the lungs there are considerable difficulties in explaining function in terms of structure or in explaining the function of every structure which can be seen with the microscope. However, a great deal of progress has been made in recent years and it is evident that a complete understanding of the lung can only come about by a synthesis of studies of structure and function.

CHAPTER 2

CONTROL OF BREATHING

Normal pulmonary ventilation results from rhythmic contraction and relaxation of the voluntary striated muscles concerned with inspiration. Under normal circumstances the subject is not aware of this action, which is continued during sleep or light anaesthesia. This automatic control of voluntary muscles is an unusual arrangement and its elucidation has proved one of the most formidable problems of physiology.

There is no single mechanism which can be said to control ventilation. Many different mechanisms can be shown to be able to exert an influence on breathing under particular circumstances, although not all are in play at any one time. It appears, for example, that during exercise the mechanisms which control the minute volume are not those which operate in the resting state. Understanding of such mechanisms is, at present, fragmentary with small islands of knowledge surrounded by seas of uncertainty, and we appear to be far from having an integrated picture of the control of breathing under all circumstances. Of necessity the subject is approached piecemeal with a good deal of detail about individual mechanisms but regrettably little about their relationship to one another.

The plan of this chapter is to commence with a discussion of the origin of the rhythmicity of breathing in the neurones of the hind-brain which appear to subserve respiration ('respiratory centres'). The efferent path is then traced to the muscles of respiration with an account of the important control function of the spindles in these muscles. The next section is concerned with the chemical control of respiration and this is followed by a discussion of the influence of respiratory reflexes and mechanical factors. Finally, some attention is paid to special situations such as breath holding, exercise and artificial ventilation.

THE ORIGIN OF THE RESPIRATORY RHYTHM

Classical Concepts of the Respiratory Centres

In 1812, Legallois published reports showing that rhythmic inspiratory movements persisted after removal of the cerebellum and all parts of the brain above the medulla, but ceased when the medulla was removed. During the next 150 years a long series of distinguished investigators carried out more detailed localization of the neurones concerned in the control of respiration and studied their interaction. Marckwald and Kronecker (1880) differentiated between inspiratory and expiratory neurones, and Lumsden (1923a–d) described and named the pneumotaxic and apneustic pontine centres. He also advanced the concept of an internal feedback mechanism by which a tonic inspiration was inhibited at the end of inspiration by discharge of the pneumotaxic centre

acting through the expiratory centre, the whole loop functioning as an internal pacemaker.

Pitts, Magoun and Ranson (1939a) described the anatomical localization of the overlapping inspiratory and expiratory neurones in the medulla, dispelling any idea of discrete 'centres'. In a later paper (1939b), they advanced the concept of the inhibition of one centre by another, or by vagal afferents from stretch sensors in the lungs. In a third paper Pitts, Magoun and Ranson (1939c) concluded that respiratory rhythmicity is caused by two separate and alternative feedback loops; one based on the pneumotaxic centre, and the other on

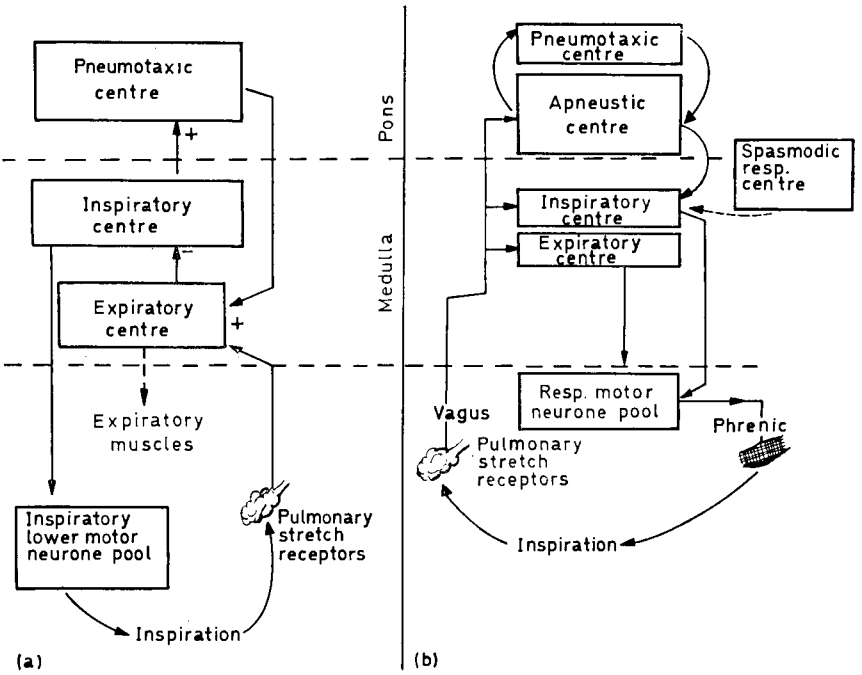


Figure 4. Classical concepts of the organization of the respiratory centres, showing the negative feedback loops believed to maintain the rhythmicity of breathing (see *text*). *Expiratory muscles are not active during quiet breathing in conscious man, and the role of the expiratory neurones is primarily that of inhibition of the inspiratory neurones. However, Freund, Roos and Dodd (1964) have presented convincing evidence that expiratory muscle activity is a normal feature of breathing in the anaesthetized patient.* ((*a*) *according to Pitts (1946); (b) from Wang, Ngai and Frumin (1957) courtesy of the authors and the American Physiological Society*)

the vagal reflex sensitive to lung stretch, the two mechanisms being similar and mutually replaceable.

The suggestion of self-limitation of inspiration by vagal impulses arising from inflation of the lung was not new and had first been made in the classical studies of Breuer (1868), previously reported by Hering (1868).* The subject was reviewed in 1946 by Pitts. The next landmark in the long series of studies of the interaction of the various respiratory centres was the paper by Wang, Ngai and

* *See* page 37 for an explanation of the relationship between the papers of Breuer and Hering.

Frumin (1957), stressing the pontile apneustic centre as the site of the inspiratory tonicity and also as the site of rhythmic inhibition by both the pneumotaxic centre and the vagus. The general plan of the respiratory centres had now reached 'classical' status and the concepts illustrated in diagrams such as *Figure 4* have been widely accepted for a number of years. However, we live in an age when the overthrow of classical concepts is almost a daily occurrence, and it should therefore cause no great surprise that the edifice shown in *Figure 4* has been strongly challenged on the basis of new experiments and new interpretations of old experiments.

Inherent Rhythmicity of the Respiratory Neurones in the Medulla

The possibility of inherent rhythmicity in the medulla follows from the finding of Pitts, Magoun and Ranson (1939b) that activity of either inspiratory or expiratory neurones of the medulla inhibits the other. Eupnoea was demonstrated with an isolated medulla by Wang, Ngai and Frumin (1957):

> 'In the present study, rhythmic respiration persisted in three medullary animals after section of all cervical dorsal roots and transection of the spinal cord at the level of the sixth cervical segment, in addition to division of all the remaining cervical nerves . . . In conventional medullary preparations, respiration is usually of the gasping type, but occasionally is indistinguishable from eupnea.'

Wang and Ngai, in a review of the general organization of central respiratory mechanisms (1964), state, 'It is therefore clear that control of respiratory rhythmicity truly resides in the medulla oblongata', a conclusion reached from many reports of transection experiments including those of Wang, Ngai and Frumin (1957). However, it is confusing to find that, in a subsequent review, Ngai (1967) states, 'It is believed that normal rhythmic respiration has its origin in the pons . . . The medullary respiratory centres, although shown to have an intricate rhythmicity, are subservient to pontile influences.' These statements can be reconciled by the view that, whereas a respiratory rhythm *can* be maintained by the medulla, *normal* breathing probably depends upon pontile influences.

There is substantial experimental evidence that control of rhythmicity resides in the inspiratory and expiratory neurones of the medulla without the necessity of involving a negative feedback loop passing outside the medulla, either through the pneumotaxic centre or through the vagus. Firstly, there is the finding of eupnoea in the medullary cat (Hoff and Breckenridge, 1949; Wang, Ngai and Frumin, 1957), to which reference was made above. Secondly, there is the demonstration by Guz and his colleagues (1964 and 1966b) that bilateral vagal block in man had no effect on the pattern of respiration. It has been suggested that apneusis (produced by mid-pontile section) is a manifestation of a form of decerebrate rigidity rather than release of the apneustic centre from the influence of the 'higher' pneumotaxic centre (Breckenridge, Hoff and Smith, 1950), although this view is disputed by Wang and Ngai (1964). A further challenge to the accepted role of the pontile respiratory centres has been the failure of Salmoiraghi and Burns (1960) to find respiratory activity during recordings from single neurones in the pons of the cat. Such activity has, however, been reported by Cohen and Wang (1959) who found an abundance of neurones with respiratory phase-spanning discharge.

Accounts of how the medullary neurones can generate the respiratory rhythm have been given by Robson (1967) and Salmoiraghi (1963). The concept is advanced that the system is bi-stable with predominant activity of either the inspiratory or the expiratory neurones. The system thus rests in either inspiration or expiration, normally cycling between the two phases in a rhythmic manner. It may thus be likened to a metronome which has two stable positions but which may be made to oscillate between them. This contrasts with Pitts' concept which is of a uni-stable system with only one resting position, that of inspiration or apneusis, which is rhythmically inter-

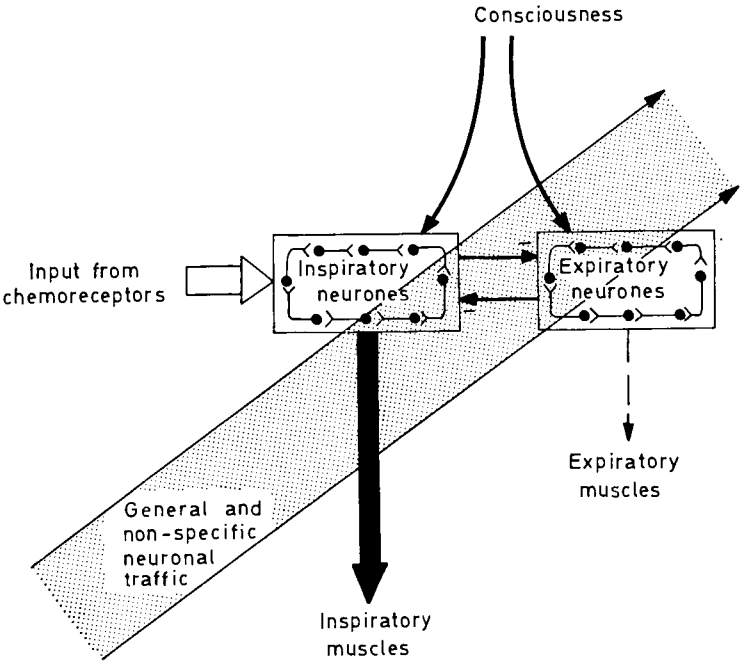


Figure 5. Concept of the generation of the respiratory rhythm within a bi-stable system of medullary neurones. Bursts develop alternately in the inspiratory and expiratory neurones, which are arranged in self-re-excitatory chains and are mutually inhibitory. Bursts in each group are terminated by an elevation of firing threshold within the group. Barbiturates cause respiratory arrest by interference with the pathways of reciprocal inhibition. The system is not self-oscillating in the absence of general neural traffic. (After Robson, 1967)

rupted by negative feedback from either the pneumotaxic centre or the pulmonary stretch receptors (*Figure 4*).

In the bi-stable system, the inspiratory and expiratory neurones are believed to be separately arranged in two groups of self-re-excitatory chains, capable of raising their activity by internal positive feedback loops. As the burst proceeds, there is a progressive rise in the firing threshold of the group which soon terminates its activity (Salmoiraghi and von Baumgarten, 1961). However, the inspiratory and expiratory groups of neurones are linked by mutually inhibitory pathways which enforce reciprocal activity (*Figure 5*). Therefore, as

the activity dies away in one group, it grows in the other, only to be terminated in due course by the development of a raised threshold in that group. Activity then recommences in the original group and so the cycle continues. It should be stressed that cyclical activity in the expiratory neurones does not necessarily imply activity of expiratory muscles and, indeed, under resting conditions, the expiratory neurones are exclusively anti-inspiratory in their action.

Maintenance of the respiratory rhythm by the medullary neurones is believed to depend upon the following factors.

(1) *The integrity of the medullary neurones.* They are known to be easily damaged by hypoxia but their intrinsic activity is not apparently depressed by barbiturates (Robson, Houseley and Solis-Quiroga, 1963).

(2) *The reciprocal innervation between the inspiratory and expiratory neurones.* Depression of these pathways appears to be the mechanism for the production of apnoea by barbiturates (Robson, Houseley and Solis-Quiroga, 1963). Arrest may be produced with continuous discharge of either inspiratory or expiratory neurones and it is possible to switch activity from one group to the other during arrest by inflation of the lungs, or by peripheral stimulation.

(3) *Maintenance of acid–base status between certain limits* (Katz and his colleagues, 1963).

(4) *The concept of the bi-stable organization of the respiratory neurones in the medulla* does not provide for spontaneous oscillation between inspiration and expiration except in the presence of general neuronal traffic through the brain stem. This may follow non-specific stimulation (such as mechanical stimulation of the larynx or dilation of the anus) or chemoreceptor stimulation by either hypoxia or hypercapnia. However, no less important is what may best be described as the state of wakefulness of the patient. The special significance of this factor for the anaesthetist is considered in the following section.

Influence of Wakefulness

Every anaesthetist has noticed the ventilatory depression which accompanies absence of stimulus to the anaesthetized patient and is equally aware of the augmentation of ventilation which follows surgical stimulus even in the presence of deep anaesthesia. In fact, provided spontaneous respiration is present at all, it is almost impossible to avoid a ventilatory response to a painful stimulus, no matter how deep the anaesthesia. The same phenomenon is observed in sleep, and depression (of the ventilatory response to carbon dioxide) is progressively more marked in the deeper levels of sleep (Ingvar and Bülow, 1963).

The interplay between wakefulness and carbon dioxide is also important in handling the common problem of post-hyperventilation apnoea in the anaesthetized patient. Douglas and Haldane (1909) observed appreciable periods of apnoea following voluntary hyperventilation, in studies which closely followed the classical paper of Haldane and Priestley describing the major role of carbon dioxide in the regulation of breathing (1905). Since ventilation is so easily influenced by voluntary control under experimental conditions, when the subject's attention is focused on his breathing, it seemed worth repeating this study with subjects who had no preconceived ideas on the role of carbon dioxide.

Fink (1961) found that 13 naïve conscious subjects all continued to breathe rhythmically during recovery from reduction of end-expiratory P_{CO_2} to 25 mm Hg or less, induced by five to ten minutes of mechanical hyperventilation. It should, however, be noted that Fink's results were not confirmed by Bainton and Mitchell (1965) or Moser, Rhodes and Kwaan (1965), who were able to obtain apnoea after hyperventilation in some, but not all, of their conscious subjects. Whatever the uncertainty which seems to exist in conscious man, there is no doubt of the ease with which apnoea may be produced by moderate hypocapnia in anaesthetized patients (Hanks, Ngai and Fink, 1961), and these studies have a most important practical bearing on the restoration of spontaneous respiration in anaesthetized patients who have been subjected to a period of artificial hyperventilation. If a patient is allowed to regain consciousness rapidly at the end of a period of light anaesthesia, it is common experience that spontaneous respiration will be re-established at a P_{CO_2} well below the apnoeic threshold (page 31). In contrast, those anaesthetists who favour a more gradual return to consciousness frequently encounter some delay in restoring spontaneous breathing, unless they take steps to raise the P_{CO_2} to the normal level or higher. After an anaesthetic with artificial ventilation, arterial P_{CO_2} is very commonly within the range 20–30 mm Hg. However, P_{CO_2} may be easily restored to within the range 40–50 mm Hg by such techniques as the administration of 5 per cent carbon dioxide in the inspired gas for five minutes during the continuation of artificial ventilation. It is then usual for spontaneous breathing to be resumed within a few seconds, even if the patient is still deeply unconscious, the additional P_{CO_2} drive seemingly being able to compensate for the relative absence of neural traffic. Alternatively, neural traffic may be generated by such manœuvres as moving the endotracheal tube in the larynx, which frequently causes an abrupt resumption of breathing.

Ondine's Curse

This is also perhaps the best place to mention the condition which Severinghaus and Mitchell (1962) have aptly called 'Ondine's curse' from its first description in German legend. The water nymph, Ondine, having been jilted by her mortal husband, took from him all automatic functions, requiring him to remember to breathe. When he finally fell asleep he died. These authors describe three patients who exhibited long periods of apnoea even when awake but who breathed on command. These patients had become apnoeic during surgery involving the high cervical cord or brain stem, but similar cases have been reported during bulbar poliomyelitis. The syndrome is also easily produced by over-dosage with some of the more recently developed synthetic opiates such as fentanyl or phenoperidine, and it seems likely that the mechanism of disruption of automatic breathing is by interference with the pathways of reciprocal innervation between the inspiratory and expiratory neurones, described above for barbiturates. The practical difference is that, in the case of barbiturate over-dosage, the patient is apnoeic and unconscious, while with opiates he may be apnoeic but conscious, thus according with the definition of Ondine's curse. Such patients show marked insensitivity to carbon dioxide and depend upon conscious voluntary control of breathing, which may require constant prompting by an attendant.

MOTOR PATHWAYS CONCERNED IN BREATHING

Efferent fibres from the inspiratory neurones of the medulla descend in the anterior and lateral columns of the cervical cord, reaching the lower motor neurones in the anterior horn of the same side. Onward transmission of the impulse is by the lower motor neurones which have their cell body in the anterior horn. However, it now appears likely that the respiratory muscles, in common with other skeletal muscles, have their tension controlled by a feedback or servo-mechanism mediated by the spindles. Campbell (1964) has reviewed the evidence for the presence of spindles in respiratory muscles, but their function is largely inferred from knowledge of their well established role in other skeletal muscles not concerned with respiration (Granit, 1955).

Two types of cell can be distinguished in the motor neurone pool of the anterior horn cell. The α motor neurone has a thick efferent fibre (12–20 μ diameter) and passes by the ventral root directly to the neuromuscular junction of the muscle fibre (*Figure 6*). The γ motor neurone has a thin efferent fibre (2–8 μ) which also passes by the ventral root but terminates in the intrafusal fibres of the muscle spindle. Contraction of the intrafusal fibres increases the tension in the central part of the spindle (the nuclear bag) causing stimulation of the annulo-spiral endings. Impulses so generated are then transmitted via fibres which lie in the dorsal root to reach the anterior horn where they have an excitatory effect on the α motor neurones. It will be seen that an efferent impulse transmitted by the γ system may cause reflex contraction of the main muscle mass by means of an arc through the annulo-spiral afferent and the α motor neurone. Thus contraction of the whole muscle may be controlled entirely by efferents travelling in the γ fibres and this has been suggested in relation to breathing (Robson, 1967).

Alternatively, muscle contraction may in the first instance result from discharge of the α and γ motor neurones. If the shortening of the muscle is unopposed, main (extrafusal) and intrafusal fibres will contract together and the tension in the nuclear bag of the spindle will be unchanged (*Figure 6*). If, however, the shortening of the muscle is opposed, the intrafusal fibres will shorten more than the extrafusal fibres, causing the nuclear bag to be stretched. The consequent stimulation of the annulo-spiral endings results in afferents which raise the excitatory state of the motor neurones, causing the main muscle fibres to increase their tension until the resistance is overcome, allowing the muscle to shorten and the tension in the nuclear bag of the spindle to be reduced.

By this mechanism, fine control of muscle contraction is possible. The message from the upper motor neurone is in the form: 'muscles should contract with whatever force may be found necessary to effect such and such a shortening', and not simply: 'muscles should contract with such and such a force'. Clearly the former message is far more satisfactory for such a task as lifting up a suitcase of which the precise weight is not known until an attempt is made to lift it. It is common experience that, provided the weight is not grossly different from the anticipated weight, we can, in fact, raise a suitcase to a predetermined distance from the floor with considerable precision without knowing the exact weight in advance. This feat can only be achieved by means of an efficient

servo-system which the spindles appear able to provide. The workings of the system are probably relayed to the cortex and provide information of 'length–tension' relationships which enable us to assess the weight of an object or the elasticity of a piece of rubber.

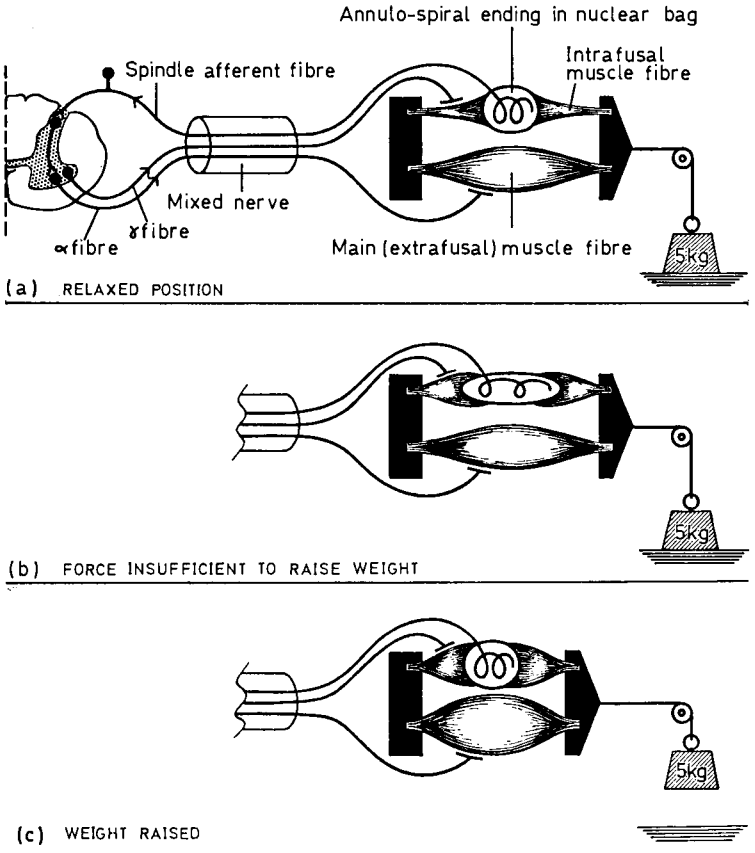


Figure 6. Diagrammatic representation of the servo-mechanism mediated by the muscle spindles. (a) shows the resting state with muscle and intrafusal fibres of spindle relaxed. In (b) the muscle is attempting to lift the weight following discharge of both α and γ systems. The force developed by the muscle is insufficient: the weight is not lifted and the muscle cannot shorten. However, the intrafusal fibres are able to shorten and stretch the annulo-spiral endings in the nuclear bag of the spindle. Afferent discharge causes increased excitation of the motor neurone pool in the anterior horn. α discharge is augmented and the weight is finally lifted by the more powerful contraction of the muscle (c). When the weight is lifted, the tension on the nuclear bag is relieved and the afferent discharge from the spindle ceases. This series of diagrams relates to the lifting of a weight, but it is thought that similar action of spindles is brought into play when the inspiratory muscles contract against augmented airway resistance

Campbell and Howell (1962) have presented evidence for believing that a similar mechanism governs the action of the respiratory muscles. According to this belief, the message conveyed by the efferent tract from the inspiratory neurones of the medulla would be in the form: 'inspiratory muscles should

contract with whatever force may be necessary to effect such and such a change in length (corresponding to a certain tidal volume)' and not simply: 'inspiratory muscles should contract with such and such a force'.

The use of the servo-loop implies that the action of the respiratory muscles must be dependent upon the integrity of the dorsal roots which contain the efferents from the annulo-spiral endings. This appears to be the case, and dorsal root section at the appropriate level causes temporary paralysis of the respiratory muscles in man (Nathan and Sears, 1960).

The spindle-servo-mechanism provides an excellent mechanism for dealing with sudden changes in airway resistance. The compensation is made at spinal level and operates within the duration of a single inspiration, long before changes in arterial blood gas tensions are able to exert their effect. It is fortunate that this mechanism remains intact during anaesthesia and even withstands moderate curarization which is supposed to act selectively against the γ system. Nunn and Ezi-Ashi (1961) investigated the ability of anaesthetized patients to compensate for added resistance to either inspiration or expiration or both, and found a surprising ability to reinforce the work of the inspiratory muscles before any change in blood gas tensions could influence the picture. In fact the latter effect reinforced (after about 90 seconds' delay) the immediate response of the spindle-servo-mechanism and, in combination, a most reassuring degree of homeostasis of ventilation was achieved. The nature and magnitude of the response to resistance is described in Chapter 4 (page 102). Inspiratory resistance causes an augmentation of tension developed in the inspiratory muscles, while expiratory resistance also causes an augmentation of inspiratory effort resulting in an increase in lung volume, until the increased elastic recoil is sufficient to overcome the expiratory resistance. These changes are explicable in the light of the function of the spindles but cannot be explained in terms of the Breuer–Hering reflexes. Relay to cortical levels is probably the mechanism of detection of external changes in compliance (Campbell and his colleagues, 1961) or resistance (Bennett and his colleagues, 1962).

CHEMICAL CONTROL OF BREATHING

Pflüger in 1868 was the first to demonstrate that breathing could be stimulated either by a reduction of oxygen content or by an increase of carbon dioxide content of the arterial blood. However, the importance of the role of carbon dioxide was not fully established until the classical work of Haldane and Priestley (1905). In one paper they presented their technique for sampling alveolar gas, showed the constancy of the alveolar P_{CO_2} under a wide range of circumstances and also demonstrated the exquisite sensitivity of ventilation to small changes in alveolar P_{CO_2}.

Until 1926 it was thought that changes in the chemical composition of the blood influenced ventilation solely by direct action on the respiratory centre, which was presumed to be sensitive to these influences although direct experimental proof was lacking. However, between 1926 and 1930 there occurred a major revision in which the existence of peripheral chemoreceptors was recognized, and the role of the carotid bodies in the control of breathing was

clearly established (de Castro, 1926; Heymans and Heymans,* 1927; Heymans,* Bouckaert and Dautrebande, 1930). A similar function for the aortic bodies was reported in 1939 by Comroe.

Division of the afferent nerves from the peripheral chemoreceptors does not greatly diminish the ventilatory response to elevation of the arterial P_{CO_2} and it has been generally believed that the respiratory centre is itself sensitive to carbon dioxide. Recent work, however, suggests that the central chemoreceptors, as they have come to be called, may actually be separate from the respiratory neurones of the medulla although located but a short distance away. There has also been a recent revival of interest in the possibility of the existence of central venous chemoreceptors. Historical developments up to 1930 have been well reviewed by Perkins (1964).

The Peripheral Chemoreceptors

The carotid and aortic bodies have a metabolism which, in proportion to their weight, is considerably higher than that of the cerebral cortex. Their perfusion, however, is about ten times as great as their metabolic rate would appear to require, so that their arterial/venous blood gas content difference is extremely small (Daly, Lambertsen and Schweitzer, 1954). Arterial/venous shunts exist which can substantially reduce the perfusion of the sinusoids.

The bodies contain large sinusoids, lined with endothelium which covers the chemoreceptor cells among which lie unmedullated nerve fibres. Electron microscopy studies have been reported by Ross (1959), but have not given any indication of the mechanism of stimulation which remains conjectural. Afferent nerves lie in the vagus (from the aortic bodies) and the glossopharyngeal nerve (from the carotid bodies).

Discharge in the afferent nerves increases in the following circumstances.

(1) *Decrease of arterial* P_{O_2}. Reduced oxygen *content* does not stimulate the bodies, provided that P_{O_2} remains normal and there is little stimulation in anaemia, carboxyhaemoglobinaemia or methaemoglobinaemia (Comroe and Schmidt, 1938). The response is non-linear and does not become appreciable until the P_{O_2} is reduced to about 60 mm Hg.

(2) *Decrease of arterial pH.* Acidaemia of perfusing blood causes stimulation of which the magnitude is the same whether the cause is due to carbonic or to 'non-respiratory' acids such as lactic (Hornbein and Roos, 1963). Quantitatively, the change produced by elevated P_{CO_2} on the peripheral chemoreceptors is considerably less than that caused by the action on the central chemosensitive areas (Schmidt, Comroe and Dripps, 1939).

(3) *Hypoperfusion of peripheral chemoreceptors* causes stimulation, possibly by causing a 'stagnant hypoxia' of the chemoreceptor cells. Hypoperfusion may result from hypotension.

(4) *Blood temperature elevation* causes stimulation of breathing.

(5) *Chemical stimulation* by a wide range of substances is known to cause increased ventilation through the medium of the peripheral chemoreceptors. These substances fall into two groups. The first comprises agents such as nicotine and acetylcholine which stimulate sympathetic ganglia. Action of this

* This work resulted in C. Heymans being awarded a Nobel Prize in 1938.

group of drugs can be blocked with ganglion-blocking agents (e.g. hexamethonium). The second group of chemical stimulants comprises substances such as cyanide and carbon monoxide* which block the cytochrome system and so prevent oxidative metabolism.

It would be attractive to offer a unified theory which would explain how this wide range of stimuli can excite the chemoreceptors by a common mechanism. For example, thought has been given to the possibility that the chemoreceptor cells might be uniquely sensitive to a fall in intracellular pH. It would then be possible to postulate their stimulation by a rise in P_{CO_2} (which lowers intracellular pH by diffusion of carbon dioxide into the cell), or by reduction of P_{O_2} (which, if sufficiently severe, would cause the cell to utilize anaerobic metabolic pathways). Hypoperfusion and poisoning of cytochrome a_3 would also prevent or diminish aerobic metabolism, and could cause intracellular acidosis from the production of lactic acid. It has also been suggested by Neil and Joels (1963) that certain stimuli (e.g. acidosis) may shunt blood past the sinusoids and so cause stagnant hypoxia in the vicinity of the chemoreceptor cells, which can then be considered to respond only to hypoxia. At the present time both theories remain conjectural and there is no firm evidence for the mechanism of action.

Apart from the well known increase in depth and rate of breathing, chemoreceptor stimulation causes a number of other effects including bradycardia, hypertension, increase in bronchiolar tone and adrenal secretion. Stimulation of the carotid bodies has predominantly respiratory effects, while the aortic bodies have a greater influence on circulation.

There is some doubt as to whether the chemoreceptors provide a significant tonic drive to respiration under normal circumstances, although slight but measurable chemoreceptor discharge persists in anaesthetized cats at oxygen tensions of 100 mm Hg. Denervation was found to cause a shift to the right of the ventilation/CO_2 response curve (page 31) with a 20 per cent rise in arterial P_{CO_2} (Mitchell and his colleagues, 1964). Some hold the view that the peripheral chemoreceptors play no part in normal breathing but act as an emergency control system designed to respond to dangerous conditions such as hypoxia, acidosis and hypotension, in which the peripheral chemoreceptors are essential for the respiratory drive which ensues.

Bilateral vagal and glossopharyngeal block was studied in two healthy volunteers by Guz and his colleagues (1966b). Apart from loss of swallowing and phonation, and the development of hypertension, there was no change in the pattern or sensation of breathing. End-tidal P_{CO_2} and respiratory rate were unchanged but there was a substantial increase in the duration of breath holding. Loss of ventilatory response to hypoxia produced by inhaling 8 per cent oxygen in nitrogen was also reported in another publication by the same team (Guz and his colleagues, 1966a). Bilateral vagal block was not found to influence ventilation in five anaesthetized patients (Guz and his colleagues, 1964). Interpretation of these studies is complicated by the fact that afferents from pulmonary stretch receptors were unavoidably blocked at the same time as those from the peripheral chemoreceptors.

* The apparent paradox between direct stimulation by carbon monoxide and lack of stimulation by the presence of a high level of carboxyhaemoglobin in the arterial blood is explained by Neil and Joels (1963).

The response of the peripheral chemoreceptors to hypoxaemia is apparently resistant to influences such as anaesthesia or hypoxia which cause depression of the central response to elevated P_{CO_2}. This earned the peripheral chemoreceptors the distinction of being described as the *ultimum moriens* (the last to die). The function of the peripheral chemoreceptors has been well covered in a series of excellent books and reviews. The reader is referred to Heymans and Neil (1958), Dejours (1962), various papers in the Haldane centenary symposium (edited by Cunningham and Lloyd, 1963), Comroe (1964) and Hornbein (1965). Consideration of the quantitative response of ventilation to chemical stimulation is postponed until after discussion of the central chemoreceptors and is then taken as the response of the entire chemosensitive mechanism.

The Central Chemoreceptors

The ventilatory response to carbon dioxide (i.e. the slope of P_{CO_2}/ventilation curve, as in *Figure 7*) is diminished by denervation of the peripheral chemoreceptors, and some 78 per cent of the respiratory response to inhaled carbon dioxide originates in the central medullary chemoreceptors (Mitchell, 1966). The central response is thus the major factor in the regulation of breathing by carbon dioxide and it has long been thought that the actual neurones of the 'respiratory centre' are themselves sensitive either to P_{CO_2} (Haldane and Priestley, 1905) or to pH (Winterstein, 1911; Gesell, 1923).

More recently attention has been turned to the role of the cerebrospinal fluid (C.S.F.) in the control of breathing. This followed the important studies of Leusen (1950 and 1954) who showed that the ventilation of anaesthetized dogs was stimulated by perfusion of the ventriculo-cisternal system with mock C.S.F. of elevated P_{CO_2} and reduced pH.

Leusen's work touched off a long series of studies aimed at localizing central chemoreceptors. They were thought to lie in contact with one or other of the reservoirs of C.S.F., since it seemed unlikely that changes in the composition of the C.S.F. could influence the respiratory neurones within the substance of the medulla in the short time required for development of the ventilatory response to inhaled carbon dioxide.

These studies were carried out mainly in the University of Göttingen (Loeschcke and Keopchen) and the University of California, San Francisco (Mitchell and Severinghaus), although various combinations of many authors appeared in numerous publications which included joint work between members of the two universities. Finally, it appeared likely that the central respiratory response to carbon dioxide was mediated mainly through superficial chemosensitive areas located on the antero-lateral aspects of the medulla, close to the origins of the glossopharyngeal and vagus nerves, and crossed by the anterior inferior cerebellar arteries (Mitchell and his colleagues, 1963).

An elevation of arterial P_{CO_2} causes an equal rise of C.S.F., cerebral tissue and jugular venous P_{CO_2}, all of which are approximately equal and about 10 mm Hg higher than the arterial P_{CO_2}.* A rise in C.S.F. P_{CO_2} causes a fall in C.S.F. pH and it was postulated by Mitchell and his colleagues that the

* Arterial/tissue P_{CO_2} difference is a function of cerebral blood flow, being smaller at high perfusion rates.

reduction in pH stimulated the respiratory neurones indirectly through receptors in the chemosensitive area. The theory was especially attractive because the time course of change in C.S.F. pH accorded with the well known delay in the ventilatory response to a change in arterial P_{CO_2} (Lambertsen, 1963; Loeschcke, 1965).

Mediation of the central effect of carbon dioxide on respiration through a change in C.S.F. pH also provided a most satisfactory explanation of the delayed ventilatory adaptation to altitude (Severinghaus and his colleagues, 1963). The changes are as follows.

(1) On acute exposure to an altitude of about 4,000 metres, the hypoxic drive from the peripheral chemoreceptors stimulates ventilation.

(2) As ventilation increases, arterial and C.S.F. P_{CO_2} fall with a concomitant rise in pH. The alkaline shift of C.S.F. reduces the ventilatory drive from the medullary chemoreceptors and this partially offsets the hypoxic drive from the peripheral chemoreceptors. An equilibrium is rapidly attained, at which the P_{CO_2} is typically only 2–5 mm Hg below normal, although the P_{O_2} is about 45 mm Hg. This degree of hypoxaemia is appreciable and, being maximal initially, may explain some of the acute distress of a rapid first ascent.

(3) This state of affairs does not persist since the C.S.F. shows a remarkable ability to restore its pH to the normal sea level value of 7·326. When the C.S.F. pH has been raised by hyperventilation, there is an active transport of unknown ions which results in movement of bicarbonate out of the C.S.F. Thus, within two or three days, the C.S.F. bicarbonate falls by about 5 mEq./l, restoring the pH to within 0·01 units of its original sea level value (Severinghaus and his colleagues, 1963). This restores to a normal level the centrally mediated ventilatory drive. The hypoxic drive of the peripheral chemoreceptors is then unopposed and drives ventilation to its full extent. Typically, at 4,000 metres, arterial P_{CO_2} settles to about 30 mm Hg and P_{O_2} to about 55 mm Hg, with a substantial improvement in saturation compared with the situation immediately after acute exposure to altitude. Voluntary hyperventilation can further increase P_{O_2} and saturation within the limits imposed by an inspired gas P_{O_2} of about 85 mm Hg.

(4) On return to sea level, the 'metabolic acidosis' (low bicarbonate) of the C.S.F. persists for a short time and the subject will overbreathe until the C.S.F. bicarbonate has been restored to the normal value by reversal of the active transport mechanism.

It seems very likely that these changes occur during prolonged periods of artificial ventilation with high minute volumes. This offers one reason why patients subjected to this treatment may demand high minute volumes, and often continue to hyperventilate after resumption of spontaneous breathing. It is not yet established whether there is appreciable loss of C.S.F. bicarbonate during the artificial hyperventilation which is commonly employed during an operation of a few hours' duration.

The stability of the C.S.F. pH is not confined to the circumstances of respiratory alkalosis of altitude but is also found in chronic respiratory acidosis and metabolic acidosis and alkalosis (Mitchell and his colleagues, 1965). Mean values of C.S.F. pH in Mitchell's study did not differ by more than 0·011 units from the normal value (7·326) in spite of mean arterial pH values ranging

from 7·334 to 7·523. The constancy of C.S.F. pH cannot be explained either by diffusion of bicarbonate between blood and C.S.F. or by renal compensation. It appears that there is a very delicate homeostatic mechanism which regulates C.S.F. pH by some presently undefined active transport between blood and C.S.F.

If the bicarbonate of the C.S.F. is altered by pathological factors, the pH is changed and ventilatory disturbances follow. Froman and Crampton-Smith (1966) described three patients who hyperventilated after intracranial haemorrhages. In each case the C.S.F. pH and bicarbonate were persistently below the normal values and it was postulated that this was due to the metabolic breakdown products of blood which contaminated the C.S.F. In a later communication, Froman (1966) reported correction of hyperventilation by intrathecal administration of 3–5 mEq. of bicarbonate.

There are considerable difficulties in determining the precise location of the medullary chemoreceptors in relation to the surface of the medulla and also in defining the relative importance of the factors which govern the pH in their vicinity. Although the ionic environment of the receptors is still not known, it appears that the pH is partly influenced by blood pH, P_{CO_2} and bicarbonate, but primarily by C.S.F. pH, P_{CO_2} and bicarbonate. Ventilation is increased more when the C.S.F. pH is lowered by reducing its bicarbonate than by raising its P_{CO_2}. This is because attempts to alter the C.S.F. P_{CO_2} by means of perfusion with mock C.S.F. are frustrated by rapid equilibration of carbon dioxide between perfusate and tissue (Mitchell and his colleagues, 1963; Pappenheimer and his colleagues, 1965). Abnormal levels of bicarbonate concentration of perfusate are, however, little altered by contact with tissue and the effect of changes in C.S.F. pH may be studied by this means.

In a study of cats with denervated peripheral chemoreceptors, Mitchell and his colleagues (1963) found that, when acid–base variables of arterial blood were held constant, acidifying mock C.S.F. by reduction of bicarbonate resulted in a stimulation of ventilation which was about 60 per cent of the level obtainable by inhalation of the corresponding concentration of carbon dioxide. This result may be compared with the findings of Pappenheimer and his colleagues (1965) who, working with anaesthetized goats, found some 60 per cent of the normal ventilatory response to inhaled carbon dioxide still remained when the pH of the C.S.F. was held constant by perfusion with mock C.S.F. of appropriate bicarbonate concentration. The goats had functioning peripheral chemoreceptors which may explain why less of the total response was found to reside in the C.S.F. receptors than in Mitchell's experiments. There is also the important consideration of species difference since the relative importance of peripheral and central chemoreceptors is known to differ markedly between certain species. The rather small differences between the results of Mitchell and Pappenheimer do not conflict with the general conclusion that the medullary response to carbon dioxide can be expressed as a linear function of the hydrogen ion concentration of the cerebral extracellular fluid (E.C.F.) somewhere close beneath the surface of the ventral aspect of the medulla.

It is not yet clear what is the relative importance of the factors governing pH and bicarbonate concentration of the E.C.F. in this area. Probably the most important factor is the C.S.F. bicarbonate, since it appears that the C.S.F.

is able to penetrate into the spaces between the glial cells without crossing any barrier to the free diffusion of ions. Other possible factors are the blood bicarbonate and the extent of active transport of ions across the blood–brain barrier which is interposed between the capillaries and the chemoreceptor areas.

It is probably deceptive to imagine clear-cut models of the receptors and their relationship to blood vessels and bulk C.S.F. The receptors presumably occupy an area of finite thickness and some of them must be closer to the surface than others. Furthermore, the C.S.F. does not have the same composition in all areas. The brain weeps E.C.F. out into the C.S.F. and, beneath the pia, factors such as blood bicarbonate, intracellular buffers and active transport mechanisms must clearly be important. One cannot expect to control the composition of the C.S.F. in these areas by the experimental perfusion of the cisterna.

It is unlikely that the last word has yet been written on this subject, and in a later paper Fencl, Miller and Pappenheimer (1966) reached the following conclusions.

(1) In the resting state, without hypoxic drive, the log of the pulmonary ventilation is directly proportional to the hydrogen ion concentration of the C.S.F., which they considered equal to the concentration in the interstitial fluid in contact with respiratory neurones.

(2) This relationship was unaltered by large changes in bicarbonate concentration of blood or C.S.F.

(3) Respiratory adaptations to chronic acidosis or alkalosis are accounted for quantitatively by observed changes in ion transport between blood and C.S.F.

(4) Concentration gradients of bicarbonate between blood and C.S.F. are maintained by an ion pump at the blood–brain barrier. Brain interstitial fluid and C.S.F. are in diffusion equilibrium with one another and there are no significant bicarbonate, chloride or hydrogen ion concentration gradients between them.

It should also be noted that Cozine and Ngai (1967), working with unanaesthetized (decerebrate) cats with denervated peripheral chemoreceptors, found that apnoea did not follow the application of local anaesthetics to the central chemoreceptor areas on the antero-lateral surface of the medulla, although the minute volume of ventilation was reduced. In anaesthetized cats apnoea was obtained. These studies suggested that the influence of the central chemoreceptors was at least shared with other zones, possibly more deeply placed.

There has been a great deal of recent interest in the central response to carbon dioxide. There is now very little doubt of the great importance of the role of the C.S.F. Readers are referred to the reviews of Kellogg (1964) and Mitchell (1966), and the symposium on *Cerebrospinal Fluid and the Regulation of Ventilation* edited by Brooks, Kao and Lloyd (1965).

Quantitative Aspects of the Chemical Control of Breathing

Integration of the chemical factors controlling breathing has been a recurrent and challenging problem of respiratory physiology. The first major attempt to relate ventilation to multiple changes of blood gas tensions and pH was made by Gray (1950) whose multiple factor theory stated that the resultant ventilation depended on the algebraic sum of the individual factors caused by changes

of P_{CO_2}, P_{O_2}, pH, etc. Hypoxia and hypercapnia were, for example, simply additive in their effect. There is now general agreement that there is a rather more complicated relationship which is best illustrated by consideration of the P_{CO_2}/ventilation response curve.

The P_{CO_2}*/ventilation response curve* is a most valuable approach to the study of factors influencing the chemical control of breathing, because it takes carbon dioxide into full account and carbon dioxide is the most important factor of all. A somewhat similar approach is now being used for the study of various factors on cardiac output and cerebral blood flow, two quantities which, like ventilation, are strongly influenced by P_{CO_2}.

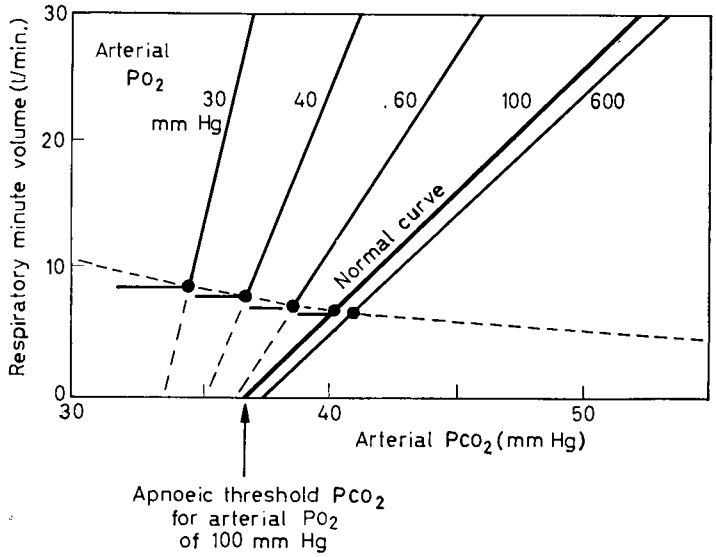


Figure 7. Ventilatory response to changes in arterial P_{CO_2} *at various levels of arterial* P_{O_2}. *The dotted curve shows the effect of changes of ventilation on arterial* P_{CO_2} *when the inspired carbon dioxide concentration is zero and carbon dioxide output is constant and basal. From this starting line are shown a series of five* P_{CO_2}*/ventilation response curves, corresponding to different values of arterial* P_{O_2}. *Elevation of arterial* P_{O_2} *above the normal value has little effect, but reduction of* P_{O_2} *causes displacement of curves to the left and a steepening of the slopes. (The values used in the construction of this graph do not relate to any one particular study but are representative of findings reported by many different laboratories. Individual studies often show surprisingly large differences, possibly explained in part by rebreathing caused by the use of large valve boxes and other breathing apparatus)*

Figure 7 shows a family of normal P_{CO_2}/ventilation response curves at various levels of arterial P_{O_2}. According to the normal convention, the variable on the *X* axis (P_{CO_2}) is considered to be driving the variable on the *Y* axis (ventilation). However, it is also possible for changes in ventilation to alter the P_{CO_2} and this relationship receives detailed consideration in Chapter 6. According to the usual convention, such a relationship should be drawn with ventilation on the *X* axis and P_{CO_2} on the *Y* axis (as in *Figure 48*), but for convenience the relationship is also included in *Figure 7* as a dotted curve which is a segment of a rectangular hyperbola. As ventilation changes, for example in response to

hypoxic drive, the arterial P_{CO_2} changes according to this relationship and the point representing the patient migrates along the dotted curve to the left. All points along this curve represent states in which there is no carbon dioxide in the inspired gas and it is also assumed that the carbon dioxide output is constant and basal at all points.

If, from any starting point along the dotted curve, the subject is given a carbon dioxide mixture to inhale, the ventilation will increase and when equilibrium is attained (after about five minutes), the new values for arterial P_{CO_2} and ventilation will lie along one of the family of straight lines represented by the five lines in *Figure 7* passing upwards and to the right. These are P_{CO_2} ventilation response curves, and the following points should be noticed.

(1) They approximate to straight lines in the range likely to be encountered in normal anaesthetic practice.

(2) The normal curve corresponding to an arterial P_{O_2} of 100 mm Hg has a mean slope of 2 l./min./mm Hg P_{CO_2}. Individual values for different subjects show very wide scatter (Lambertsen, 1960). The slope is often designated by the symbol 's'.

(3) Elevation of arterial P_{O_2} has little effect on the curve.

(4) Depression of arterial P_{O_2} causes displacement of the curve to the left and a steepening of the slope. The curves form a fan which radiates from a point on or slightly below the *X* axis (Lloyd, Jukes and Cunningham, 1958; Nielsen and Smith, 1951).

(5) Extensions to the response curves are shown in *Figure 7* below the dotted curve which defines the effect of ventilation on P_{CO_2}. These extensions are of two types. The first is an extrapolation of the curve to intersect the *X* axis (zero ventilation) at a P_{CO_2} known as the apnoeic threshold P_{CO_2}. If P_{CO_2} is depressed below this point, apnoea commonly results, particularly in the anaesthetized patient, and the extension of the curve is a graphical representation of Haldane's post-hyperventilation apnoea. The second type of extension is horizontal and to the left, like a golf club, representing the response of the subject who continues to breathe regardless of the fact that his P_{CO_2} has been reduced. This has been discussed above in relation to wakefulness, but persistent breathing is much more likely to occur in hypoxia.

(6) The slope of the P_{CO_2}/ventilation response curve (*s*) is a measure of the response of the entire ventilation mechanism to the stimulus of carbon dioxide. It may be influenced by many factors apart from the sensitivity of the central chemoreceptors, and these are summarized in *Figure 52* according to the site of interference with the response. Diffuse airway obstruction is a most important factor (Clark, Clarke and Hughes, 1966).

The effect of metabolic acidosis is to displace the whole fan of curves to the left while metabolic alkalosis displaces to the right. Mathematical relationships demonstrating the interaction of P_{CO_2}, P_{O_2} and metabolic acid–base balance have been reviewed by Lloyd and Cunningham (1963). Denervation of peripheral chemoreceptors somewhat reduces the effect of P_{CO_2}, abolishes the effect of moderate degrees of metabolic acid–base imbalance and reverses the effect of hypoxia (Mitchell, 1966).

If P_{CO_2} is raised above about 80 mm Hg, the linear relationship between P_{CO_2} and ventilation is lost. As P_{CO_2} is raised a point of maximal ventilatory

stimulation is reached (probably within the range 100–200 mm Hg), and thereafter the ventilatory stimulation is reduced until, at very high P_{CO_2}, the ventilation is actually depressed below control value and finally apnoea results, at least in the dog and almost certainly in man as well. It does not appear to be possible to arrest breathing in the cat by this means in spite of elevation of P_{CO_2} to more than 500 mm Hg (Hornbein, personal communication; Raymond and Standaert, 1967). The full P_{CO_2}/ventilation curve is thus something like a parabola rising from the apnoeic threshold P_{CO_2} (about 36 mm Hg), reaching a peak at about 150 mm Hg and returning to base line at a P_{CO_2} of the order of 300 mm Hg. Few examples of complete P_{CO_2}/ventilation response curves throughout the full range have been published and ethical considerations preclude such studies in man. The general form of the curve is, however, probably not unlike the thick curve in *Figure 8* which is derived from a study of dogs

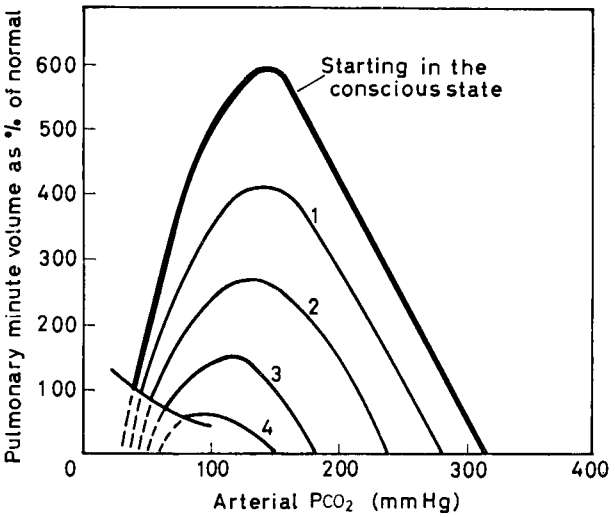


Figure 8. The probable form of complete P_{CO_2}*/ventilation response curves carried through to the point of apnoea. Such curves have never been obtained in man and their form is inferred from work on dogs* (see *text*). *The heavy curve is the probable form which would be obtained starting in conscious man without additional anaesthesia other than carbon dioxide itself. Curves 1–4 show the likely form which would be obtained in various depths of anaesthesia. Curve 4 is probably similar to that which would be obtained with 2–2·5 per cent halothane (end-expiratory concentration). The broken lines show extrapolation back to apnoeic threshold* P_{CO_2}. *Rather similar curves have recently been produced for the cat anaesthetized with dial-urethane (Raymond and Standaert, 1967). Apnoea was not obtained and the lowest ventilation was about 50 per cent of control at* P_{CO_2} *of about 400 mm Hg*

(Graham, Hill and Nunn, 1960). The other curves in *Figure 8* show the progressive modifications occurring with anaesthesia of graded depth (*see* below). The effects of changes in P_{CO_2} on ventilation are also discussed in Chapter 11 (page 316).

The response curves above have been described in relation to arterial P_{CO_2}.

It seems likely that internal jugular or C.S.F. P_{CO_2} might be more appropriate and these have been shown to give particularly straight curves. Alternatively, in the clinical environment it may be more convenient to use end-expiratory P_{CO_2} as a substitute for arterial P_{CO_2} although this is not satisfactory in conditions such as chronic bronchitis, which are associated with a marked arterial/end-expiratory P_{CO_2} difference (*see* Chapter 11). Methods of obtaining response curves are summarized at the end of this chapter.

Effect of drugs and anaesthetics.—Displacement of the P_{CO_2}/ventilation response curve is probably the best way of defining the 'depressant' or 'stimulant' effect of a drug on ventilation. Determination of the effect of a drug on the response curve is far more informative than simple measurements of ventilation or P_{CO_2}, without regard to the interaction of these two variables. For example, decrease in ventilation may simply reflect a decrease in metabolic rate without any true depression of breathing.

Although there are minor differences with individual drugs, those which are stimulant to ventilation cause a displacement to the left with a steepening of slope. The effect is thus broadly similar to that of hypoxia (*Figure 7*) and it is therefore important that measurements of the effect of a drug be made when hypoxic drive is minimal as, for example, when the arterial P_{O_2} is in excess of say 150 mm Hg. Aminophylline (6 mg./kg.) causes a displacement to the left and change of slope (Stroud and his colleagues, 1955), which is roughly similar to the response produced by reduction of arterial P_{O_2} to 50 mm Hg (*Figure 7*) although the effect differs from hypoxic drive in that it is not dependent upon the peripheral chemoreceptors. Other drugs which have been shown to have similar effects include salicylates and doxapram (*see* reviews by Lambertsen, 1964, and Severinghaus and Larson, 1965). The narcotic antagonists (e.g. nalorphine and levallorphan) given alone are not stimulant to respiration and, in fact, displace the response curve in the same manner as the opiates themselves. Nevertheless, they are able to reverse the effects of opiates themselves on the P_{CO_2}/ventilation response curve (Thomas and Tenney, 1955). Finally, it should be noted that any non-specific arousal state may be associated with a displacement of the curve to the left. This may occur with anxiety, fear or with very light levels of ether anaesthesia (Cobb, Converse and Landmesser, 1958), or nitrous oxide anaesthesia (Eckenhoff and Helrich, 1958).

Depressant drugs displace the P_{CO_2}/ventilation response curve to the right. In the case of opiates, there is usually little change in slope but, with general anaesthetics, the displacement is accompanied by an appreciable flattening of the curve. The degree of this change is a function of the dose of the depressant agent and itself may be represented on a dose/response curve. Graded effects may be typically produced by halothane, and *Figure 9* has been constructed from the data of Munson and his colleagues (1966). They demonstrated qualitatively similar changes with fluroxene and cyclopropane. Essential points to be noted in *Figure 9* are as follows.

(1) Starting points are displaced to the right by deepening anaesthesia along the ventilation/P_{CO_2} relationship curve. This indicates a rising P_{CO_2} with a falling ventilation.

(2) When challenged with exogenous (or rebreathed endogenous) carbon dioxide, the slope of the P_{CO_2}/ventilation curve is progressively diminished as

the anaesthesia is deepened. Finally, the curve becomes flat and there is then no ventilatory response to P_{CO_2}. Beyond this point a negative slope may be found which would mean that an elevation of P_{CO_2} would depress breathing.

(3) The intersection of the extrapolation of the curve on the *X* axis moves to the right with the curve. The apnoeic threshold P_{CO_2} is thus raised with deepening anaesthesia.

Full P_{CO_2}/ventilation response curves throughout the range of P_{CO_2} have very seldom been studied in the anaesthetized state. Data of Graham, Hill and Nunn (1960) and of Merkel, Eger and Severinghaus (quoted in Severinghaus and Larson, 1965) suggest that curves would have the general form shown in *Figure 8.* Actual values relevant to man are not known and the numbers on the curves simply indicate arbitrary depths of anaesthesia. However, curve 4 is probably similar to that which would be obtained with 2–2·5 per cent halothane (end-expiratory concentration).

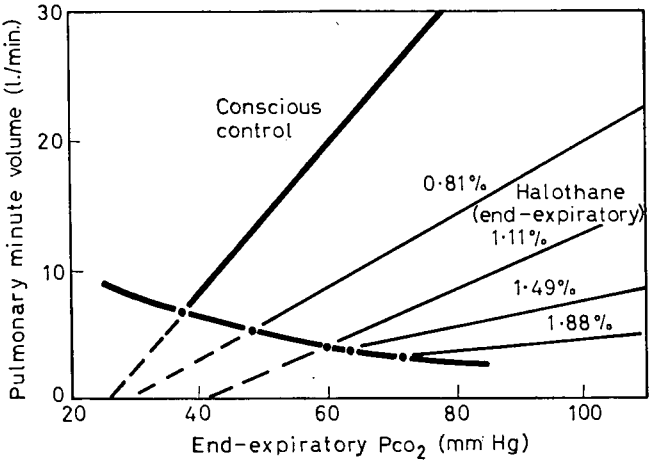


Figure 9. Displacement of P_{CO_2}*/ventilation response curve with different end-expiratory concentrations of halothane. The curve sloping down to the right indicates the pathway of* P_{CO_2} *and ventilation change resulting from depression without the challenge of exogenous carbon dioxide. The dotted lines indicate extrapolation to apnoeic threshold* P_{CO_2}*. The curves have been constructed from the data of Munson and his colleagues (1966). It will be noted that their curve for the conscious state differs from the normal shown in Figure 7. There is, in fact, wide divergence in the values for slope reported by different workers. A rather similar set of curves has been obtained for methoxyflurane by Dunbar, Ovassapian and Smith (1967) except that these workers did not observe the same degree of displacement to the right of the initial* P_{CO_2} *at different depths of anaesthesia before the carbon dioxide challenge. Roughly similar changes in slope were reported for equipotent concentrations of the two agents*

In the case of the inhalational anaesthetic agents it would be useful to know whether there are significant differences in their respiratory depressant effects, considered in relation to their anaesthetic effects. This is a difficult problem and an important first step has been taken in establishing iso-anaesthetic concentrations. Saidman and Eger (1964) have made an arbitrary but highly

practical decision to use lack of motor response to skin incision as the indication of 'anaesthesia', for which any one of a dozen different end-points might have been chosen. The minimal anaesthetic concentration (MAC) of an anaesthetic is defined as the minimal end-expiratory concentration which will prevent gross movement following skin incision. Dosage of anaesthetic agents may then be expressed as MAC 1, MAC 2, MAC 3, etc. For example, the MAC for halothane is 0·7 per cent for man: MAC 2 would then be 1·4 per cent; MAC 3, 2·1 per cent; and so on. The same MAC number should produce equal depths of anaesthesia for all anaesthetic agents and the problem of relative respiratory depression then resolves to measurement of the degree of ventilatory depression at the same MAC number for different agents. This is a laborious undertaking but Munson and his colleagues (1966) have produced evidence to show that halothane produces 50 per cent depression of slope of P_{CO_2}/ventilation response curve at MAC 1, while MAC 2·5 of cyclopropane is required for a similar effect. Ether spares ventilation to an even greater extent.

Ventilatory effects of inhalational anaesthetic agents are unlikely to be simply a matter of 'central depression of respiratory neurones'. Ether and cyclopropane are known to raise the level of circulating catecholamines, and noradrenalin is known to increase the slope of the P_{CO_2}/ventilation response curve (Cunningham and his colleagues, 1963; Dejours, 1966). Ether, furthermore, has a curare-like effect upon neuromuscular transmission in high dosage and may also stimulate ventilation as a result of the development of an arousal state in response to its irritant vapour. Finally, different agents vary greatly in the degree to which they sensitize the pulmonary stretch receptors (*see* page 37), although the relevance of this is not clear.

It has not yet been established how far surgical stimulus may restore a P_{CO_2}/ventilation response curve displaced by a general anaesthetic. There is no doubt that ventilation is stimulated by painful stimuli even during fairly deep anaesthesia and it seems likely that the slope of the response curve would also be steepened. The ventilatory state of the patient should thus be regarded as the result of the interplay between anaesthetic and stimulus.

Barbiturates have little effect upon ventilation in sedative or light 'sleep dosage'. However, larger doses which are sufficient to abolish the motor response to skin incisions are probably associated with similar changes to those shown for halothane in *Figure 9* (Bellville and Seed, 1960). Moyer and Beecher (1942) found the ventilatory response to carbon dioxide was progressively diminished with deepening anaesthesia induced with either thiopentone or hexobarbitone. In very deep anaesthesia, total loss of response to carbon dioxide (12 per cent) was obtained when the response to hypoxia was still present. The depressant effect of barbiturates is primarily on tidal volume and the respiratory frequency may be actually increased.

Opiates are well known to depress ventilation and, at high dosage, reduction in respiratory frequency is particularly marked. In normal clinical dosage, both tidal volume and frequency are reduced with an increase of resting P_{CO_2} of about 3 mm Hg after 10 mg. of morphine and 4 mm Hg after 150 mg. of pethidine (Loeschcke and his colleagues, 1953). In low dosage (up to 10 mg. morphine) the P_{CO_2}/ventilation response curve is displaced to the right with little decrease in slope. However, at higher dosage a well marked reduction in slope becomes apparent, with the general effect being again broadly similar to

the family of curves shown for halothane in *Figure 9*. Restoration of the slope and displacement of the P_{CO_2}/ventilation response curve may be obtained either by the narcotic antagonists (e.g. nalorphine or levellorphan) or by the use of non-specific analeptics. Opiates in high dosage will usually produce apnoea before consciousness is lost (*see* page 21 under 'Ondine's curse').

Sleep causes slight displacement of the P_{CO_2}/ventilation response curve to the right with the degree depending upon the depth of sleep, estimates of P_{CO_2} elevation ranging from zero to 9 mm Hg. Response to hypoxia is unimpaired by sleep. This is fortunate since continued hyperventilation is essential for survival at altitude.

The quantitative effect of drugs upon ventilation has received a great deal of attention in recent years and the reader is referred to reviews by Bellville and Seed (1960), Lambertsen (1964), Severinghaus and Larson (1965) and Ngai (1967).

REFLEX CONTROL OF BREATHING

Certain reflexes have already been discussed. Firstly, there are the reflex arcs with afferent limbs arising in the peripheral chemoreceptors, which have been considered under the heading of chemical control (page 24). Secondly, there is the ventilatory response to pain, which has already been considered in relation to the arousal state which is caused by pain. There remain, however, a number of neural control mechanisms which are more appropriately considered specifically under the heading of reflexes.

Baroreceptor Reflexes

The most important groups of arterial baroreceptors are in the carotid sinus and around the aortic arch. These receptors are primarily concerned with regulation of the circulation but a decrease in pressure produces hyperventilation, while a rise in pressure causes respiratory depression and, in the limit, apnoea (Heymans and Neil, 1958). This is the likely cause of apnoea produced by a massive dose of catecholamines. Baroreceptors are sensitized by diethyl ether (Robertson, Swan and Whitteridge, 1956), cyclopropane (Price and Widdicombe, 1962) and halothane (Biscoe and Millar, 1964). This effect has been considered mainly in relation to circulatory control during anaesthesia and the respiratory implications are not yet established.

Pulmonary Stretch Reflexes

There are a large number of different types of receptors in the lungs (*see* review by Widdicombe, 1964) sensitive to inflation, deflation, mechanical and chemical stimulation. Afferents from all are conducted by the vagus, although some fibres may be additionally carried in the sympathetic. The stretch receptors of the small air passages and alveoli are of great interest in the control of breathing, and have seldom been far from the centre of the stage since the associated inflation and deflation reflexes were described by Hering (1868) and Breuer (1868).

It is perhaps appropriate at this point to explain the relationship between these two authors who produced two papers of identical title in the same journal from the same department in the same year. Breur was a clinical

assistant and apparently the work was at his own instigation. However, Hering who was the head of the department, published his assistant's work under his own name, in accord with the custom of the time. Breuer's participation was mentioned in Hering's paper but he was not a co-author. Later in the same year, Breuer was permitted to publish a much fuller account of his work under his own name. Rahn has made the admirable suggestion that Breuer's primary role should be recognized by renaming the reflexes the Breuer–Hering inflation and deflation reflexes (Perkins, 1964).

The inflation reflex consists of inhibition of inspiration in response to a sustained inflation of the lung. An exactly similar effect may be obtained by obstructing expiration so that an inspiration is retained in the lungs. It has been explained above that, at least in animals, rhythmic breathing may be governed by a negative feedback loop from the pulmonary stretch receptors via the vagus and the expiratory neurones of the medulla (*Figure 4*). It has also been shown in cats that the common inhalational anaesthetics, particularly trichloroethylene, sensitize the pulmonary stretch receptors and so would be expected to cause an enhancement of the inflation reflex (Whitteridge and Bülbring, 1944). This is in contrast to Head's conclusion (1889) that ether and chloroform paralysed vagal endings. Whitteridge and Bülbring concluded that the sensitization of the stretch receptors was largely responsible for the shallow breathing seen in trichloroethylene anaesthesia, but observed that trichloroethylene and cyclopropane could have opposite effects on respiratory rate while both agents were causing sensitization of stretch receptors. They further state that these agents 'must exert another action on a second set of pulmonary endings, or on the respiratory centre, or on extra-pulmonary endings'. Ngai, Katz and Farhie (1965) showed that, in midcollicular decerebrate cats, the marked tachypnoea produced by trichloroethylene was not prevented by bilateral vagotomy and carotid denervation. It would, therefore, seem that there is no solid foundation for the oft repeated view that trichloroethylene causes tachypnoea as a result of sensitization of the pulmonary stretch receptors.

Generations of medical students have been brought up with the unquestioned belief in the role of the Breuer–Hering reflex in man. This appears to have resulted from an unwarranted extrapolation of animal findings to man without regard for species difference. Widdicombe (1961) compared the strength of the inflation reflex in eight species and found the reflex weakest in man. His method for the human subjects was to weight the bell of a spirometer connected to spontaneously breathing, lightly anaesthetized patients. Inflation to transpulmonary pressures of 7–11 cm H_2O did not produce apnoea lasting longer than 10 seconds, in contrast to the rabbit in which increases of transpulmonary pressure of 5–7 cm H_2O on two occasions killed rabbits by asphyxia during the prolonged apnoea that followed. Widdicombe's traces show some reduction of tidal volume in the human subjects but the movement of a weighted spirometer bell at an increased lung volume is a very indirect measure of inspiratory effort.

The view that the Breuer–Hering inflation reflex is weak if not absent in man is supported by the response of anaesthetized patients to expiratory resistance. This is discussed at some length on pages 102–104, but the essential feature is that the patients respond by an increased inspiratory force until the

lung volume is increased to the point at which the increased elastic recoil is sufficient to overcome the expiratory resistance (Campbell, Howell and Peckett, 1957). With high resistance the lung volume increases in a series of steps, with ever-increasing end-inspiratory pressure associated with increasing inspiratory effort (Nunn and Ezi-Ashi, 1961). This remarkable series of changes, which can be confirmed by any anaesthetist, provides clear evidence that lung inflation in the anaesthetized human subject augments the force of contraction of the inspiratory muscles in complete contrast to what might be expected if the effect of the Breuer–Hering inflation reflex were dominant. This provides no proof of the absence of the inflation reflex, but shows that its effect, if present, is overcome by other mechanisms producing an opposite effect. The role of the spindles has been discussed earlier in this chapter (page 22) and on page 102.

The deflation reflex consists of an augmentation of inspiration in response to deflation of the lung. This has received little attention in relation to anaesthetized man, but Widdicombe (1961) concluded that it was weak or absent in anaesthetized humans, but strong in other animals which he studied.

The inflation and deflation reflexes were the basis of the Selbststeuerung (self-steering) hypothesis advanced by Hering and Breuer in 1868. This concept has played a major role in theories of the control of breathing and, even though its role in man may be questionable, it remains a classical example of a physiological auto-regulating mechanism.

Head's paradoxical reflex.—Head (1889), working in Professor Hering's laboratory, described a reversal of the inflation reflex, which could be elicited during partial block of the vagus nerves in the course of thawing after cold block. Under these conditions, inflation of the lung of the rabbit causes strong maintained contractions of an isolated diaphragmatic slip (Curve VI, Plate I in Head, 1889). Many authors have reported that, with normal vagal conduction, sudden inflation of the lungs of many species may cause a transient inspiratory effort before the onset of apnoea due to the inflation reflex (Widdicombe, 1961). A similar response may also be elicited in newborn infants (Cross and his colleagues, 1960), but it has not been established whether this 'gasp reflex' is analogous to Head's paradoxical reflex. Widdicombe was unable to detect the response in patients anaesthetized with thiopentone but many anaesthetists will know that the response may be elicited in patients who receive opiates (particularly pethidine) in dosage sufficient to reduce the respiratory frequency to less than about five breaths per minute. Transient compression of the reservoir bag often causes an immediate deep gasping type of inspiration and the respiratory frequency may be conveniently raised by manual triggering. This response does not appear to have been studied in detail in anaesthetized man. There is a possible relationship between the reflex and the mechanism of sighing which may be considered a normal feature of breathing (Bendixen, Smith and Mead, 1964).

The Cough Reflex

The cough reflex may be elicited by mechanical stimuli arising in the larynx, trachea, carina and main bronchi. Chemical stimuli are effective at a lower

level (Widdicombe, 1964). The central co-ordination of the motor activity is little understood and the response is complex:

(1) an inspiration, which takes into the lungs a volume of air sufficient for the expiratory activity;
(2) build-up of pressure in the lungs by contraction of expiratory muscles against a closed glottis;
(3) forceful expiration through narrowed airways with high *linear* velocity of gas flow which sweeps irritant material up towards the pharynx.

The mechanism of the narrowing of the airways is discussed in Chapter 4 (page 91). Transient changes of pressure up to 300 mm Hg may occur in the thorax, arterial blood and the C.S.F. during the act of coughing (Sharpey-Schafer, 1953).

The section above has not exhausted the large number of reflexes which appear to influence control of breathing. Apnoea may be caused by non-specific stimulation of many parts of the autonomic system as, for example, by a blow in the upper abdomen. Breathing is also profoundly modified by sneezing and swallowing. Important reflexes arise from joints and tendons, and respiration may be stimulated by movements of the limbs of anaesthetized animals (*see* page 43). There is also the question of the afferents arising from the chest wall which influence breath holding and the sense of adequacy of ventilation experienced by a paralysed but conscious patient during artificial ventilation (*see* page 43). For a more extensive review of the reflexes relevant to breathing, the reader is referred to Widdicombe (1964).

BREATH HOLDING

The integration of factors governing the duration of breath holding is a fascinating problem which has been the subject of a great deal of research. Induced apnoea is an important feature of practical anaesthesia and its consequences are discussed in various places in this book. This section is restricted to a consideration of the factors influencing the duration of voluntary breath holding.

Blood-gas Tensions

When the breath is held after air breathing, the arterial P_{CO_2} is remarkably constant at the breaking point and values are normally close to 50 mm Hg. This does not mean that P_{CO_2} is the sole or dominant factor and concomitant hypoxia is probably more important. Oxygen breathing greatly delays the onset of hypoxia during breath holding and times may be considerably extended with consequent elevation of P_{CO_2} at the breaking point. The relationship between P_{CO_2} and P_{O_2} at breaking point, after varying degrees of pre-oxygenation, is shown in *Figure 10*. Guz and his colleagues (1966b) observed marked prolongation of breath holding after vagal and glosso-pharyngeal block but advanced cogent reasons for believing that this was not due primarily to block of the chemoreceptors. Oxygen breathing would also prevent the chemoreceptor drive but this did not prolong breath holding to the same extent as the nerve block.

Lung Volume

Breath-holding time is directly proportional to the lung volume at the onset of breath holding, other factors being constant. In part this is related to the onset of hypoxia, since an appreciable part of the total body oxygen store is in the alveolar gas (page 357).

It seems likely that the effect of lung volume and its change is mediated by afferents arising from both chest wall and the lung itself. Following the experiments of Guz mentioned above, Campbell and his colleagues (1967)

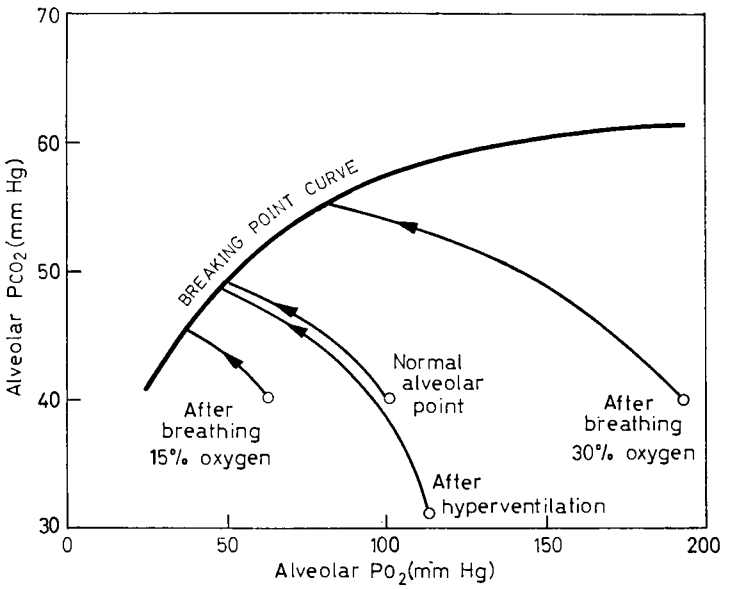


Figure 10. The 'breaking point' curve defines the coexisting values of alveolar P_{O_2} *and* P_{CO_2}*, at the breaking point of breath holding, starting from various states. The normal alveolar point is shown* (P_{O_2}, *100 mm Hg;* P_{CO_2}, *40 mm Hg*) *and the curved arrow shows the changes in alveolar gas tensions which occur during breath holding. Starting points are displaced to the right by preliminary breathing of oxygen-enriched gas mixtures, and to the left by breathing mixtures containing less than 21 per cent oxygen. Hyperventilation displaces the point representing the alveolar gas tensions to the right and downwards. The length of the arrows from starting point to the 'breaking point' curve gives an approximate indication of the possible duration of breath holding. This can clearly be prolonged by oxygen breathing or by hyperventilation, maximal prolongation occurring after hyperventilation with 100 per cent oxygen. (Data for construction of the 'breaking point' curve have been taken from Ferris and his colleagues (1946) and Otis, Rahn and Fenn (1948))*

have reported an equally impressive prolongation of breath-holding time following curarization of conscious subjects. Their explanation is that the distress leading to the termination of breath holding is caused by *frustration* of reflex motor response from pulmonary afferents blocked in the experiment of Guz. The motor response consists of involuntary contractions of the respiratory muscles, including the diaphragm, which have been found to increase progressively during breath holding (Agostini, 1963). These contractions *should* produce movement which would be detected by joint and tendon receptors in

the chest wall. However, in breath holding, movement is prevented by closure of the glottis and there is an 'inappropriateness' between the muscle activity and the (lack of) movement which results. This accords with the idea of 'inappropriateness' advanced as a general hypothesis to explain the sensation of dyspnoea (Campbell and Howell, 1963). The discomfort of breath holding would then be regarded as an extreme form of inappropriateness, differing only quantitatively from that of mechanically hindered breathing.

According to this hypothesis, the discomfort of breathing could be alleviated at the following points:

(1) block of pulmonary afferents causing the involuntary contraction of the respiratory muscles (Guz and his colleagues, 1966b);

(2) prevention of the involuntary contraction of the respiratory muscles (Campbell and his colleagues, 1967);

(3) prevention of the *frustration* of the contractions of the respiratory muscles by permitting chest movement without alleviating the changes in alveolar P_{CO_2} and P_{O_2}.

Prolongation of breath-holding time by prevention of frustration of contraction of respiratory muscles may be convincingly demonstrated by Fowler's experiment (1954). After normal air breathing, the breath is held until breaking point, which is usually about 60 seconds. If the expirate is then taken in a bag and immediately re-inhaled, there is a marked sense of relief although it may be shown that the rise of P_{CO_2} and fall of P_{O_2} is quite uninfluenced by the manœuvre.

Extreme durations of breath holding may be attained after hyperventilation and pre-oxygenation. Times of 14 minutes have been reached and the limiting factor is then reduction of lung volume to residual volume as oxygen is removed from the alveolar gas by the circulating pulmonary blood (Klocke and Rahn, 1959).

EXERCISE

The problem of the mechanisms concerned in the production of the hyperventilation which accompanies exercise is perhaps not relevant to the anaesthetist. It is, however, an interesting subject and the control of breathing can hardly be considered without mention of the difficulties which surround the problem of exercise.

Contrary to earlier ideas, it is now clear that, except in very heavy exercise, the primary factor cannot be changes in arterial P_{CO_2} and P_{O_2}, because the former is frequently below and the latter above the normal values during light and moderate exercise. Even in the post-operative state, Bay, Nunn and Prys-Roberts (1968) were able to show that pulmonary ventilation was much greater in shivering patients, although the mean values for arterial blood-gas tensions were almost identical in shivering and non-shivering patients. It is also true that the hyperventilation commences within the first one or two seconds of exercise and *anticipates* the metabolic demand rather than reacts in response to it.

The early onset of hyperventilation in exercise may be due in part to secretion of catecholamines and mental factors but reflex factors are quantitatively

more important, since instant hyperventilation occurs with electrically induced exercise in the anaesthetized animal (Kao, 1963). Chordotomy and crossed circulation experiments have shown that only neurogenic stimuli can account for the early onset of hyperventilation and the abrupt decrease in ventilation at the end of the exercise. Humoral factors may be relevant during steady state exercise and during the repayment of the oxygen debt (Dejours, 1964).

ARTIFICIAL VENTILATION

During artificial ventilation of conscious patients with partial or total respiratory failure, the effector responses are in the hands of the medical attendants while afferent stimuli may still be perceived by the patients. Although patients usually complain if their arterial P_{CO_2} rises above the normal value, they are seldom satisfied by a normal value and frequently demand a ventilation which reduces the P_{CO_2} within the range 25–35 mm Hg. It appears, however, that in most cases what they are seeking is a satisfying movement of the chest wall rather than hypocapnia. Thus, if apparatus dead space is added to the airway or if carbon dioxide is added to the inspired gas, the arterial P_{CO_2} may be elevated without eliciting any complaint until the P_{CO_2} exceeds the normal value (about 40 mm Hg).

Prolonged hyperventilation with hypocapnia probably resets the C.S.F. pH to normal by active bicarbonate transport (page 28), requiring the patient to continue hyperventilation during the return to spontaneous breathing. However, it is also possible for a patient to become acclimatized to a high minute volume without hypocapnia. During studies with added apparatus dead space, Smith, Spalding and Watson (1962) showed that, in the transition from artificial ventilation to spontaneous respiration, patients would endeavour to maintain the original high minute volume without regard for the P_{CO_2} which, without the added apparatus dead space, would frequently fall substantially below the level maintained during artificial ventilation. In this state the patients appeared to be driven by a volume requirement and did not respond to added carbon dioxide until their P_{CO_2} was raised above the level maintained during artificial ventilation.

OUTLINE OF CLINICAL METHODS OF ASSESSMENT OF FACTORS IN CONTROL OF BREATHING

At the time of writing, it is unusual to make measurements of factors in the control of breathing other than in the course of research. For clinical purposes, ventilatory failure is detected by measurement of P_{CO_2} but, by itself, this measurement does not give any specific information on any factors in the control of breathing. However, if the measurement of P_{CO_2} is combined with simultaneous measurement of ventilation, over a range of values of P_{CO_2}, this gives a useful indication of the ability of the ventilatory mechanism to respond to elevation of P_{CO_2}, although the response may be modified by mechanical factors such as resistance to breathing.

The basis of the methods for determination of P_{CO_2}/ventilation response curves consists of measurement of minute volume by any convenient method (*see* Chapter 6, page 171) with various concentrations of carbon dioxide in the

inspired gas, usually ranging from zero to 5 per cent. Ventilation is usually reasonably stable within about five minutes and simultaneous measurements of ventilation and P_{CO_2} are made at that time. P_{CO_2} may be measured in arterial blood or end-expiratory gas and suitable methods are outlined at the end of Chapter 11 (page 323).

Response curves may be determined at different values of P_{O_2} but the study of a fan of curves, as in *Figure 7*, becomes excessively time consuming. Results are obtained more rapidly by keeping ventilation approximately constant while two factors are changed in opposite directions (e.g. P_{CO_2} might be raised while P_{O_2} is also raised: the P_{CO_2} stimulus would thus increase while the hypoxic drive diminished) (Lloyd and Cunningham, 1963).

In clinical situations it may be useful to avoid the necessity of supplying carbon dioxide gas mixtures. This may be done by measuring ventilation and P_{CO_2} with the patient breathing through different volumes of apparatus dead space. As the apparatus dead space is increased, simultaneous values of P_{CO_2} and ventilation will trace out the P_{CO_2}/ventilation response curve. A second method is to raise the alveolar P_{CO_2} by rebreathing, and again the increasing simultaneous values of ventilation and P_{CO_2} while rebreathing from a bag will trace out a response curve (Clark, 1968). Allowance must be made for changes in P_{O_2} and account should be taken of the time lag between the actual P_{CO_2} and the ventilatory response which it evokes.

Since P_{CO_2}/ventilation response curves approximate to straight lines over the clinical range, it is not necessary to make a large number of paired measurements. The resting point breathing air may be used as the origin, but it must be remembered that most methods of measurement of ventilation require the introduction of some apparatus dead space causing the first point to be displaced some way along the response curve. Results may be plotted as in *Figures 7 and 9*.

It is fairly simple to measure the ability of an unconscious patient to respond to added external resistance to breathing. A variety of imposed resistors may be used but a simple water bubbler is often convenient (Nunn and Ezi-Ashi, 1961). The immediate response is probably an indication of the integrity of the spindle-servo-mechanism, while the secondary response is probably mediated by change in P_{CO_2}.

CHAPTER 3

ELASTIC RESISTANCE TO VENTILATION

The function of the lung is governed by physical factors to a greater extent than is that of any other organ in the body. Chapter 1 commenced with the statement that transfer of gases across the alveolar-capillary membrane is in response to partial pressure gradients in accord with the laws of physics and not as a result of vital activity such as secretion. The movements of gas and blood within the lung may also be considered as largely passive and in accord with physical laws, there being only minor control exerted through biological mechanisms within the lung itself.

The lung cannot, of course, be considered entirely from a physical point of view. Its formation and the maintenance of its structural integrity clearly depend upon vital activity which is still poorly understood. It is also true that respiration is greatly facilitated by the surfactant in the alveolar lining fluid, by carbonic anhydrase and by many other substances which are actively formed by living cells. Furthermore, the lung can, to a limited extent, influence the distribution of gas and blood within itself by the action of rather weak homeostatic mechanisms and, in response to various noxious stimuli, the resistance of the air passages may be increased to the point of total obstruction. However, none of these considerations detracts from the view that, under normal circumstances, both ventilation and perfusion are largely passive and are driven by forces external to the lung. The response of the lung to these forces can, in the first instance, be best understood as the response of a mechano-physical system.

Ventilation of the lung normally occurs in response to contraction of the respiratory muscles. Other forces may be used such as the application of intermittent positive pressure to the airways or mechanical deformation of the chest, and these may be almost equally effective. Both natural and artificial forces are employed in overcoming the resistance or hindrance of the lung/chest wall system to movement and the main sources of resistance fall into two main categories:

(1) Elastic resistance of tissue.
(2) Frictional resistance to gas flow.

Additional minor sources of resistance are inertia of gas and tissues, and frictional resistance afforded by the viscous flow of tissue during deformation. Work performed in overcoming frictional resistance is dissipated as heat and lost. Work performed in overcoming elastic resistance is stored as potential energy and elastic deformation during inspiration is normally used as the source of energy for expiration.

The present chapter is concerned with the elastic resistance afforded by

lungs and chest wall. These structures are arranged concentrically and their elastic resistances are therefore additive.

THE FUNCTIONAL RESIDUAL CAPACITY (F.R.C.)*

It is convenient to start a discussion on the elastic forces by considering the functional residual capacity. This is the relaxed equilibrium volume of the lungs when there is no muscle activity and no pressure difference between alveoli and atmosphere. Equilibrium is attained when the elastic recoil of the lungs is exactly balanced by the elastic recoil of the thoracic cage, which exerts its force in the opposite direction. If the thorax is opened in the paralysed patient, the lung tends to collapse but the chest wall tends to expand to a volume some 500 ml. above the F.R.C. The equilibrium at the F.R.C. is analogous to two springs joined together at one end, with the other ends anchored separately to fixed points. In equilibrium, the tension in each spring is the same (*Figure 11c*).

Figure 11a shows the static balance at F.R.C. in the upright position when the lung volume is about 3,500 ml. Anaesthetists and others interested in the unconscious patient are more concerned with the supine position, which is shown in *Figure 11b*. The diaphragm is pressed higher into the thorax by the weight of the viscera, resulting in a reduction of F.R.C. to about 2,500 ml. The reduced lung volume together with the altered direction of the weight of the heart results in important changes of pressure which will be further discussed below.

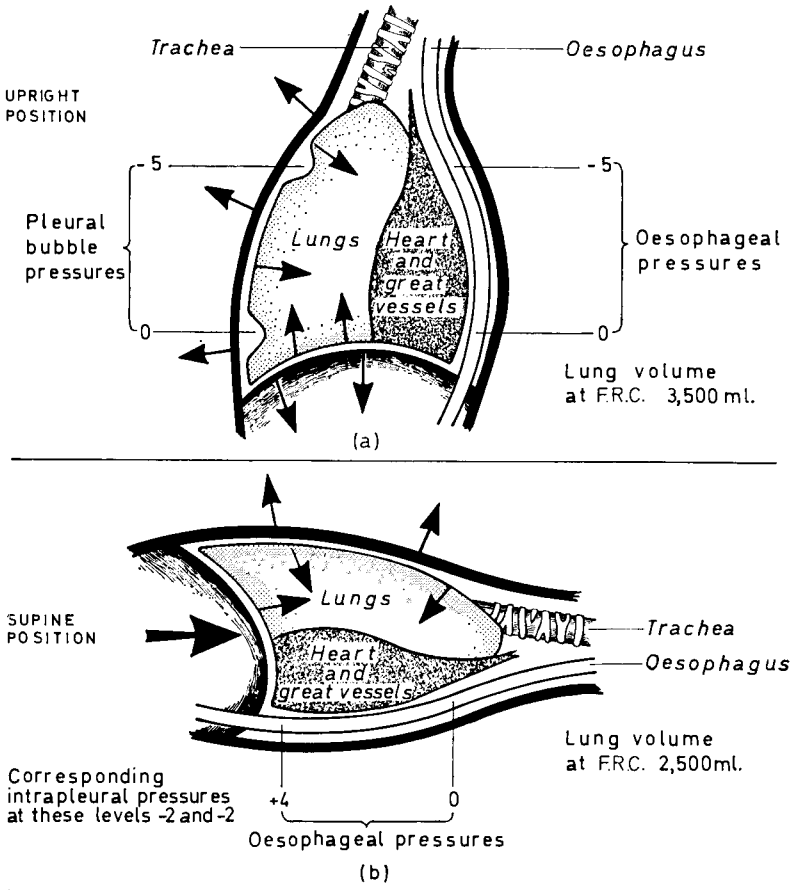
Failure to recognize the important effects of changes in posture has caused some confusion in the understanding of the respiratory physiology of the anaesthetized patient. Most physiological studies in man are carried out in the upright or sitting posture and it is all too easy to extrapolate the results to anaesthetized man without regard for the effect of the change of posture. Many of the so-called abnormalities of anaesthesia may well prove to be due to nothing more than the prolonged immobility in the supine position.

The Intrathoracic Pressure

The inward recoil of the lungs is balanced by the outward recoil of the chest wall to produce a subatmospheric pressure in the space between these structures. It might therefore be expected that gas or tissue-fluid would accumulate in the potential space, but fluid is absent because the difference in pressure between the pleural capillaries and the pleural 'space' is normally less than the osmotic pressure of the plasma proteins. Gas is absent because the sum of the partial pressures of gases in venous blood is always less than atmospheric for reasons which are explained in Chapter 12 (page 366). Therefore there will be a pressure gradient between any gas which finds its way into the pleural cavity and the gases carried in systemic venous blood. As a result, gas loculi in the pleural cavity, or elsewhere in the body, must ultimately be absorbed.

The term 'negative intrapleural pressure' is semantically incorrect because there is no intrapleural space to exhibit a pressure and also because a 'negative pressure' is physically impossible. 'Subatmospheric pressure' is the correct

* Nomenclature of lung volumes is set out in *Figure 1*.



MECHANICAL ANALOGY OF STATIC RELATIONSHIPS

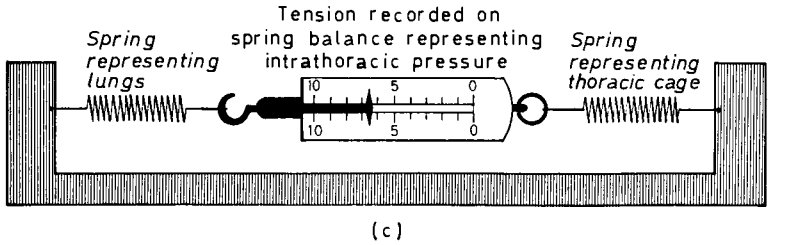


Figure 11. Intrathoracic pressures: static relationships in the resting end-expiratory position. The lung volume corresponds to the functional residual capacity (F.R.C.). The figures in (a) and (b) indicate the pressure relative to ambient (atmospheric) in cm H_2O. The arrows show the direction of elastic forces. The heavy arrow in (b) indicates displacement of the abdominal viscera. In (c) the tension in the two springs is the same and will be indicated on the spring balance. In the supine position: (1) the F.R.C. is reduced; (2) the intrathoracic pressure is raised; (3) the weight of the heart raises the oesophageal pressure above the intrapleural pressure

term for what is often loosely described as negative pressure. The concept of intrapleural pressure is difficult to understand. If a small bubble of gas is introduced into the pleural cavity, its pressure may be measured but this will be found to vary according to the amount of gas introduced and also according to the location of the bubble (Farhi, Otis and Proctor, 1957; Banchero and his colleagues, 1967). The lungs have an over-all specific gravity of about 0·3 so that if two bubbles are introduced into the pleural cavity, one 10 cm. below the other, the pressure in the lower bubble will be about 3 cm H_2O higher than in the upper bubble. Greater differences may be found in the region of the heart since the mean specific gravity of the thoracic contents approaches unity in the vicinity of the heart and great vessels. Thus the 'intrapleural pressure' is not an entity with a single value and nowadays it is usual to measure the intra-oesophageal pressure instead. A soft balloon on the end of a catheter is passed into the middle third of the oesophagus, in which region there is minimal interference from movements of the head or from changes of posture. It is probable that the pressure recorded within the balloon is close to or slightly above 'local intrapleural' pressure at that level. Details of technique have been described by Milic-Emili and his colleagues (1964) and Milic-Emili, Mead and Turner (1964).

Oesophageal pressure in the upright subject changes according to the point at which it is measured. The pressure rises as the balloon descends, the change being roughly in accord with the specific gravity of the lung. When the lung volume is 40 per cent of vital capacity, the pressure is about 5 cm H_2O below mouth pressure with the balloon 32–35 cm. beyond the nares, the highest point at which the indicated pressure is free from artefacts due to mouth pressure and tracheal and neck movements. When the balloon is advanced, the observed pressure rises, gradually at first, but then more rapidly, to become equal to mouth pressure when the balloon is about 45–50 cm. beyond the nares (Milic-Emili, Mead and Turner, 1964).

In the supine position, the lung volume is reduced and this factor alone will bring the oesophageal pressure closer to atmospheric, because the elastic recoil of the lungs is less at lower lung volume. In addition, the heart and great vessels tend to overlie the oesophagus and raise the intra-oesophageal pressure above the level of the true intrathoracic pressure at that level. Further descent of a measuring balloon down the oesophagus increases this effect as the balloon passes behind the heart (*Figure 11*) but there is usually a zone, some 32–40 cm. beyond the nares where the oesophageal pressure is close to atmospheric and probably only about 2 cm H_2O above the neighbouring intrathoracic pressure.

The effect of the weight of the mediastinal contents is found only in the supine position and not in the prone or lateral positions (Ferris, Mead and Frank, 1959). With faulty positioning of the oesophageal balloon, the effect may vary during the respiratory cycle, giving fictitiously high swings of intra-thoracic pressure (Knowles, Hong and Rahn, 1959).

Factors Influencing the F.R.C.

At the end of a normal expiration, there remains slight tension in the inspiratory muscles: this is more marked in the untrained subject breathing

into unfamiliar respiratory apparatus. *Figure 12a* shows the slight decrease in end-expiratory lung volume which usually occurs immediately after the induction of anaesthesia. This is probably due to the combination of loss of

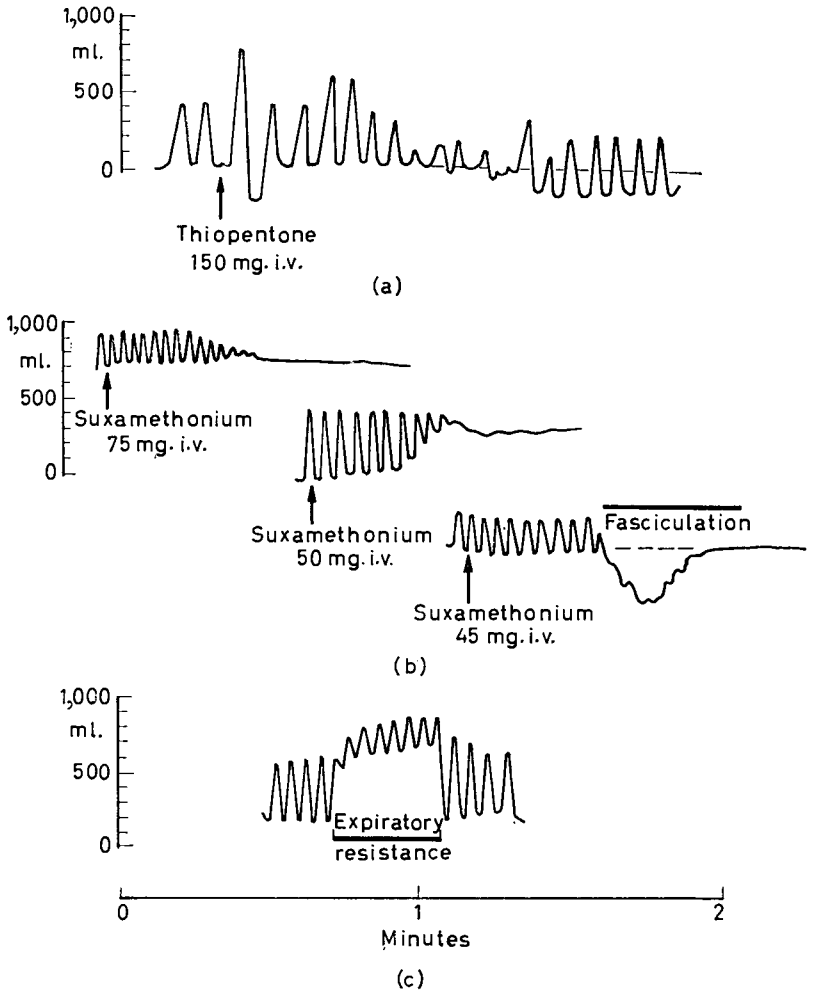


Figure 12. Three situations resulting in changes of the F.R.C. during anaesthesia (all traces are read from left to right). (a) Induction of anaesthesia. End-expiratory inspiratory muscle tone is usually abolished and expiratory muscle activity commences. (b) Production of neuromuscular blockade with suxamethonium in three successive patients. Marked expiratory muscle activity was present before the blockade in the second patient; gross fasciculation occurred in the third patient. (c) An expiratory threshold resistor of 5 cm H_2O. This caused an increase in inspiratory muscle tension and end-expiratory lung volume, resulting in greater elastic recoil available for expiration against the resistor

end-expiratory tone in the inspiratory muscles and the appearance of expiratory muscle activity which seems to be a regular feature of general anaesthesia (Freund, Roos and Dodd, 1964).

Figure 12b shows changes in lung volume which may follow neuromuscular blockade during anaesthesia. The upper left trace shows simple loss of respiratory movement, with the lung volume becoming fixed at the previous end-expiratory level. In the centre trace, the lung volume settled above the previous end-expiratory lung volume, suggesting that this was depressed below the F.R.C. by expiratory muscle activity before the blockade. The lower right trace of *Figure 12b* shows depression of lung volume below F.R.C. during fasciculation. In each case the lung volume during paralysis is the F.R.C. and reduction of lung volume below this level is known to impair oxygenation of the arterial blood (Nunn and his colleagues, 1965b; *see* page 143).

Expiratory resistance to breathing, either in the patient's air passages or in external breathing apparatus, may prevent the completion of expiration which is normally passive. The resulting increase in F.R.C. may be seen during the acute application of an expiratory resistor to an anaesthetized patient (*Figure 12c*), or in chronic respiratory disease in which expiratory airway resistance is present. The increased lung volume results in a greater elastic recoil being available to overcome the resistance (page 51) and also increases the calibre of the airways since the volume of the smaller air passages is roughly proportional to the volume of the lungs as a whole.

Mention has already been made of the effect of changes in posture on the forces acting on the lower side of the diaphragm (*Figure 11*). More detailed information on the resulting changes in F.R.C. is given in *Table 3.*

Table 3

Effect of posture on functional residual capacity

Conscious subject	Values for the F.R.C.
Supine position	2,500 ml.
Upright position	3,500 ml.
*Anaesthetized patient**	Changes in the F.R.C. relative to the value in the supine position
30° Trendelenburg	− 95 ml.
30° Reverse Trendelenburg	+ 213 ml.
Lateral	+ 300 ml.
Lithotomy	− 67 ml.
Prone	+ 70 ml.

* After Wood-Smith, Horne and Nunn, 1961.

ELASTIC RECOIL OF THE LUNGS

It is by no means easy to grasp the quantitative aspects of the combined elastic system of lungs plus chest wall. The approach in this chapter is to consider first the elastic recoil of the lungs and then to discuss the chest wall as an elastic system. Finally, the entire system is considered together with an explanation of the rather difficult pressure/volume relationships of the lungs within the intact chest.

In some conditions, there have been few reported measurements of pulmonary elastic resistance. In such cases, total elastic resistance of lungs plus chest wall has been presented where it seems likely that its value is influenced predominantly by changes in elastic recoil of the lung.

The Transmural Pressure Gradient

If the lungs are removed from the thorax and the air passages remain open, the air within the lungs will gradually be expelled. At all lung volumes, the

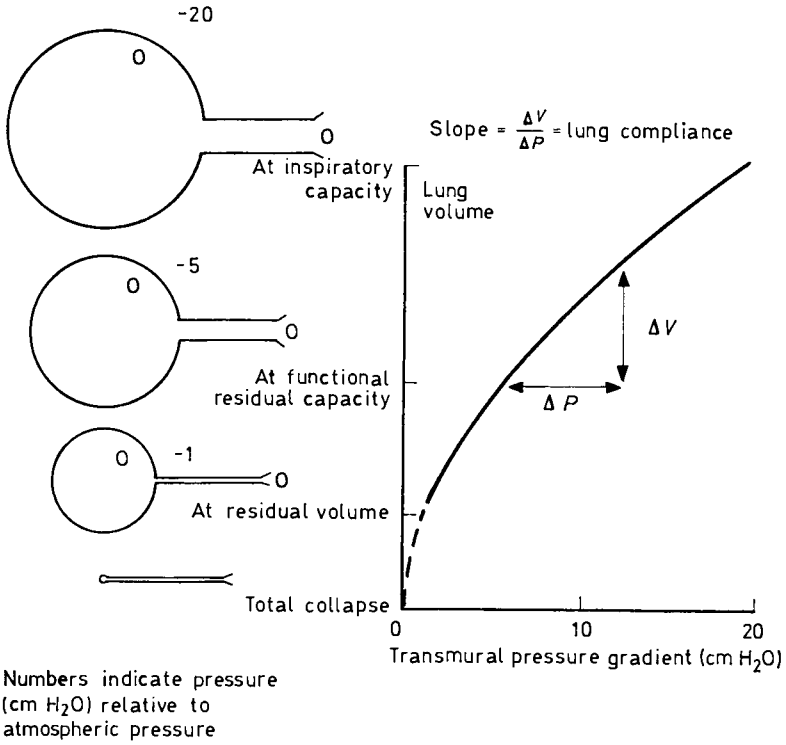


Figure 13. Lung volume bears a curvilinear relationship to the difference in pressure between the alveoli and the intrathoracic space (the transmural pressure gradient). Over the normal tidal range, the relationship approximates to linear and the slope is the lung compliance. The calibre of the air passages falls as the lung volume decreases. At the residual volume (maximal voluntary expiration), some alveoli are isolated by airway closure. Pressure in these alveoli may rise above atmospheric. Once gas is sequestered in an alveolus, collapse can only occur by absorption of contained gases by the pulmonary blood. Values in this diagram relate to the upright position

pressure within the alveoli is greater than that surrounding the lungs. The difference (the transmural pressure gradient) is related to the lung volume, and its magnitude at various lung volumes is shown in *Figure 13*. As the lung volume diminishes, three important changes take place:

(1) The transmural pressure gradient diminishes.

(2) The small air passages become narrower, and one by one become totally obstructed.

(3) There is a tendency for alveoli to collapse.

Closure of the smaller air passages tends to prevent total collapse of the alveoli, unless the sequestered gas trapped therein can be removed by the pulmonary blood flow which continues to perfuse the alveoli after the air passages are collapsed. This is most likely to happen if the alveoli contain high concentrations of oxygen or soluble anaesthetic gases such as cyclopropane and nitrous oxide. Absorption is very slow if the trapped alveoli contain air (Webb and Nunn, 1967).

The Limitation of Expiration

As expiration proceeds into the expiratory reserve, there is a progressive rise in airway resistance due to the closure of small air passages as shown in *Figure 13* (Cheng, Godfrey and Shepard, 1959). There is, however, likely to be an important regional difference, with airway closure occurring preferentially in the dependent parts of the lungs (Milic-Emili and his colleagues, 1966). Slagter and Heemstra (1955) reported oesophageal pressures of the order of 30 cm H_2O at the end of maximal expirations and this suggested that total airway obstruction must have occurred. Although their pressure measurements may have been influenced by pressure of the heart against the oesophagus, it does seem likely that extensive, if not total, airway obstruction plays some part in limiting a maximal expiration at least in older subjects (Leith and Mead, 1967). However, these latter workers have found the airways to be still open at residual volume in younger subjects. Agostoni and Torri (1962) have suggested that maximal expiration may be limited by reflex antagonism in the respiratory muscles.

Relationship between Lung Volume and Transmural Pressure Gradient

The relationship shown in *Figure 13* between lung volume and transmural pressure gradient is typical of an elastic structure. Hooke's law states that stress is proportional to strain. In this case the stress is the change in the transmural pressure gradient, and the strain is the change in the lung volume. The relationship is valid over limited ranges, such as that encountered in normal breathing, and may be stated as follows:

$$\frac{\text{change in lung volume}}{\text{change in transmural pressure gradient}} = \text{a constant}$$

The constant is known as the compliance. The relationship, it should be noted, is independent of the actual pressures and is solely a matter of transmural pressure gradient.

If lung volume is plotted against transmural pressure gradient, the slope ($\Delta V/\Delta P$) of the graph equals the compliance (*Figure 13*). Over a wide range the plot shows a gradual curve with the slope (compliance) falling as the lung volume is increased. However, over the normal range of tidal volumes, the measured compliance is little affected by the magnitude of the tidal volume studied.

Compliance and Elastance

It is perhaps unfortunate that two terms are used to define the elasticity of the lung. We have already met the term compliance, which is the volume change per unit change of transmural pressure gradient. Its units of measurement are ml. (or l.) per cm H_2O. Stiff lungs have a *low* compliance.

The other term is *elastance*, which is the reciprocal of compliance:

$$\frac{\text{change in transmural pressure gradient}}{\text{change in lung volume}} = \text{elastance}$$

The units of measurement are centimetres of water per litre. *Stiff* lungs have a *high* elastance.

Static and Dynamic Compliance

Static compliance is the volume change divided by transmural pressure gradient change, at the point of zero air flow, but after the preceding inflow of air has been sufficiently slow for distribution throughout the lung to be solely in accord with regional elasticity. Alternatively, a pause may be made between the volume change and the measurement of the transmural pressure gradient, to allow redistribution of gas in accord with regional elasticity. *Dynamic* compliance is the volume change divided by transmural pressure gradient change, at the point of zero air flow, but after the previous inflow of air has been sufficiently rapid for dynamic factors to influence its distribution throughout the lung.

The two types of compliance would be identical if the regional rates of filling were always in proportion to the compliance of each region. Each alveolus would then take up its correct proportion of the inspired tidal volume, no matter how rapid the inflow rate of gas. The pressure in each alveolus would be identical and no redistribution would follow the sudden interruption of an inspiration. This ideal state of affairs is shown in *Figure 14a.*

Usually the regional rates of filling of the lung are not in proportion to the regional differences in compliance, since there is a considerable variation in regional airway resistance which is not necessarily inversely related to compliance. *Figure 14b* shows two alveoli representative of those found in patients with emphysema. On the left is a fairly stiff alveolus with a short wide duct; this is known as a *fast alveolus* since gases pass in and out of it fairly quickly. On the right is a more compliant alveolus with a long narrow tortuous duct; this is known as a *slow alveolus* since it takes a long time to fill or to empty.

If air is passed rapidly into a lung containing fast and slow alveoli, it will initially be preferentially distributed to the fast alveoli and the value for the compliance will reflect only those alveoli which have had time to be filled. If, on the other hand, air is passed into such a lung very slowly, distribution among the alveoli is in accord with their individual compliance, so that a large proportion enters the slow alveoli with the high compliance. A fast inflation will thus indicate a low compliance, while a slow inflation will indicate a high compliance (Cherniack, Adamson and Hildes, 1955).

A fall in pulmonary compliance with increasing respiratory frequency has been demonstrated in asthmatic and emphysematous patients by Otis and his colleagues (1956) and by Channin and Tyler (1962). The same effect has been

detected to a lesser extent in normal subjects by Mills, Cumming and Harris (1963). Frequency-dependent changes in compliance become more pronounced if airway resistance is increased with bronchoconstrictor drugs (Otis and his colleagues, 1956). The latter workers, however, found scarcely any change in compliance when respiratory frequency was varied in normal subjects.

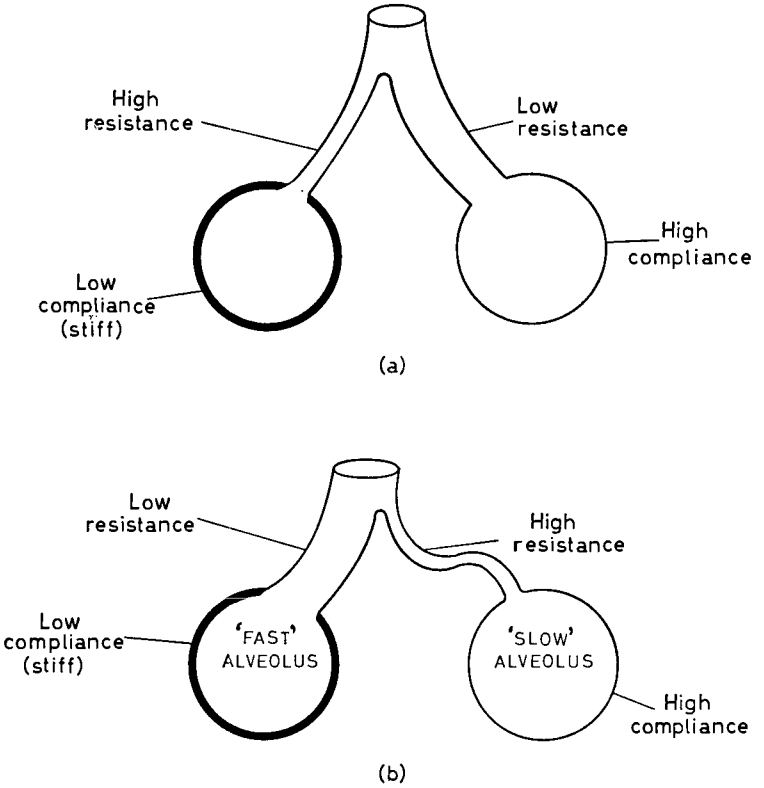


Figure 14. Schematic diagrams of alveoli to illustrate conditions under which static and dynamic compliances may differ. (a) represents an idealized state which is probably not realized even in the normal subject. The reciprocal relationship between resistance and compliance results in gas flow being preferentially delivered to the most compliant regions, regardless of the rate of inflation. Static and dynamic compliance are equal. (b) illustrates a state which is typical of many patients with respiratory disease. The alveoli can conveniently be divided into fast and slow groups. The direct relationship between compliance and resistance results in inspired gas being preferentially delivered to the stiff alveoli if the rate of inflation is rapid. An end-inspiratory pause then permits redistribution from the fast alveoli to the slow alveoli. Static compliance is higher than dynamic

Watson (1962a) has studied the effect of duration of inspiration on the lung compliance of five patients with respiratory paralysis. He demonstrated a marked increase in compliance when inspiration was extended from 0·5 to 1·7 seconds, and a less marked increase with further extension to 3·0 seconds. Changes in the waveform of inflation pressure, on the other hand, had no detectable effect on compliance.

It is difficult to be dogmatic on how slow an inspiration must be to merit classification as 'static'. Butler, White and Arnott (1957) studied inspirations lasting for 20 seconds and detected a fall in transmural pressure as long as five seconds after the cessation of gas flow. They have perhaps reached the ultimate in measurement of 'static' compliance and have certainly reported some of the highest values for lung compliance.

A considerable degree of non-uniformity of distribution of inspired gas is very likely to be present in those patients with abnormal respiratory function in whom we are particularly interested. In such patients, much confusion may be caused by the dependence of the measured compliance on the rapidity of inflation. It is very difficult to standardize rates of inflation and it may therefore be preferable to measure the static rather than the dynamic compliance. Comroe and his co-authors of *The Lung* (1962) have taken the unqualified term compliance to mean static compliance. Nevertheless, it is the dynamic

Table 4

Reported values for compliance (ml./cmH_2O)

Lung compliance				
Conscious,	upright,	static	200	
		dynamic	180	
	supine,	static	150	
		dynamic	140	
Paralysed and anaesthetized,	supine,	static	153	(Butler and Smith, 1957)
			171	(Foster, Heaf and Semple, 1957)
		dynamic	84	(Howell and Peckett, 1957)
			80	(Gold and Helrich, 1965)
Thoracic cage compliance				
Reported values are not significantly different from			200	
Total compliance				
Conscious,	upright,	static	150	
		dynamic	100	
	supine,	static	120	
		dynamic	90	
Paralysed and anaesthetized,	supine,	static	62	(Nims, Connor and Comroe, 1955)
			86	(Butler and Smith, 1957)
			78	(Howell and Peckett, 1957)
			90	(Foster, Heaf and Semple, 1957)
			70	(Bromage, 1958)
			62	(Safar and Aguto-Escarraga, 1959)
			68	(Bodman, 1963)
			76	(Don and Robson, 1965)
		dynamic	57	(Howell and Peckett, 1957)
			56	(Campbell, Nunn and Peckett, 1958)
		'kinetic'	59	(Don and Robson, 1965)

Notes

Volume changes should be measured under conditions of body temperature and pressure (saturated). This has not been specifically stated by some authors and might yield a value 10 per cent low if no correction had been applied.

Static implies that inspiration was sustained for several seconds and not just long enough to secure 'no-flow' conditions.

In the conscious subject, studies are far too numerous for individual citation. A reasonable 'mean' value has been derived.

compliance which is important in the ventilation of an apnoeic patient. It is of no value to the patient to have plenty of highly compliant alveoli which are so slow that they cannot be used during inflation at any reasonable respiratory frequency.

Much of the confusion over the compliance of emphysematous patients stems from the distinction between static and dynamic compliance. The static compliance is usually raised as a result of the destruction of septa. However, an equally important lesion of emphysema is high and irregular airway resistance. This results in abnormal distribution in favour of the fast alveoli which tend to have the lower compliance. The dynamic compliance is therefore reduced.

Similar considerations apply to the lung compliance during anaesthesia. Butler and Smith (1957) measured an extreme form of static compliance, allowing as long as 20 seconds for inflation. They obtained values which were considerably higher than values for the dynamic compliance obtained by Howell and Peckett (1957) during rhythmic ventilation of anaesthetized patients. Both groups, however, demonstrated a reduction in pulmonary compliance during anaesthesia (*Table 4*).

A sustained inflation is thought to drive about 500 ml. of blood from the lungs and it is also likely that elastic tissue yields somewhat under these conditions. Both these effects will tend to raise the observed compliance but cannot easily be distinguished from changes in distribution of gas.

The Nature of the Forces causing Recoil of the Lung

For many years it was believed that the recoil of the lung was due entirely to stretching of the yellow elastic fibres present in the lung parenchyma. However, in 1929, von Neergaard showed that a lung completely filled with and immersed in water, had an elastance which was less than the normal value obtained when the lung was filled with air. He concluded that much of the 'elastic recoil' was due to surface tension acting throughout the vast air/water interface lining the alveoli.

Surface tension at an air/water interface produces forces which tend to reduce the area of the interface. Thus, in a bubble the gas pressure within the bubble will be higher than the surrounding pressure, because the surface of the bubble is in a state of tension. Alveoli resemble bubbles in this respect but differ in their being connected with the exterior through the system of air passages.

The pressure in a bubble is above ambient by an amount depending on the surface tension of the liquid and the radius of curvature of the bubble, according to the Laplace equation:

$$P = \frac{2T}{R}$$

where P is the pressure within the bubble (dyn/sq. cm.), T is surface tension of the liquid (dyn/cm.), and R is radius of the bubble (cm.).

On the left of *Figure 15a and c* is shown a typical alveolus of radius 0·010 cm. Assuming that the alveolar lining fluid has a surface tension of 20 dyn/cm., the pressure within the bubble will be 4,000 dyn/sq. cm., which is approximately

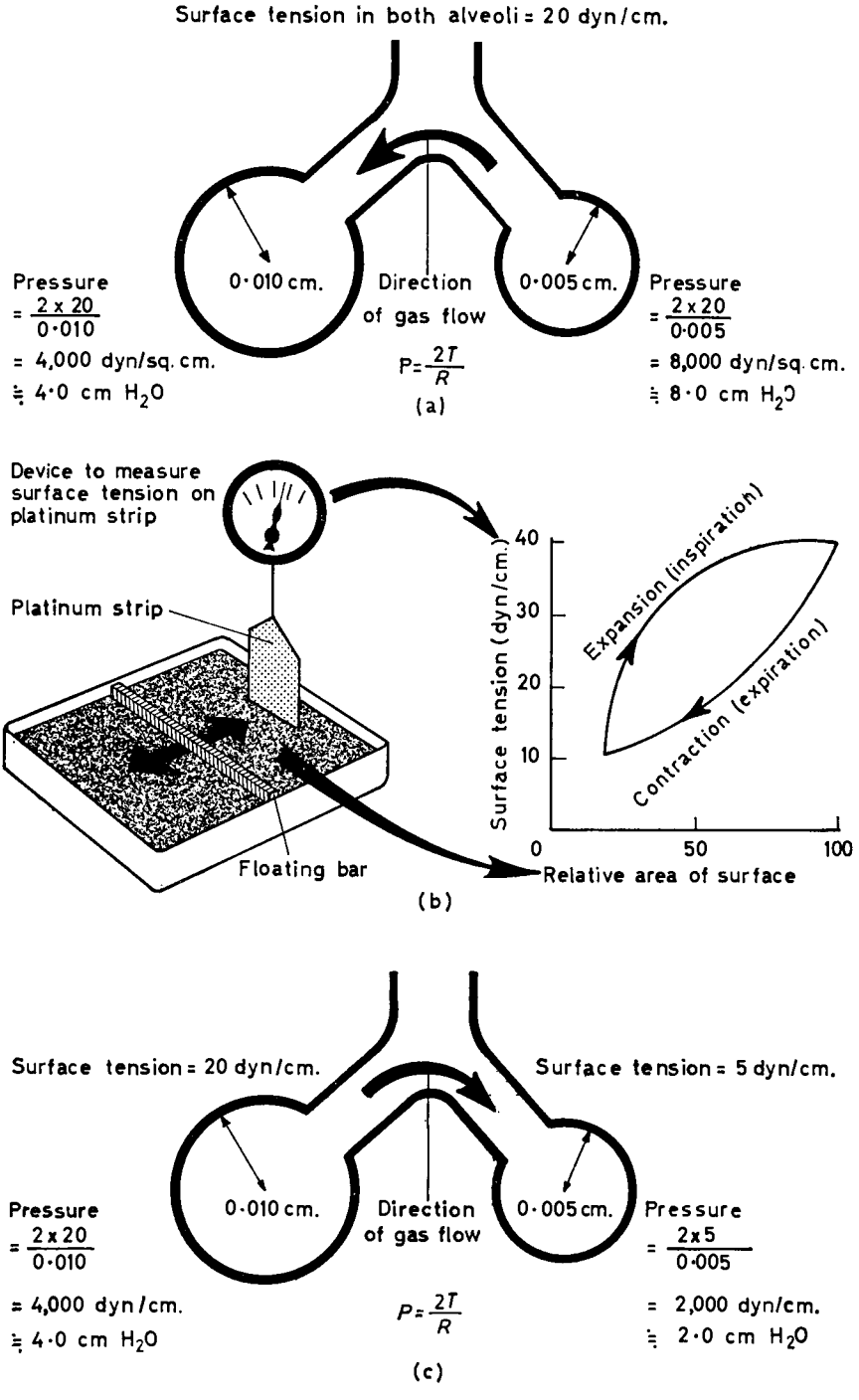


Figure 15. Surface tension and alveolar transmural pressure. (a) The pressure relations in two alveoli of different size but with the same surface tension of their lining fluids. (b) The changes in surface tension in relation to the area of the alveolar lining film. (c) The pressure relations of two alveoli of different size when allowance is made for the probable changes in surface tension

4 cm H_2O,* rather less than the transmural pressure gradient at the F.R.C. It is clear from consideration of the Laplace equation that if the alveolar lining fluid had a surface tension of 72 dyn/cm. (the value for pure water), the lungs would be exceedingly stiff (transmural pressure gradient, 14·4 cm H_2O).

Although it appears inevitable that surface tension must make a contribution to the retractive forces of the lung, two difficulties must be resolved. The first problem is that the pressure in small bubbles is higher than in large bubbles, a conclusion that stems directly from the Laplace equation. From this one might expect that the pressure in a small alveolus would be greater than in a large one. This state of affairs is shown in *Figure 15a*, and would result in a progressive discharge of each alveolus into a larger one, until eventually only one gigantic alveolus would be left. Instability would be inevitable, except in the unlikely event of all the alveoli being exactly the same size. Such a state of affairs would not, of course, be compatible with life, and no such instability exists in the normal lung.

The second problem concerns the relationship between lung volume and the transmural pressure gradient. According to the Laplace equation, one would expect the retractive forces of the lung to increase as the lung volume decreased, a relationship which is certainly true of a bubble. If this were true of the lung, one would expect the lung to decrease in volume according to a vicious cycle, with the tendency to collapse increasing progressively as the lung volume diminished. This, of course, does not happen in the normal lung and the retractive forces decrease as the lung volume is reduced.

The reconciliation of these two problems with the forces which must be produced by the surface tension of the alveolar lining fluid has been one of the most interesting developments in pulmonary physiology. The dilemma was clear to von Neergaard (1929) who concluded that the surface forces in the alveolar lining fluid must be less than would be expected from the properties of simple liquids and, furthermore, that the surface tension must be variable. This has indeed proved to be the case. The original observations of Pattle (1955) on bubbles in lung froth and later studies on alveolar extracts (Brown, Johnson and Clements, 1959) have demonstrated that the surface tension of the alveolar lining fluid is variable and decreases as its surface area is reduced, to attain very low levels which are well below the normal range for body fluids such as plasma.

This effect may be demonstrated by the measurement of surface tension at one end of a trough of alveolar extract. If a floating bar is moved sideways along the trough, the surface film may be concentrated at the end of the trough where the surface tension is being measured. This apparatus is shown diagrammatically in *Figure 15b*, together with a typical result obtained when the area of the surface film is cycled between expansion and contraction.

Alveolar extract with an expanded surface film has a surface tension in the range 30–40 dyn/cm., a value which is close to that of plasma but, as the surface film is concentrated, the surface tension falls to about 10 dyn/cm. On expansion, the surface tension rises, but the pathway of change is different during expansion (inspiration) and contraction (expiration).

When an alveolus decreases in size, the surface tension of the lining fluid falls

* There are many possible units of measurement for pressure. Some of them are quite confusing, and they have been listed in Appendix B.

to a greater extent than the corresponding reduction of radius, so that the transmural pressure gradient ($= 2T/R$) diminishes. Therefore the elastic recoil of small alveoli is less than that of large alveoli. This accords with the observed pressure/volume relations shown in *Figure 13.* It also explains why small alveoli do not discharge their contents into large alveoli (*see* lower part of *Figure 15c*).

The alveolar surfactant.—The strange features of the surface tension of alveolar lining fluid are due to the presence of a surfactant, which is probably a lipoprotein. It is believed to form a film about 50 Å in thickness, floating on the surface of the alveolar lining fluid. The lipoprotein, which has not yet been identified, is highly insoluble but freely permeable to gases. It exerts a surface pressure which counteracts the surface tension of the alveolar lining fluid itself and this effect is greater when the surface film is reduced in area and the concentration of the lipoprotein at the surface is raised. Its origin is not known but it is present in foetal lungs during the last three months of pregnancy. Much detailed information is available in reviews by Pattle (1963, 1965, 1966).

It is now well established that the surfactant is absent or diminished in the respiratory distress syndrome of the newborn, formerly known as hyaline membrane disease (Avery and Mead, 1959; Pattle and his colleagues, 1962). This provides a satisfying explanation of the stiffness of the lungs and the pulmonary shunting which is thought to be due to scattered atelectasis caused by instability of the type shown in the upper part of *Figure 15a.* It is not clear whether reduction of surfactant activity can explain other pathological conditions but it seems likely that it occurs in the stiff-lung syndrome which sometimes follows cardiac surgery when a pump-oxygenator has been used (Tooley, Finley and Gardner, 1961; Tooley and his colleagues, 1961; Nahas and his colleagues, 1965a and b).

Pulmonary transudation is also influenced by surfactant activity. Surface tension causes a pressure gradient across the alveolar–capillary membrane (of the order of 4 cm H_2O) which, together with the above-atmospheric pressure in the pulmonary capillaries (about 7 cm H_2O), tends to favour transudation. These pressures are counteracted by the osmotic pressure of the plasma proteins (about 35 cm H_2O) so that transudation does not normally occur. Diminished surfactant activity would elevate the pressure gradient across the alveolar-capillary membrane and, if sufficiently severe, would tip the balance in favour of transudation. This may be the cause of the 'hyaline membrane' in the respiratory distress syndrome of the newborn.

Finally, it is interesting to note that the lung, although it behaves like an elastic body, is not really an elastic body in the usual sense of the term. Its recoil is governed largely by surface tension, but with the surface tension varying with lung volume. Its obedience to Hooke's law appears to be fortuitous.

Hysteresis

So far we have considered the static pressure/volume relationships of the lung as though they were repeatable and reversible (*Figure 13*). This, however, is not the case. If the lungs are slowly inflated and then slowly deflated, the

pressure/volume curve for static points during inflation differs from that obtained during deflation. The two curves form a loop which becomes progressively broader as the tidal volume is increased (*Figure 16*). (It must be stressed that these loops are not caused by airway resistance although it will be shown in Chapter 4 that airway resistance also causes the production of looped pressure/volume curves during *dynamic* changes in lung volume.) (*See also Figure 20.*)

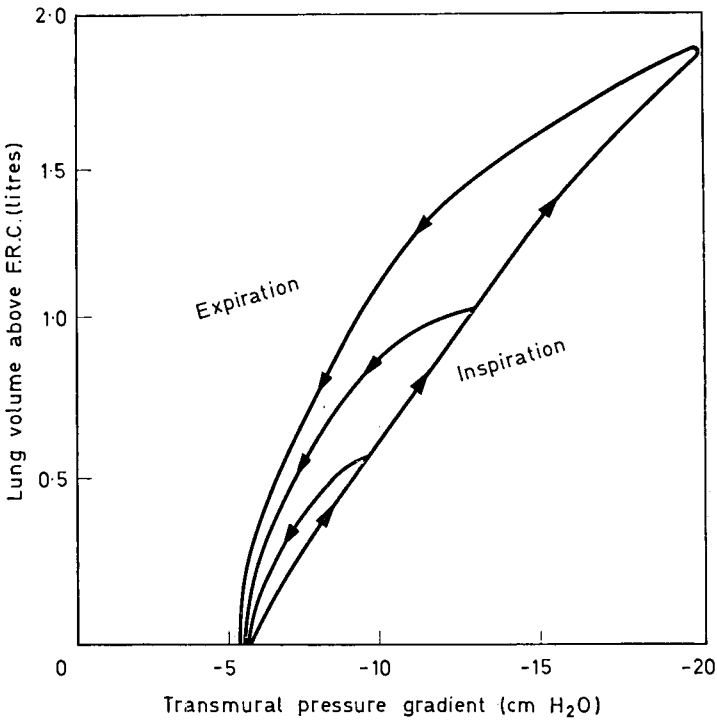


Figure 16. Static plot of lung volume against transmural pressure gradient (intra-oesophageal pressure relative to atmosphere at zero air flow). Note that inspiratory and expiratory curves form a loop which gets wider the greater the tidal volume. These loops are typical of elastic hysteresis. For a particular lung volume, the elastic recoil of the lung during expiration is always less than the distending transmural pressure gradient required during inspiration at the same lung volume

Expressed in words, the loop in *Figure 16* means that rather more than the expected pressure is required during inflation, and rather less than the expected recoil pressure is available during deflation. This resembles the behaviour of perished rubber which is reluctant to accept deformation under stress and, once deformed, is again reluctant to return to its original shape. This phenomenon is common in elastic bodies, and is given the term 'elastic hysteresis'. Few elastic materials are entirely free of it.

Four theories have been advanced to explain pulmonary elastic hysteresis. The first is based on the loop obtained when surface tension is measured at changing areas of alveolar lining fluid. We have already seen, in *Figure 15*, that

in vitro experiments have shown the surface tension to be much lower during contraction of the film than during expansion at the same area (Brown, Johnson and Clements, 1959). Assuming that the same changes occur *in vivo*, we would expect the component of the 'elastic' recoil due to surface tension to be lower during expiration than during inspiration at the same lung volume.

The second theory is based on alveolar closure and is also ultimately related to surface tension forces. *Figure 17* shows the pressure/volume relations of a soap bubble blown on the end of a rigid tube. During the formation of a bubble, the radius of curvature of the soap solution decreases at first until it equals that of the pipe. This is the minimum value, and any further expansion is associated with an increase of radius of curvature. If the surface tension is constant, it follows that the pressure within the bubble will rise to a maximum when its radius equals that of the pipe, and thereafter it will fall. This relationship is shown to the right of *Figure 17a.*

During the initial phase of bubble formation, while the radius of curvature is still falling towards its minimum value, the bubble is stable. That is to say that, if a number of bubbles communicate, the pressure will be highest in the largest bubbles, and therefore they will all tend towards the same volume. However, as the bubble grows, once its radius of curvature has passed its minimum (equal to the radius of the tube), the bubble becomes unstable. Under these conditions the larger the bubble, the lower is its pressure (disregarding changes in surface tension for the moment). Small bubbles would then tend to discharge into large bubbles as shown in the upper part of *Figure 15a.* Instability of this type occurs whenever the curve (*Figure 17*) has a negative slope (upwards and to the left).

The pressure/volume relationship of an alveolus is likely to differ from that of a bubble in two respects. Firstly, there are the tissue retractive forces, and secondly, the surface tension of the alveolar lining fluid falls with the surface area as we have seen above. Mead (1961) has suggested that the probable relationship resembles that shown in *Figure 17b.* There are two stable states for the alveolus, separated by an unstable zone which is rapidly traversed in either direction.

The alveolus is stable when it is reasonably well expanded but, as its volume diminishes, it reaches a point (V_2, P_2) when the slope of the pressure/volume curve is negative. The alveolus then becomes unstable and the volume falls rapidly to V_0 (collapse). As the lungs are re-expanded, the transmural pressure gradient increases to the point P_1 while the collapsed alveolus increases its volume insignificantly from V_0 to V_1. At this point the alveolus again becomes unstable and the volume rapidly increases to V_3. Collapse thus occurs at a larger volume but at a lower pressure than the conditions under which re-expansion takes place. Somewhat parallel changes occur during the inflation of a toy balloon, which has similar pressure/volume relationships. At a critical point, when its diameter is a few inches, it suddenly becomes easier to inflate. This is the point at which its elastic limit is reached and after which it behaves more like a bubble than an elastic structure. It may easily be demonstrated that the pressure in a balloon falls as it expands over its working range.

The anaesthetist has no difficulty in visualizing the critical opening and closing of alveoli. At thoracotomy, scattered groups of alveoli can be seen snapping shut as the exposed lung is allowed to collapse, while, during

re-expansion, the same alveoli are popped open at a higher pressure, and a lower volume, than that at which they collapsed.

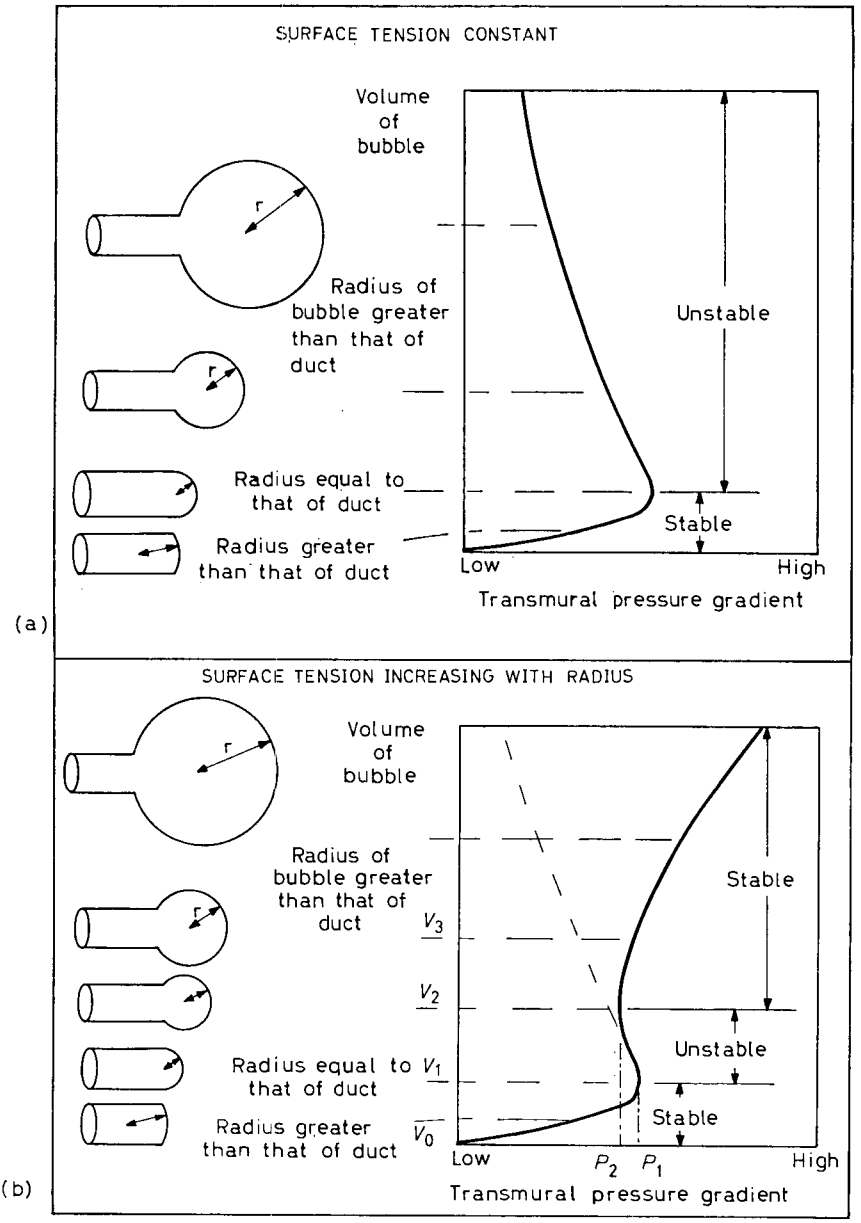


Figure 17. Static pressure/volume relations of a bubble. (a) illustrates a normal bubble, while (b) portrays a hypothetical bubble whose surface tension is related to the radius of the bubble in the same way as for alveolar lining fluid. Bubbles are unstable (in relation to other communicating bubbles) whenever the slope of the pressure/volume curve is negative (upwards and to the left). (Redrawn after Mead, 1961)

It seems possible that this type of collapse may occur in a proportion of alveoli during a normal expiration. Re-expansion, which implies recruitment of additional alveoli, would occur during inspiration but at a higher transmural pressure gradient and smaller lung volume than those which prevailed during expiration. Therefore, there may be more alveoli open during expiration than during inspiration at the same lung volume (Mead, Whittenberger and Radford, 1957). It is to be expected that this would result in the compliance being higher during expiration.

The third theory to account for pulmonary hysteresis is stress relaxation of elastic tissue. It is to be expected that this tissue, in common with other elastic bodies, will yield to some extent during deformation. The fourth theory is the expulsion of blood from the pulmonary circulation during a sustained inspiration. Blood-filled vessels make a small contribution to the total elasticity of the lung.

It is difficult to assess the contribution of these four mechanisms to the observed hysteresis. Mead (1961) has pointed out that the distinction is not entirely academic, since the mechanism illustrated in *Figure 17* would imply a considerable degree of pulmonary collapse and pulmonary shunting during late expiration and early inspiration.

Factors Affecting Lung Compliance

Rate of inflation.—We have already considered the distinction between static and dynamic compliance, and the effect of rate of inflation (Watson, 1962a). Given perfect distribution, static and dynamic compliance would be identical and quite independent of rate of inflation. However, maldistribution of the type shown in *Figure 14* occurs in many forms of chronic lung disease, particularly emphysema. *Table 4* shows some evidence of differences between static and dynamic compliance during anaesthesia, from which we may infer that the rate of distribution of inspired air does not always accord with regional variations in compliance.

Lung volume.—It is important to remember that compliance is related to lung volume (Marshall, 1957). The same pressure gradient will drive more air into the lungs of an elephant than into the lungs of a mouse, simply because there is more lung in the elephant. Compliance is most conveniently related to the F.R.C. and the actual elasticity of the lung should be expressed by the fraction:

$$\frac{\text{compliance}}{\text{F.R.C.}}$$

This is sometimes known as the specific compliance. The measured compliance of children, and to a less extent women, is less than that of adult men. However, the ratio of compliance to F.R.C. is almost the same for both sexes and all ages down to neonatal. The factor of lung volume is also eliminated when the elastance is recorded as the distension pressure, which is arbitrarily defined as the transmural pressure difference required to increase the lung volume by 10 per cent of total lung capacity (Butler and Smith, 1957).

Posture.—Attention has already been directed towards the difficult problems associated with the effect of posture on compliance. Not only is the lung volume

decreased when posture is changed from upright to supine, but special difficulties are introduced into the measurement of intrathoracic pressure by means of an oesophageal balloon (page 48). When these factors are taken into account, it appears unlikely that changes in posture are associated with appreciable changes of the (specific) compliance.

Recent ventilatory history.—There is now ample evidence that shallow regular breathing causes a progressive reduction of lung compliance, which may be restored to normal by a single deep breath (Butler and Smith, 1957; Mead and Collier, 1959). Post-mortem appearances and measurements of lung volumes suggest strongly that the reduction in compliance is due to alveolar collapse. The mechanism of this is likely to be a combination of unexpelled secretions and the type of collapse described above in relation to hysteresis. Failure of the surfactant film may also be a factor.

Great interest has been aroused by the possibility that similar changes should occur during the regular monotonous breathing of anaesthetized patients. Whether breathing is spontaneous or artificial, it is seldom punctuated by sighs during anaesthesia. Watson (1961) has demonstrated a doubling of lung compliance within four minutes of discontinuing artificial ventilation of a patient with poliomyelitis. Bendixen, Hedley-White and Laver in their classic paper of 1963 have shown falls of compliance* during artificial ventilation of anaesthetized patients, with rapid restoration of compliance to control values following manual hyperinflation of the lungs. In this study, Bendixen did not report the tidal volumes, but it may be presumed that they were not large since arterial P_{CO_2} values were higher than is usual for artificially ventilated anaesthetized patients. Respiratory frequencies ranged from 20 to 25 breaths per minute. Bromage (1958) found no evidence of a reduction of total static compliance during sustained hyperventilation of anaesthetized patients.

Pulmonary blood volume.—The pulmonary blood vessels probably make a small contribution to the total stiffness of the lungs. Pulmonary vascular congestion is associated with a reduced compliance and this may result from the Müller manœuvre, left heart disease or septal defects.

Age.—One would have expected that age would have influenced the elasticity of the lungs as it appears to influence the elasticity of almost all other tissues of the body. However, Butler, White and Arnott (1957) were unable to detect any correlation between age and compliance, when due allowance had been made for predicted changes in lung volume. This accords with the concept of lung 'elasticity' being determined mainly by surface forces.

Restriction of chest expansion.—Elastic strapping of the chest reduces the lung compliance but also causes a roughly proportionate reduction in F.R.C. The compliance remains reduced if the lung volume is returned to normal, either by a forced inspiration against the restriction or by removal of the restriction. Normal compliance is instantly regained by taking a single deep breath (Caro, Butler and DuBois, 1960). It is likely that the cause of the reduction of compliance is alveolar collapse. The delayed restoration of normal compliance is due to the hysteresis-like effect described above.

* This study reported total compliance (i.e. lung plus chest wall).

*Anaesthesia.**—It is well established that pulmonary compliance is reduced during anaesthesia (*Table 4*). This reduction is fundamental to the understanding of the practice of artificial ventilation and the design of mechanical ventilators. It now seems unlikely that the change in compliance is the result of the action of anaesthetic agents and drugs upon the lung parenchyma or the pulmonary circulation. *d*-Tubocurarine is known to reduce the compliance of anaesthetized dogs, probably due in part to the release of histamine (Safar and Bachman, 1956), but relaxants have not been found to alter the total static compliance in anaesthetized man (Bromage, 1958). Changes of compliance observed during anaesthesia are probably due to one or more of the following factors.

(1) Anaesthetized patients are commonly in the supine position, which decreases the lung volume in comparison with the upright position and may also introduce the artefact of the mediastinal weight into the measurement of oesophageal pressure. Control measurements have often been made in the upright position and comparison is therefore not valid.

(2) The ventilatory history of the anaesthetized patient is often conducive to alveolar collapse and airway closure.

(3) Studies of arterial Po_2 during anaesthesia persistently show that some 5–10 per cent of the pulmonary blood flow does not pass through ventilated alveoli. It is not yet proved that this flow is through collapsed alveoli but, if this is the case, the reduction in number of functioning alveoli would be sufficient to cause an appreciable reduction in compliance.

(4) It is possible that the spatial distribution of inspired gas is altered during anaesthesia or artificial ventilation, since the forces acting on the chest are not the same. If such an altered distribution occurs, it is likely that compliance would be less than normal. This has been compared to blowing up a balloon lying in a napkin ring. The pattern of inflation would be altered and the compliance diminished.

(5) It is possible, though unproved, that anaesthesia impairs the action of the surfactant in the alveolar lining fluid.

(6) Bromage (1958) has shown a reduction of total static compliance following noxious stimuli (strong ether vapour or surgery). It was thought that this reduction was due to bronchoconstriction leading to diminution of ventilated area and altered distribution of inspired gas.

(7) Anaesthesia with spontaneous respiration commonly results in a reduction of pulmonary ventilation, and Gold and Helrich (1965) have demonstrated a most convincing relationship between depression of tidal volume and reduction of pulmonary compliance.

(8) Anaesthesia may be associated with pulmonary hypervolaemia causing splinting of the lungs.

Disease.—Perhaps the only pathological condition leading to increase in compliance is emphysema. We have already noted that this increase is only in the static measurement, while dynamic compliance is decreased due to

* A number of studies in this section relate to measurements of total compliance (lung plus chest wall) because few actual measurements of pulmonary compliance have been made during anaesthesia. These studies have been included because there seems little reason why anaesthesia should alter the compliance of the thoracic cage and the results probably reflect changes in pulmonary compliance.

maldistribution of inspired gas in favour of fast stiff alveoli. The dynamic compliance is of greater importance in the management of the emphysematous patient and the change in static compliance is largely of academic interest. For practical purposes the lungs of an emphysematous patient are stiff.

Many conditions reduce both the static and the dynamic lung compliance. The F.R.C. may be reduced in a lung of normal stiffness, but a true increase in stiffness (reduction of specific compliance, or compliance ÷ F.R.C.) may result from the presence of oedema fluid, congested pulmonary vessels or from the deposition of fibrous tissue in the lungs. The last may result from many forms of chronic inflammation, such as tuberculosis or sarcoidosis. Extreme reduction in lung compliance occurs in organized pleural effusions, and in deficiency of the surfactant, occurring in the respiratory distress syndrome of the newborn (hyaline membrane disease) and occasionally following the use of extracorporeal pump-oxygenators.

ELASTIC RECOIL OF THE THORACIC CAGE

An excised lung will always tend to contract until all the contained air is expelled, or until all the airways are obstructed. On the other hand the thoracic cage, in the absence of respiratory muscle activity, is tending to expand its volume above the F.R.C. If air is allowed to enter the pleural cavities freely, the thoracic cage will expand to a volume about a litre greater than the F.R.C.

It is only in the absence of muscle activity that the thoracic cage can be considered as an elastic structure. During normal inspiration, the pressure difference between the inside and the outside of the thoracic cage reflects the strength of contraction of the muscles rather than the elasticity of the structures. In the conscious subject, the elasticity or compliance of the thoracic cage can only be determined when the respiratory muscles are completely relaxed, and this is difficult to achieve. During anaesthesia with paralysis, the situation is very much easier and the compliance of the thoracic cage is indicated as follows:

$$\text{compliance of thoracic cage} = \frac{\text{change in lung volume}}{\text{change in atmospheric-to-intrathoracic pressure difference}}$$

The measurement is actually seldom of much interest in itself. Howell and Peckett (1957) and Butler and Smith (1957) are agreed that thoracic cage compliance is unaltered by anaesthesia. A typical value is of the order of 200 ml./cm H_2O (supine).

Effect of Posture

When gas enters the lungs, the increase in volume is obtained more by the descent of the diaphragm than by the expansion of the rib cage. Displacement of the viscera is, therefore, an important factor in the measured 'elasticity' of the thoracic cage. Not surprisingly, posture has an important effect, since displacement of the viscera is more difficult in the supine position and this would be shown as a reduction of the observed compliance of the 'thoracic cage'. The study by Ferris and his colleagues (1952) suggests that the thoracic cage compliance is 30 per cent greater when the subject is seated. Lynch, Brand and Levy (1959) have found a reduction of total static compliance of 60 per cent when the anaesthetized patient is turned from the supine to the

prone position: much of the difference is likely to be in diminished elasticity of the thoracic cage and diaphragm.

Other Factors Influencing Compliance of Thoracic Cage

Apart from abdominal muscle tone, there are no physiological factors of importance which influence the compliance of the thoracic cage. External factors of importance are tight clothing and weights resting on the trunk. It is not unusual for surgical assistants to lean on the anaesthetized patient and the effect on respiration of this practice was studied by Nunn and Ezi-Ashi (1961). A weight of 5 kg. on the sternum (supine position) caused no appreciable change in minute volume, but when applied to the epigastrium (thus hampering the descent of the diaphragm during inspiration), the minute volume was reduced by 20 per cent per 10 kg. applied.

Increased resistance to deformation of the chest wall may occur in obesity, old age or kyphoscoliosis (Lynch, Brand and Levy, 1959). More superficial tissues may offer appreciable resistance in scleroderma and in radiation fibrosis following treatment of carcinoma of the breast.

The restricting effect of the chest wall is lost during thoracotomy when the total compliance rises by 45 per cent (Brownlee and Allbritten, 1956).

STATIC PRESSURE/VOLUME RELATIONSHIPS OF THE LUNG PLUS CHEST WALL

From the clinical standpoint, it is impossible to distinguish between the elasticity of lungs and chest wall. The sensation imparted to the hand during artificial ventilation by manual compression of the reservoir bag is that of a single elastic body, and the simplest measurements of compliance available to the anaesthetist (*see* below) measure the compliance of the lung plus chest wall. This is the value which, together with the airway resistance, governs the practice of artificial ventilation.

The total compliance of lung plus chest wall is related to the individual compliances of lungs and chest wall according to the following expression:

$$\frac{1}{\text{total compliance}} = \frac{1}{\text{lung compliance}} + \frac{1}{\text{thoracic cage compliance}}$$

$$\frac{1}{85} = \frac{1}{150} + \frac{1}{200}$$

(static values for the supine anaesthetized subject, ml./cm H_2O).

The alternative measure of elasticity, the elastance, may be added directly, and is much more convenient in this respect:

$$\text{total elastance} = \text{lung elastance} + \text{thoracic cage elastance}$$

$$11{\cdot}7 = 6{\cdot}7 + 5{\cdot}0$$

(corresponding values, cm H_2O/l.).

Calculation of Required Inflation Pressure

The sustained inflation pressure required for a particular tidal volume is given by the following equation:

$$\text{required sustained inflation pressure} = \frac{\text{required tidal volume}}{\text{total static compliance}}$$

For example, if the total static compliance is 85 ml./cm H_2O, a tidal volume of 850 ml. will be obtained by a sustained pressure of 10 cm H_2O. This would hardly be a satisfactory method of artificial ventilation as full inspiration would require several seconds. This is because we are considering static values, and have taken no account of the resistance to gas flow which prolongs the time required for entry of gas into the various parts of the lungs. It is common practice to use an inflation pressure at least double the static pressure calculated to produce the required tidal volume. The inspiratory phase may then be cut short before equilibrium is attained, and, by this means, inspiration is reduced to a reasonable duration. In the example quoted above, we might use an inflation pressure of 20 cm H_2O which, if continued indefinitely, would produce a tidal volume of 1,700 ml. We would, however, terminate inspiration before equilibrium and could thus obtain a tidal volume of 850 ml. in a reasonably short time. This device is fundamental to many aspects of anaesthesia and carries the name 'overpressure'. It is discussed in some detail in Chapter 5 (*see Figure 42*).

Relationship between Alveolar, Intrathoracic and Ambient Pressures

Qualitatively, the relationship between these pressures is the same in the upright and supine positions, but the actual values are altered by changes in posture. Two series of diagrams have therefore been prepared to accompany the text. *Figure 18* depicts the upright position and uses typical values drawn from physiological studies in the conscious subject. *Figure 19* depicts the anaesthetized patient in the supine position, and employs values which are culled from a considerable range of published material (*Table 4*).

In the paralysed patient, inflation is achieved by raising the alveolar pressure relative to the pressure surrounding the trunk. Either the airway pressure is raised (intermittent positive pressure ventilation) or the pressure surrounding the trunk is lowered (cabinet respirator). In each case, the alveolar/ambient pressure gradient is increased, and the effects are probably identical. At all lung volumes, the intrathoracic pressure is less than the alveolar pressure by an amount equal to the transmural pressure gradient (*Figure 13*) but, during passive inflation of the lungs, the intrathoracic pressure rises in relation to ambient pressure. Intrathoracic pressure is approximately equal to ambient at a lung volume about a litre greater than the F.R.C. in the upright position, but at a much lower lung volume in the supine position. This is the same volume which would be assumed by the chest wall if air were allowed to enter the pleural cavities freely. If the lungs are then inflated further, the chest wall is stretched beyond its equilibrium position, and consequently the intrathoracic pressure rises above ambient. These changes are shown diagrammatically and are also displayed on static pressure/volume diagrams (*Figures 18 and 19*). At all times, the following relationship holds:

$$\begin{matrix}\text{alveolar/ambient}\\ \text{pressure difference}\end{matrix} = \begin{matrix}\text{alveolar/intrathoracic}\\ \text{pressure difference}\end{matrix} + \begin{matrix}\text{intrathoracic/ambient}\\ \text{pressure difference}\end{matrix}$$

Due attention must be paid to the sign of the pressure differences.

During spontaneous respiration the alveolar pressure equals ambient at the ends of inspiration and expiration when no gas is flowing through the respiratory tract.

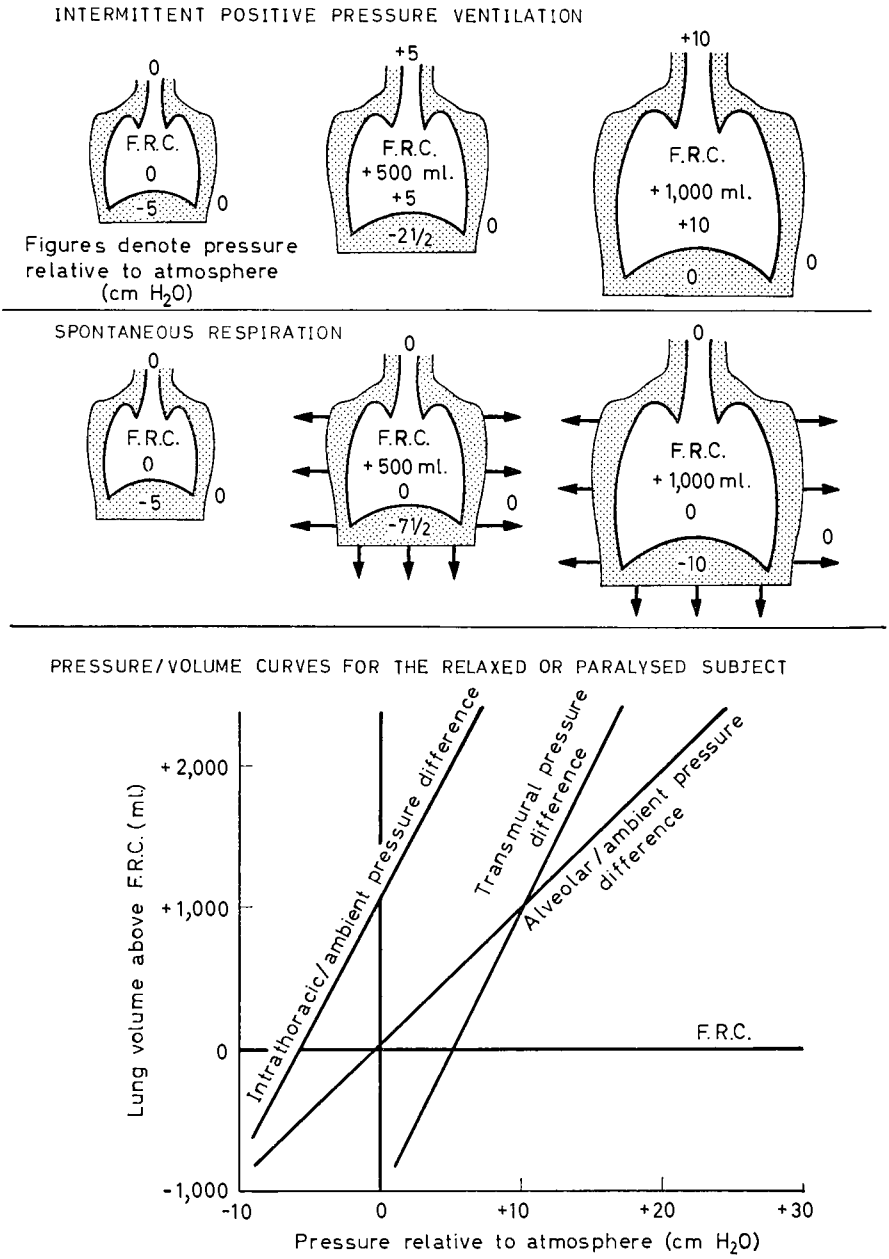


Figure 18. Static pressure/volume relations for the intact thorax for the conscious subject in the upright position. The transmural pressure gradient bears the same relationship to lung volume during both types of ventilation. The intrathoracic to ambient pressure difference, however, differs in the two types of ventilation due to muscle action during spontaneous respiration. At all times:

$$\frac{\text{alveolar/ambient}}{\text{pressure difference}} = \frac{\text{alveolar/intrathoracic}}{\text{pressure difference}} + \frac{\text{intrathoracic/ambient}}{\text{pressure difference}}$$

(due attention being paid to the sign of the pressure difference). Lung compliance, 200 ml./cm H_2O; thoracic cage compliance, 200 ml./cm H_2O; total compliance, 100 ml./cm H_2O

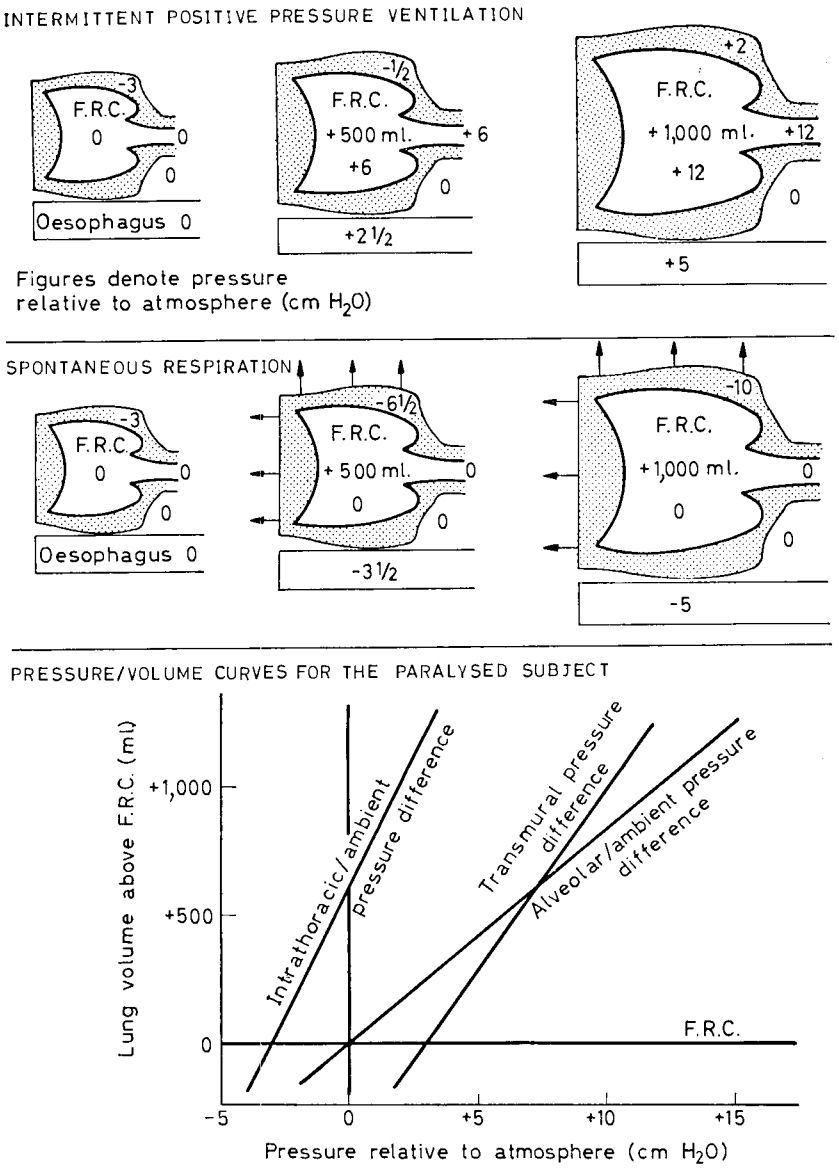


Figure 19. Static pressure/volume relations for the intact thorax for the anaesthetized patient in the supine position. The transmural pressure gradient bears the same relationship to lung volume during both types of ventilation. The intrathoracic-to-ambient pressure difference, however, differs in the two types of respiration due to muscle action during spontaneous respiration. At all times:

$$\begin{matrix}\textit{alveolar/ambient} \\ \textit{pressure difference}\end{matrix} = \begin{matrix}\textit{alveolar/intrathoracic} \\ \textit{pressure difference}\end{matrix} + \begin{matrix}\textit{intrathoracic/ambient} \\ \textit{pressure difference}\end{matrix}$$

(due attention being paid to the sign of the pressure difference). The oesophageal pressure is assumed to be 3 cm H_2O higher than intrathoracic at all times. Lung compliance, 150 ml./cm H_2O; thoracic cage compliance, 200 ml./cm H_2O; total compliance, 85 ml./cm H_2O

The alveolar/intrathoracic pressure difference is a function of lung volume and lung compliance exactly as described above for artificial ventilation. As before, the alveolar/ambient pressure difference equals the algebraic sum of its two components, and in this case the two components must always be equal but of opposite sign at the times of zero air flow.

It is not easy to think in terms of intrathoracic pressure during spontaneous or artificial ventilation of anaesthetized patients. However, *Figures 18 and 19* show how it is possible to arrive at a reasonable estimate of its value, which has an important influence on venous return.

PRINCIPLES OF MEASUREMENT OF COMPLIANCE

Compliance of the various structures is defined as follows:

$$\text{total compliance} = \frac{\text{change in lung volume}}{\text{change in alveolar/ambient pressure gradient}}$$

$$\text{lung compliance} = \frac{\text{change in lung volume}}{\text{change in alveolar/intrathoracic pressure gradient}}$$

$$\text{chest wall compliance} = \frac{\text{change in lung volume}}{\text{change in ambient/intrathoracic pressure gradient}}$$

all measurements being made at the time of zero air flow at the end of inspiration or expiration.

Measurements of chest wall compliance (and total compliance, which includes chest wall compliance) are only meaningful if there is no tone in the respiratory muscles. This means that, in practice, such measurements can only be made in paralysed subjects or, so it is said, in trained subjects who are able to relax their muscles completely.

Changes in lung volume are measured with a spirometer or by integration of a pneumotachogram. Points of zero air flow are best detected with a pneumotachograph.

Static pressures can be measured with a simple water manometer, but rapidly changing pressures require the use of transducers which give an electrical output proportional to pressure. Pressure differences can be measured directly by the use of a double-ended manometer (such as a U-tube filled with water) which is connected between the two points concerned. It has been explained above that intrathoracic or intrapleural pressure varies according to the site at which it is measured, and there is now a widespread convention to accept the pressure in the upper third of the oesophagus as representative of the 'intrathoracic pressure'. Details of measurement of oesophageal pressure by an air-filled balloon have been described by Milic-Emili and his colleagues (1964). Alveolar pressure equals mouth pressure when no gas is flowing. It cannot be measured directly.

Static Compliance

In the *paralysed subject* this is a simple measurement. The lungs are inflated with a known volume of air by any suitable means (such as the pre-set gas syringe described by Janney (1959)), and the inflation pressure is measured

after an interval to allow for equilibration of regional pressure differences, etc. Since this is a static measurement, the simplest form of manometer is adequate and a water-filled U-tube may be used. If only inflation pressure is measured, only total compliance may be determined. If intrathoracic pressure is also measured, it is possible to derive lung and chest wall compliance separately.

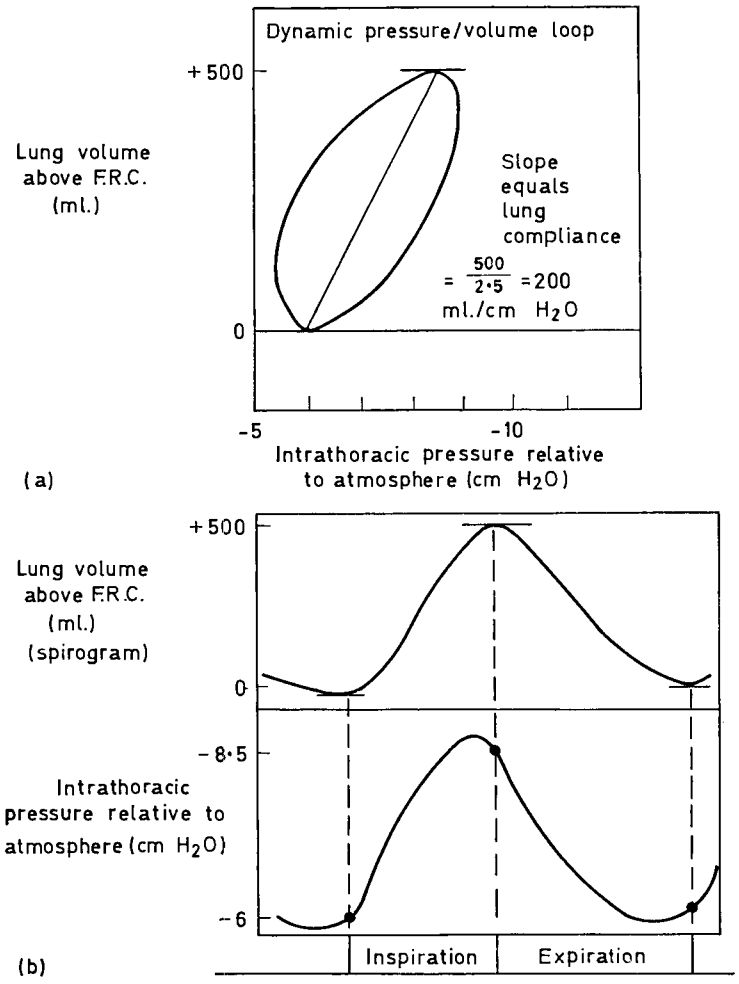


Figure 20. Measurement of dynamic compliance by simultaneous measurement of tidal excursion (lung volume relative to F.R.C.) and intrathoracic pressure (relative to atmosphere). In (a) these parameters are displayed as the Y *and* X *co-ordinates on a two-dimensional plotting device (e.g. cathode ray oscillograph). In (b) they are displayed simultaneously against time on a two-channel oscillograph. In each case, lung compliance is derived as lung volume change divided by transmural pressure gradient change. The transmural pressure gradient is indicated by the intrathoracic pressure (relative to atmosphere) when the lung is not changing. At these times, the alveolar pressure must equal the atmospheric pressure since no gas is flowing. End-expiratory and end-inspiratory 'no-flow' points are indicated in (b). They correspond to horizontal parts of the loop in (a)*

Alternatively, the lungs may be inflated by a constant-flow device such as the Pufflator described in the following chapter in relation to *Figure 37* (Don and Robson, 1965) or the measurement may be made during a passive expiration into a spirometer (Nims, Connor and Comroe, 1955).

In the *conscious subject* a known volume of air is inhaled and the subject then relaxes against a closed airway. The various pressure gradients are compared with the resting values (F.R.C.). It is usually very difficult to ensure that the respiratory muscles are relaxed, but the measurement of lung compliance is valid since the static alveolar/intrathoracic pressure difference is unaffected by respiratory muscle activity.

Dynamic Compliance

These measurements are made during rhythmic breathing, but compliance is calculated from pressure measurements which are made at the points when no gas is flowing, usually at the end-inspiratory and end-expiratory 'no-flow' turn-round points. When gas is flowing, pressures are dependent in part on the resistance to gas flow and, therefore, compliance cannot be derived directly. Two methods are in general use.

Loops.—The required pressure gradient and the respired volume are displayed simultaneously as X and Y co-ordinates on some device which permits the display of two-dimensional phenomena (e.g. a cathode ray oscilloscope, an X/Y plotter or various photographic devices). The resultant trace forms a loop (*Figure 20a*). The no-flow points, when mouth pressure equals alveolar, are identified as the points when the trace is horizontal. The lung compliance equals the slope of the line joining these points, when mouth/intrathoracic pressure difference is measured. Other parts of the loop reflect the resistance to gas flow, and this is discussed in Chapter 4.

Multi-channel recording of volume, pressure gradient and flow rate.—This method differs from the one described above only in the manner of display. The two co-ordinates of the loop (volume and pressure) are plotted simultaneously (against time) on a pen oscillograph (*Figure 20b*). The volume difference is derived from the volume trace and divided by the change in the appropriate pressure gradient measured at the no-flow points. The no-flow points may be identified as the horizontal points of the volume trace (*Figure 20b*) or, more elegantly, by noting the point of phase reversal of a pneumotachogram on a third channel. The pneumotachogram may also be integrated to give volume and, thereby, it is possible to dispense with a spirometer. This method was introduced in 1927 by von Neergaard and Wirz (1927a) and has been used during anaesthesia by Gold and Helrich (1965). Both lung and chest wall compliance may be measured by recording the appropriate pressure differences, and the method is equally suitable for spontaneous and artificial ventilation.

CHAPTER 4

RESISTANCE TO GAS FLOW

Gas flows from a region of high pressure to one of lower pressure. The rate at which it does so is a function of the pressure difference and the resistance to gas flow of the connecting passage (*Figure 21*). The precise relationship between pressure difference and gas flow rate depends upon the nature of the flow which is usually described as being either *laminar* (streamline) or *turbulent*. This distinction is helpful for gaining an understanding of the problem, but it should not be thought that there is a rigid separation between the two types of flow. In most situations relevant to pulmonary ventilation, the flow pattern is transitional, being neither entirely laminar nor entirely turbulent. Furthermore, the flow pattern may vary between different regions of the respiratory tract. For example, there may be laminar flow in the trachea while there is turbulent flow in the larynx.

Coexistence of laminar and turbulent flow makes the quantification of resistance to gas flow rather untidy and imprecise. The approach in this chapter is to consider laminar and turbulent flow separately and then to consider methods of quantifying resistance in the presence of transitional or mixed flow patterns. Physiological and clinical aspects are discussed later.

LAMINAR FLOW

Characteristics of Laminar Flow

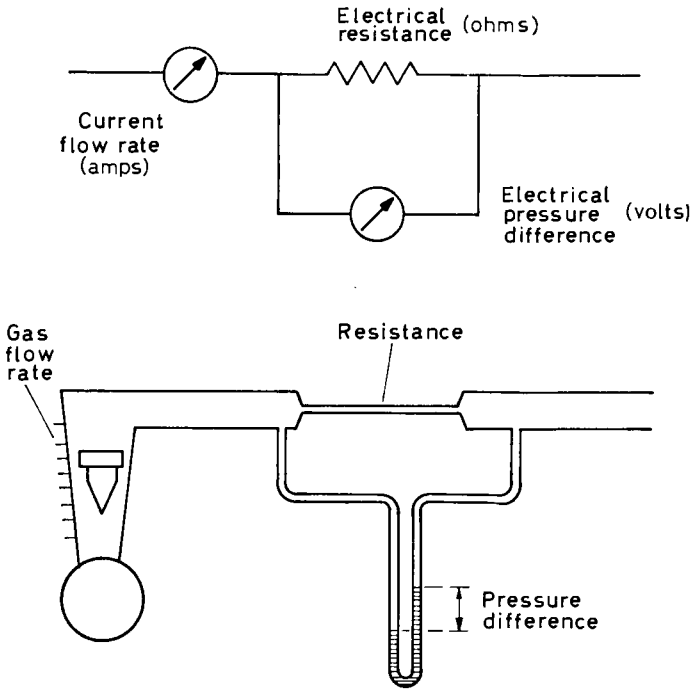
When gas flows slowly along a straight unbranched tube, the pattern of flow conforms to an infinite series of concentric cylinders of gas which slide, one over the other, with the peripheral cylinder stationary, and the central cylinder moving fastest (*Figure 22*). If the composition of the gas entering a region of laminar flow is suddenly changed, the new gas advances down the tube with a cone front. As a general rule, laminar flow is inaudible.

Flushing Effect of Laminar Flow

The advancing cone front of laminar gas flow means that some gas may reach the end of a connecting tube before the total amount of gas entering the tube equals the volume of the tube (*Figure 22*). In terms of anatomical dead space, laminar flow of inspired gas may result in some gas reaching the alveoli when the inspired tidal volume is less than the actual anatomical dead space (defined as the geometrical volume of the conducting air passages). This was foreseen by Rohrer in 1915, and it was demonstrated by Briscoe, Forster and Comroe in 1954 that a tidal volume as small as 60 ml. resulted in some inspired gas reaching the alveoli of conscious man. There can be little doubt that this mechanism plays an important part in the survival of anaesthetized intubated

patients with tidal volumes of the order of 100 ml. Such levels occur during deep anaesthesia with spontaneous respiration, and the patients usually come to no obvious harm.

Although the cone front of laminar flow can reduce the effective volume of conducting tubes, it is also inefficient for purging an unwanted gas from a tube.



$$\text{Resistance} = \frac{\text{Pressure difference}}{\text{flow rate}}$$

Figure 21. Electrical analogy of gas flow. Resistance is pressure difference per unit flow rate. Resistance to gas flow is analogous to electrical resistance (provided that flow is laminar). Gas flow corresponds to electrical current (amps); gas pressure corresponds to potential (volts); gas flow resistance corresponds to electrical resistance (ohms); Poiseuille's law corresponds to Ohm's law

Quantitative Relationships during Laminar Flow

Working with long, straight, unbranched tubes, Hagen and Poiseuille independently demonstrated the relationships which are set out in the following expression:

$$\text{gas flow rate} = \text{pressure gradient} \left(\frac{\pi \times (\text{radius of tube})^4}{8 \times \text{length of tube} \times \text{gas viscosity}} \right)$$

Note that gas flow rate is proportional to the fourth power of the radius. Thus, with a constant pressure gradient, a doubling of the tube radius (or diameter)

results in a sixteenfold increase in flow. Similarly, a sixteenfold increase in pressure is needed to maintain the same flow rate if the diameter of the tube is halved. This effect is more familiar to the anaesthetist in relation to the selection of cannulas for intravenous infusions, but is also true for endotracheal tubes and their connectors.

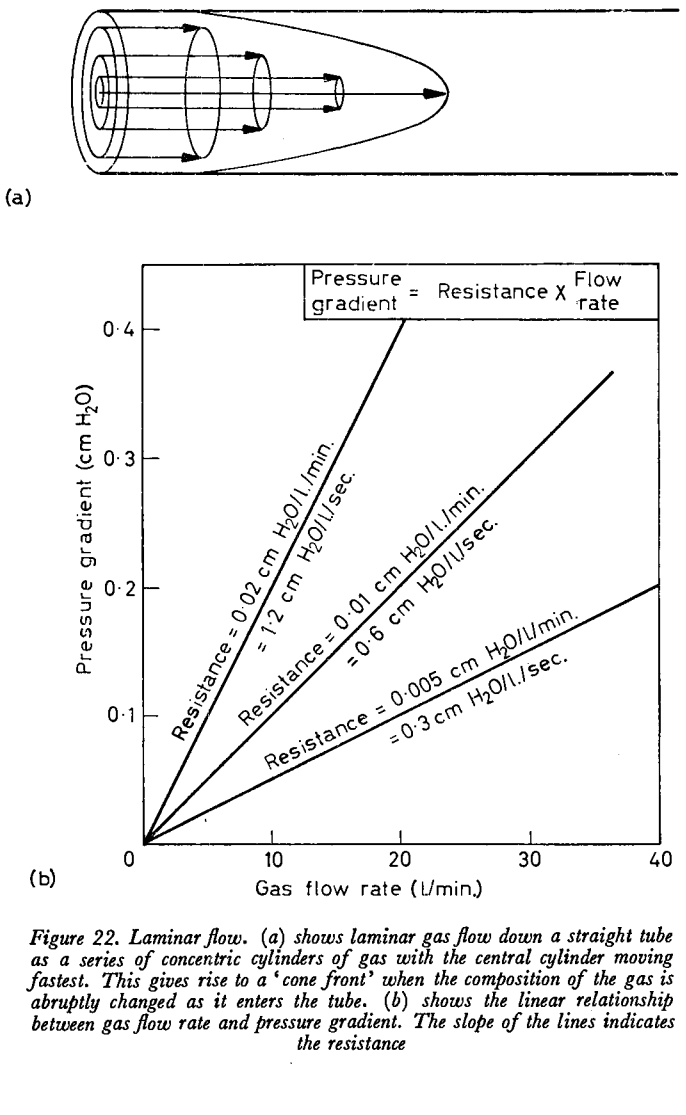


Figure 22. Laminar flow. (a) shows laminar gas flow down a straight tube as a series of concentric cylinders of gas with the central cylinder moving fastest. This gives rise to a 'cone front' when the composition of the gas is abruptly changed as it enters the tube. (b) shows the linear relationship between gas flow rate and pressure gradient. The slope of the lines indicates the resistance

It should be stressed that gas viscosity is the only property of the gas which influences resistance during laminar flow. This is in contrast to density, which is the relevant property during turbulent flow. For example, 70 per cent nitrous oxide/30 per cent oxygen is about 10 per cent less viscous than air although it is about 50 per cent more dense. Therefore, under conditions of

laminar flow, resistance to 70 per cent nitrous oxide/30 per cent oxygen will be slightly less than to air. The substitution of a gas of low density but high viscosity (such as helium) will do nothing to improve gas flow under these conditions. However, when there is difficulty in breathing due to excessive airway resistance, it is almost axiomatic that gas flow is largely turbulent and, under such conditions, density and not viscosity is important. Therefore, low density is almost always the property to be sought in alleviating the effects of high airway resistance.

Assuming that the gas mixture and the geometric properties of the conducting tubes are constant, the Poiseuille equation indicates that pressure gradient will be directly proportional to gas flow rate. Therefore, for any flow rate, pressure gradient divided by flow rate will be constant.

$$\frac{\text{pressure gradient}}{\text{flow rate}} = \text{a constant}$$

This constant may be called the resistance and is, in fact, equal to:

$$\frac{8 \times \text{length of tube} \times \text{gas viscosity}}{\pi \times (\text{radius of tube})^4}$$

Figure 22 shows a plot of pressure gradient against gas flow rate. For laminar flow the plot is a straight line, of which the slope (pressure gradient/flow rate) equals the resistance. A steep slope means a high resistance, while a shallow slope indicates low resistance.

In the Hagen–Poiseuille equation, the units of resistance relate to absolute units of flow and pressure (ml./min. and dyn/sq. cm. respectively). It is, however, permissible to use other units for flow and pressure, in which case the resistance must be expressed in corresponding terms. For respiratory gas flows, resistance is commonly expressed as centimetres of water per litre per second. Resistance to blood flow is often given as millimetres of mercury per litre per minute (*see* Appendix A).

The concept of a constant value for the resistance is only valid in the presence of laminar flow. It will be seen below that the 'resistance' is not constant when flow is turbulent, and therefore it may be meaningless to give a numerical value for resistance under such circumstances. This is unfortunate as some degree of turbulence is almost always present, even in quiet breathing.

One occasionally reads of resistance to gas flow expressed in terms of pressure (strictly a misnomer for pressure gradient). Resistance can only be expressed in terms of pressure gradient if one particular flow rate is stipulated or if the pressure gradient is independent of gas flow rate. This occurs with well designed pressure-relief valves, water blow-off valves, etc. Such devices are known as threshold resistors and are considered below (page 80).

Conductance

It is occasionally convenient to refer to conductance rather than resistance. These two quantities are reciprocally related, and conductance is measured in units such as litres per second per centimetre of water. As with resistance, conductance is only constant during laminar flow, and the term is meaningless when there is an appreciable turbulent component.

Electrical Analogy of Laminar Gas Flow

The relationship between resistance, pressure gradient and gas flow rate during laminar flow is faithfully represented by the simple electrical analogy shown in *Figure 21.* It will be seen that Poiseuille's law is analogous to Ohm's law. Electron flow rate (amps) corresponds to gas flow rate; potential difference (volts) corresponds to pressure difference (or gradient); resistance to electron flow (ohms) corresponds to resistance to gas flow. There is no simple electrical analogue for turbulent gas flow.

TURBULENT FLOW

Characteristics of Turbulent Flow

High flow rates, particularly through irregular tubes, result in a breakdown of the orderly flow of gas described as laminar. The molecules of gas have an irregular movement superimposed upon their general progression along the tube (*Figure 23*). A cone front does not, therefore, occur and the front of a new gas introduced into the system is square. Turbulent flow will arise in a long, straight, unbranched tube if the flow rate is high enough (*see* below), but turbulence is particularly likely to occur when the diameter or the direction of a tube is changed abruptly, or when branching occurs. It is often possible to hear gas flow when it is largely turbulent.

Effects of Turbulent Flow

The absence of a cone front means that no new gas can reach the end of a tube until the volume of gas which has entered the tube is close to the geometrical volume of the tube. The effective dead space is thus maximal when flow is turbulent. On the other hand, turbulent flow is the most efficient for purging a tube of the contained gas.

The serious consequences of excessive resistance to gas flow almost always arise under conditions when the gas flow is turbulent. Avoidance of resistance may, therefore, almost always be considered in relation to turbulent gas flow.

Quantitative Relationships during Turbulent Flow

Quantitative relationships differ from those observed with laminar flow in two important respects:

(1) The pressure gradient required to produce a given gas flow rate is proportional to the square of the gas flow rate.

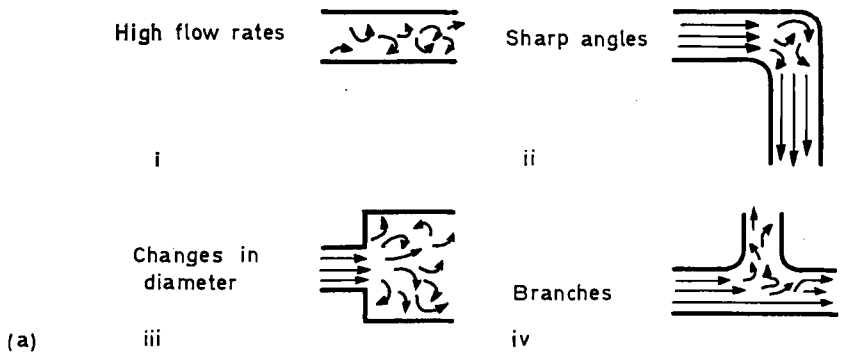
(2) The pressure gradient required to produce a given gas flow rate through a given passage is proportional to the density of the gas and is independent of its viscosity.

The pressure gradient, in theory, is inversely proportional to the fifth power of the radius (or diameter) of the tube (Fanning equation).

The square law relating pressure gradient and flow is shown in *Figure 23.* Since resistance is defined as pressure gradient divided by flow rate, it will be seen that the 'resistance' is not constant but rises in proportion to the flow rate. It is thus meaningless to assign a fixed value for the resistance (defined as pressure drop divided by flow rate) when the flow is turbulent. Alternative methods of defining the resistance are discussed below.

Conditions which Determine the Nature of Gas Flow

We have seen that irregular and branching tubes tend to result in turbulence which may be confined to the immediate region of the irregularity. Abrupt changes in diameter almost invariably cause turbulence, and the square law relationship between pressure gradient and flow rate may easily be demonstrated for certain types of endotracheal catheter mounts.



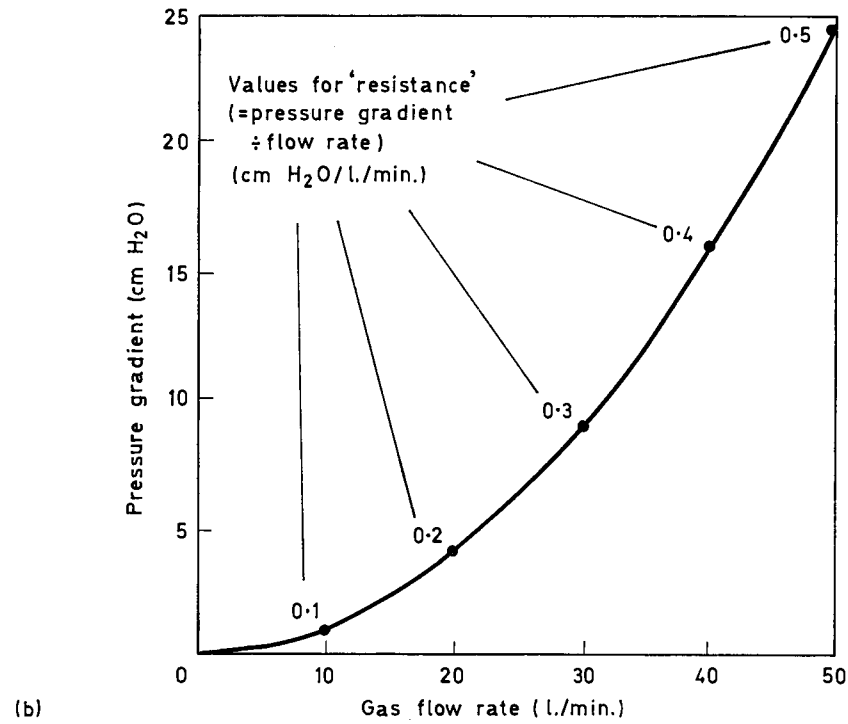


Figure 23. Turbulent flow. (a) shows four circumstances under which gas flow tends to be turbulent. (b) shows the square law relationship between gas flow rate and pressure gradient when flow is turbulent. Note that the value for 'resistance', calculated as for laminar flow, is quite meaningless during turbulent flow

In the case of long straight unbranched tubes, the nature of the gas flow may be predicted from the following: (1) the viscosity of the gas; (2) the density of the gas; (3) the diameter of the tube; and (4) the gas flow rate. The prediction is carried out by calculating Reynolds' number. This is a non-dimensional quantity derived from the following formula:

$$\frac{\text{mean linear velocity of gas} \times \text{tube radius} \times \text{gas density}}{\text{gas viscosity}}$$

each term being expressed in centimetre/gramme/second units. Alternatively, Reynolds' number may be expressed in terms of gas flow rate (mean linear velocity of gas times cross-sectional area of tube). The property of the gas which affects the Reynolds' number is the ratio of the density to the viscosity. This equals the reciprocal of the *kinematic viscosity* which is the viscosity per unit gas density (*Table 5*).

Table 5

Physical properties of anaesthetic gas mixtures relating to gas flow

	Viscosity relative to air	*Vapour density relative to air*	$\frac{\textit{Vapour density}}{\textit{viscosity}}$ *relative to air*
Oxygen	1·11	1·11	1·00
70%N_2O/30%O_2	0·89	1·41	1·59
80%He/20%O_2	1·08	0·33	0·31

When Reynolds' number is less than 1,000, flow is laminar. Above a value of 1,500 flow is entirely turbulent. Between these values both types of flow coexist. The critical values have been determined experimentally, and opinions differ as to the precise values which should be adopted. The figures used here were chosen by Cooper (1961), in an exhaustive study of the resistance of respiratory apparatus.

An example of the relevance of Reynolds' number to problems of gas flow during anaesthesia is shown in *Figure 24*, which indicates the nature of the gas flow to be expected when air, or a mixture of oxygen with either helium or nitrous oxide, passes at various flow rates through tubes of different diameters.

Viscosities of respirable gases do not differ greatly but densities vary by as much as seventyfold (between hydrogen and sulphur hexafluoride). The use of a less dense gas not only reduces the tendency to turbulence but also reduces the resistance to any turbulent flow which is still present. Different gases make an appreciable difference to resistance and this should be borne in mind when the resistance of anaesthetic apparatus is determined by studying air flow, or when a patient with severe resistance to breathing is anaesthetized with nitrous oxide.

THRESHOLD RESISTORS

Certain resistors are designed to allow no gas to pass until a certain threshold pressure is reached. Such devices are generally familiar as the type of safety

valve fitted to boilers and pressure cookers. Ideally, the flow should be zero below the threshold pressure, but once this pressure is reached, high flows should be possible without further increases in pressure gradients across the valve. Unfortunately, this ideal is seldom realized in the commercially available

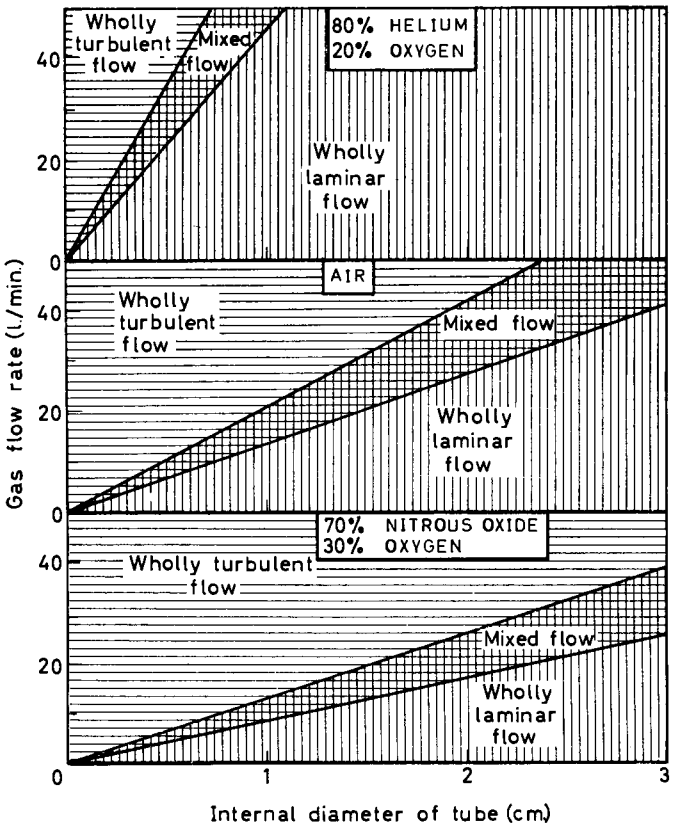


Figure 24. Graphs to show the nature of the gas flow through tubes of various diameters for three different gas mixtures; 25 l./min. is a typical peak flow rate during spontaneous respiration. It will be seen that the nature of flow in the trachea and in endotracheal tubes will be markedly dependent on the composition of the gas mixture

pressure-relief valves used in anaesthesia (*see* 'relief valve' in *Figure 25*). The essential feature in design is sufficient clearance to minimize flow resistance once the valve is open. A water bubbler forms a rough and ready threshold resistor, but a more sophisticated device is needed to obtain really constant pressure at varying flow rates (Smith, 1962). Unidirectional valves can be regarded as special forms of threshold resistors with very low opening pressures.

A threshold resistor is the only type of resistance which may be quantified by pressure drop alone without reference to gas flow rate.

QUANTIFICATION OF 'RESISTANCE' WHEN GAS FLOW IS PARTLY LAMINAR AND PARTLY TURBULENT

In a long straight tube, gas flow tends to be laminar at low flow rates, but becomes progressively more turbulent as the flow rate is increased until eventually full turbulence is reached. *Figure 24* shows that the mixed type of flow must occur commonly under the conditions of anaesthesia. There is thus considerable difficulty in ascribing a numerical value to the 'resistance' of either a patient's air passages or a piece of respiratory apparatus. A number of alternative methods are in use and are detailed below.

Measurement of Pressure Difference at a Single Flow Rate

This method has been used as a simple screening test for resistance and it may be useful if the type of flow is similar in every instance. It can, however, be grossly misleading if the pattern of flow is different. In the examples shown in *Figure 25*, the Heidbrink relief valve and the vaporizers have the same 'resistance' at a flow rate of 32 litres per minute. However, above and below this flow rate, markedly different pressures are needed to maintain the same flow rate through the two types of resistor.

Determination of Two Constants for 'Resistance'

This approach considers resistance as comprising two components, one for laminar flow and the other for turbulent flow. An equation is then derived which expresses the pressure gradient required to maintain flow as the sum of two terms corresponding to the two types of flow:

$$\text{pressure gradient} = \underset{\left[\begin{smallmatrix}\text{laminar}\\ \text{component of}\\ \text{resistance}\end{smallmatrix}\right]}{k_1\,(\text{flow})} + \underset{\left[\begin{smallmatrix}\text{turbulent}\\ \text{component of}\\ \text{resistance}\end{smallmatrix}\right]}{k_2\,(\text{flow})^2}$$

k_1 contains all the constant factors of the Hagen–Poiseuille equation (gas viscosity, tube radius, etc.), while k_2 includes all the constant factors in the corresponding equation for turbulent flow (gas density, tube radius, etc.). This approach was used by Rohrer in his classical post-mortem study of the human air passages in 1915. He derived the following equation for the flow resistance of the human air passages:

$$\text{pressure gradient} = 0{\cdot}79\,(\text{flow}) + 0{\cdot}81\,(\text{flow})^2$$

(pressure being measured in cm H_2O and flow rate in l./sec.). More recent studies on living patients (Fry and his colleagues, 1954) have given the values:

$$\text{pressure gradient} = 1{\cdot}50\,(\text{flow}) + 0.71\,(\text{flow})^2$$

Both components are increased in emphysema. This type of equation is cumbersome and can only be an approximation of the true relationship, but nevertheless has proved useful.

Determination of Constants K and n

Over a surprisingly wide range of flow rates, the equation above may be condensed into the following single term expression:

$$\text{pressure gradient} = K\,(\text{flow})^n$$

In this equation the exponent n has a value of 1 in purely laminar flow and 2 in purely turbulent flow. With mixed flow the value of n varies between 1 and 2. K is an omnibus constant comprising the various constituents of the constants k_1 and k_2 mentioned above. It is clear that this equation cannot apply throughout the whole range of flows since the value of n must change from 1 to 2, as the flow pattern changes from purely laminar to purely turbulent. Nevertheless, it is found in practice that the values of both K and the exponent n are often

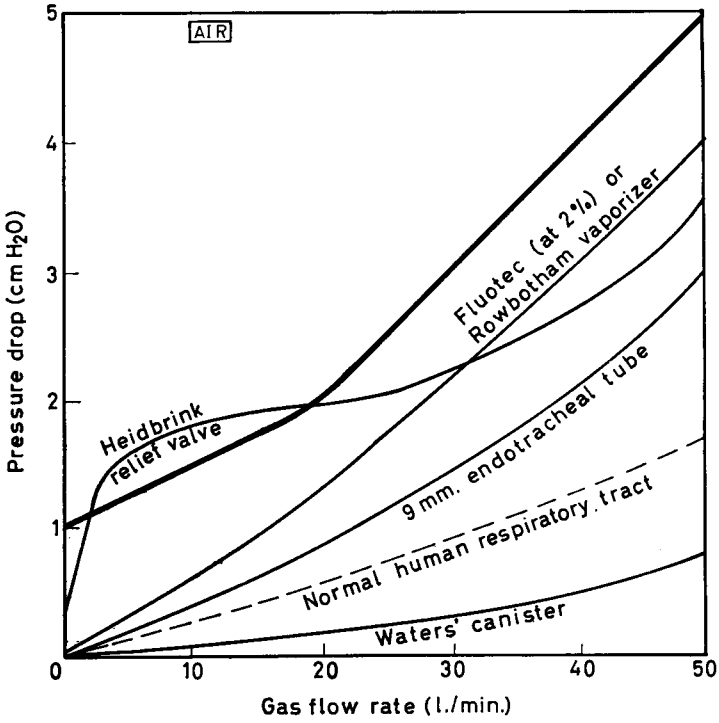


Figure 25. A linear plot of pressure drop against gas flow rate for various pieces of anaesthetic apparatus, compared with the normal human respiratory tract. The heavy line is the author's suggested upper limit of acceptable resistance for an adult patient. With 70 per cent N_2O/30 per cent O_2, the pressure drop is about 40 per cent greater for the same gas flow when the flow is turbulent. There is little difference when the flow is chiefly laminar

reasonably constant throughout the range of flows encountered in clinical practice. This method of statement of resistance has the advantage that the nature of the flow is indicated by the value of n. However, it must be remembered that the expression is at best an approximation and, furthermore, is only applicable between limits which should be stated. The expression has been used by Cooper (1961) for assessment of the resistance of breathing apparatus.

Using this convention, resistance of the normal human respiratory tract may be expressed as follows:

$$\text{pressure gradient} = 2{\cdot}4\ (\text{flow})^{1{\cdot}3}$$

This does not differ by more than 10 per cent from the two-term expression above, over the range of flow 0·2–3·0 litres/second.

Flow Rate/Pressure Gradient Plot (linear)

Probably the best all-round method of describing resistance to gas flow is by constructing a plot of pressure gradient against flow rate on linear graph paper. This, of course, will relate only to a particular air passage and a particular gas or gas mixture. *Figure 25* shows a typical plot for a variety of anaesthetic

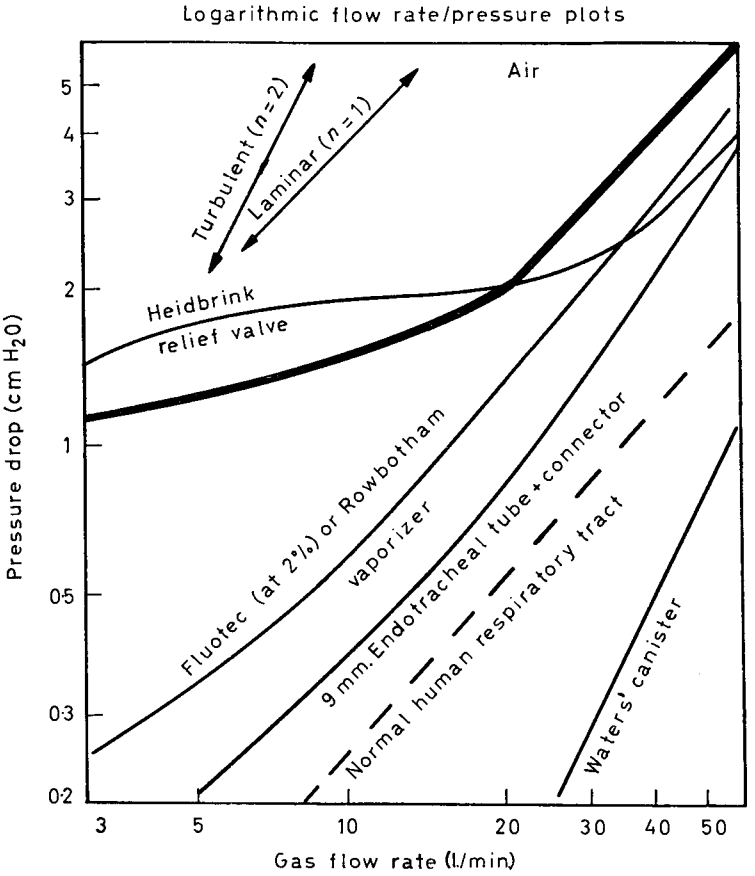


Figure 26. The data of Figure 25 replotted on logarithmic co-ordinates. Note that many of the curves become straight lines. A slope of 2 indicates wholly turbulent flow; a slope of 1 indicates wholly laminar flow; a slope of zero indicates a threshold resistor

components compared with the normal human air passages. This method of presentation is particularly valuable for describing the performance of threshold resistors. Once these are beyond their opening pressure, gas flow often tends to be turbulent and so they commonly present S-shaped flow rate/pressure gradient characteristics which cannot be conveniently expressed in mathematical form.

Cathode ray tubes or *X–Y* recorders may be used to make direct plots of pressure gradients against flow rates during respiration. This is a particularly elegant method for displaying the resistance of the nose or external breathing apparatus. One deep breath is sufficient for displaying the characteristics of flow in both directions.

Flow Rate/Pressure Gradient Plot (logarithmic)

Logarithmic plots have two great virtues. Firstly, they enable a wide range of values to be displayed. Secondly, many curves become straight lines when values are plotted as their logarithms. Both considerations apply to the problems of display of resistance to gas flow. When log pressure is plotted against log flow, the curve will be a straight line for both linear and turbulent flow, with a slope of 1 in the former case and 2 in the latter. The slope equals the value for the exponent n in the expression:

$$\text{pressure gradient} = K\ (\text{flow})^n$$

Figure 26 shows the data from *Figure 25* replotted on logarithmic co-ordinates. The following advantages of the logarithmic plot may be claimed:

(1) Low flow rates may be distinguished on the same plot as very high flow rates.

(2) Laminar flow is distinguished by a slope of 1·0. Turbulent flow is distinguished by a slope of 2·0. The degree of turbulence may thus easily be derived from the slope.

(3) The slope is often fairly constant throughout a wide range of flows. Under these circumstances, the flow rate/pressure gradient characteristics can be plotted from only two experimental observations.

MINOR SOURCES OF RESISTANCE TO GAS FLOW

There remain a number of sources of resistance to gas flow which have not been considered. Fortunately they are all small and can usually be ignored.

(1) The frictional resistance of lung tissue to deformation offers a resistance to gas flow equal, in the normal subject, to about a fifth of the resistance to gas flow through the air passages. Pulmonary tissue resistance is increased in the diseases grouped together as pulmonary fibrosis. Certain methods of measurement of resistance include the pulmonary tissue component, and the total quantity so measured is known as *pulmonary resistance.* Other methods, notably the body plethysmograph (*see* below), exclude the pulmonary tissue component, and the quantity so measured is specified as the *airway resistance.*

(2) Moving parts of external breathing apparatus can offer a resistance analogous to pulmonary tissue resistance. Good design should minimize this.

(3) The thoracic cage, diaphragm and abdominal contents offer a resistance to the flow of gas, but this component is difficult to measure.

(4) Respired gases, moving parts of breathing apparatus, lung and chest wall have appreciable inertia and, therefore, offer resistance to changes in direction of gas flow. This component is usually negligible.

INCREASED AIRWAY RESISTANCE

It is unusual to measure airway resistance in clinical practice, and the degree

of resistance is commonly assessed in terms of the response of the patient. Four grades may be recognized.

Grade 1. Slight resistance, against which the patient is able to sustain indefinitely an increased respiratory effort sufficient for the maintenance of alveolar ventilation. Arterial blood gas levels remain within normal limits (arterial P_{CO_2} 36–44 mm Hg).

Grade 2. Moderate resistance, against which a considerable respiratory effort is required to avert a deterioration in blood gas levels. In some patients the increased effort is well sustained and the arterial P_{CO_2} does not rise appreciably in spite of substantial resistance. In cases of chronic bronchitis and obstructive airway disease, such patients have been referred to as 'pink puffers', in contrast to 'blue bloaters' who allow their ventilation to decrease in the face of a similar degree of resistance.

Grade 3. Severe resistance, against which no patient is able to sustain an increased respiratory effort sufficient to prevent a deterioration in blood gas levels which threatens the life of the patient. This means a rise in P_{CO_2} above about 80 mm Hg. The corresponding fall of P_{O_2} is often influenced by abnormalities of distribution which are usually present. Thus, in patients with obstructive airway disease, the fall in P_{O_2} is usually greater than the rise in P_{CO_2} and the latter is a better indication of the ventilatory state.

Grade 4. Respiratory obstruction may be defined as an increase of airway resistance against which neither the patient himself, nor artificial ventilation, can achieve a ventilation sufficient to maintain life. The limiting factor is usually hypoxia.

It is not possible to define the actual levels of resistance which separate these grades, since much will depend on the duration of the obstruction and the ability of the patient to increase his respiratory effort. The disturbance of ventilation and blood gas levels are the most practicable methods of assessment.

Sites of Increased Airway Resistance

External Apparatus

Respiratory apparatus often causes resistance which is considerably higher than that afforded by the normal human respiratory tract (*Figure 25*). It is difficult to say what level of resistance is unacceptable and when design must be considered faulty. It should be remembered how very high the airway resistance of a 'normal' patient may be during anaesthesia (Bodman, 1963), and how very powerful are the compensatory powers of the anaesthetized patient (page 101). As a general guide, the heavy line in *Figure 25* indicates a level of resistance which may be considered excessive.

When a number of resistors are joined in series to form an anaesthetic gas circuit, they may interact upon one another in a very complex manner. In general, they summate after the manner of electrical resistors in series, but detailed studies show that they may alter the pattern of air flow through one another so that the combined resistance cannot be predicted (Smith, 1961). It is even possible that the total resistance may be *less* than that of individual components.

The most important sources of external resistance are narrow tubes, and generators of turbulence such as sharp bends and sudden changes in diameters. It is well known that a reduction in diameter of a tube will increase the pressure gradient between its ends by a factor equal to at least the fourth power of the reduction in diameter. *Figure 27* shows this effect illustrated by various sizes of endotracheal tubes.

Vaporizers are classified fairly sharply into those which are suitable for draw-over use and those which require an external source of energy to drive gas

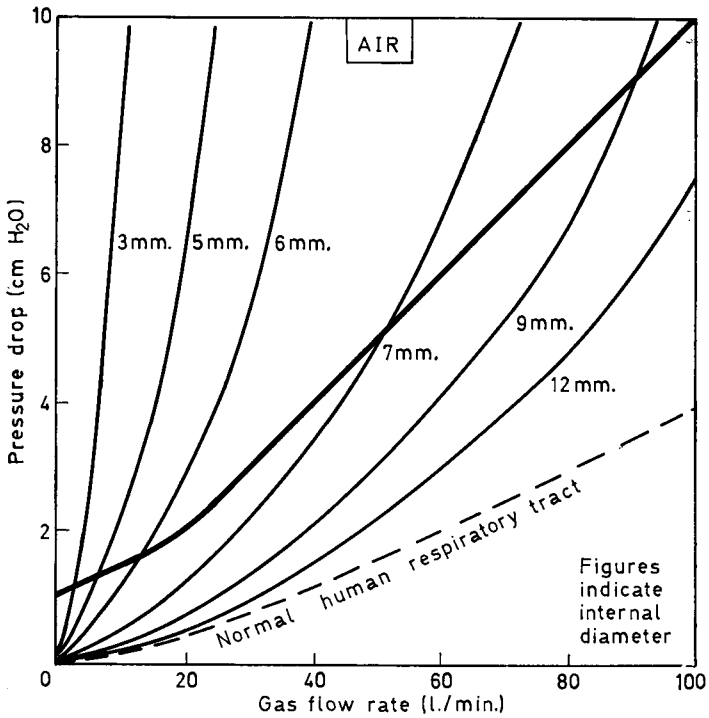


Figure 27. Flow rate/pressure drop plots of a range of endotracheal tubes, with their connectors and catheter mounts. The heavy line is the author's suggested upper limit of acceptable resistance for an adult. Pressure drop does not quite increase according to the fourth power of the diameter (inverse) because the catheter mount offered the same resistance throughout the range of tubes. With 70 per cent N_2O/30 per cent O_2, the pressure drop is about 40 per cent greater for the same gas flow rate when flow is turbulent, but little different when the flow is chiefly laminar

through them. The Rowbotham and Fluotec (mark II) vaporizers are normally regarded as falling within the latter category but, in fact, offer less resistance than a catheter mount with an 8 mm. Magill tube (providing the setting of the Fluotec does not exceed 2 per cent; Nunn, 1961b).

Countless published articles describe the resistance of anaesthetic apparatus. Very simple methods of measurement of resistance are available, and it is valuable for anaesthetists to spend a little time on the measurement of the

resistance of the apparatus which they customarily use. Not only will they derive valid figures for their own apparatus, but they will also learn a great deal about the concept of 'resistance' which cannot easily be gleaned from a textbook.

No aspect of apparatus resistance approaches the clinical importance of obstruction. This is prone to occur at certain well known sites and is always potentially lethal.

(1) Closure of taps fitted to the Y-piece of some makes of circle apparatus. Such taps should be removed.
(2) Closure of taps to reservoir bags during use with low flows of fresh gases.
(3) Kinking of endotracheal tubes, and clenching of teeth on them.
(4) Obstruction of endotracheal tubes and their connectors by foreign bodies, herniated cuffs, dilatations of their walls, etc.

The danger is greatest when using unfamiliar apparatus, but it is always incumbent on the anaesthetist to carry out a functional test of the apparatus before commencing an anaesthetic.

The Upper Air Passages

As in the case of external apparatus, the effects of changes in resistance are of small importance compared with obstruction. The causes of upper respiratory tract obstruction may be conveniently classified in the customary manner:

(1) Obstruction due to foreign material within the lumen.
(2) Obstruction due to thickening or contraction of the walls of the air passages.
(3) Obstruction due to displacement of the walls of the air passages, by forces acting from outside.

Obstruction due to foreign material within the lumen.—Gastric contents, blood and forgotten packs are the most important foreign bodies which may obstruct the upper air passages.

Obstruction due to contraction of muscles occurs in laryngeal spasm, inspiratory stridor and coughing, but *thickening of the mucosa* is the dominant factor in nasal resistance and in laryngeal and cricoid oedema. The larynx may also be obstructed by neoplasm and by membranous diphtheria.

Obstruction due to outside forces may occur with retropharyngeal abscess, Ludwig's angina, thyroid enlargement and, most commonly, relaxation of the muscles of the tongue. The last usually affords the major preoccupation for the beginner in the field of anaesthesia. Three studies have correlated lateral radiographs with the degree of pharyngeal obstruction occurring in the unconscious patient (Safar, Escarraga and Chang, 1959; Morikawa, Safar and DeCarlo, 1961; Ruben and his colleagues, 1961). In the conscious subject, the antero-posterior distance from the back of the tongue to the posterior pharyngeal wall is about 10 mm. Relaxation of the muscles between the tongue, larynx and chin causes marked reduction of this clearance in the unconscious subject, changes being similar for prone and supine positions provided the position of the head is unchanged relative to the trunk. Clearance is, however, markedly dependent upon the flexion of the head at the atlanto-occipital joint. Flexion

usually results in total obstruction, while extension usually increases the clearance to a value comparable with that in the conscious subject. Further improvement is obtained by closing the mouth, which puts further tension on the soft parts. Finally, the mandible may be protruded in the time-honoured manœuvre of the anaesthetist. The workers listed above are agreed that extension of the neck is the single most effective method of minimizing airway resistance.

Clearing of the airway by these means inevitably increases the anatomical dead space of the pharynx. A study by Nunn, Campbell and Peckett (1959) showed that, between the positions of neck flexion and neck extension with jaw protrusion, the anatomical dead space is increased by 70 ml. A patient with hypoventilation might thus pass over the narrow margin into respiratory failure as a result of over-enthusiastic attempts to minimize resistance in the pharyngeal airway. Therefore, if for some reason artificial ventilation is not practicable, it is preferable to secure the airway with an endotracheal tube or at least an oropharyngeal artificial airway. The significance of upper airway obstruction during use of the manual methods of artificial ventilation (e.g. Holger Nielsen technique) is outlined on page 142.

Carcinoma of the larynx, diphtheria, cricoid and subcricoid oedema can all give rise to a severe narrowing of the air passages which may remain undetected in the hospital patient who is at rest. Provided he remains calm, he can withstand surprisingly high resistance. However, once he is alarmed and starts to struggle, he enters a vicious cycle of raised oxygen consumption, increased ventilatory demand, increased pressure gradients, panic and struggle, leading to further increase in oxygen consumption.

It is difficult to say what degree of resistance will precipitate such a crisis, but a number of years ago the author encountered a patient who, five days after gastrectomy, suddenly developed intense dyspnoea. Laryngoscopy revealed a ring of oedematous tracheal mucosa about the level of the cuff on the endotracheal tube used at operation. The lumen of the trachea would not admit a 4 mm. endotracheal tube (the smallest in the emergency kit), and the patient died before tracheostomy could be completed. The interval between lying quietly in bed and death had not exceeded 20 minutes, and it is likely that the oedema had been present for a considerable time before the patient became aware of its presence. Increase in minute volume would then increase the pressure gradient according to the square of the change in minute volume and it is easy to understand the mounting panic of the patient.

The Lower Air Passages

Obstruction of the lower air passages is serious since it cannot be relieved by intubation or tracheostomy. Increased resistance is a most important feature of many respiratory diseases.

Obstruction due to foreign material within the lumen may result from inhaled gastric contents, blood, ruptured lung abscess, excessive secretions, drowning, pulmonary oedema or displacement of tumours fungating into the bronchi. Inflatable blockers and packing may be deliberately introduced during thoracic surgery. In the absence of effective coughing, obstruction by foreign material can only be cleared by suction or sometimes by postural drainage if the material is sufficiently liquid.

Thickening of the mucosa or constriction of the bronchiolar musculature is a common response to a wide variety of allergens and irritants, including bronchial instrumentation with inadequate anaesthesia. Of particular importance to the anaesthetist is the development of these forms of resistance after inhalation of gastric contents. In the rabbit at least, it appears to be the acid of the gastric contents which is primarily responsible (Mendelson, 1946), and a solution of sodium bicarbonate may be used for bronchial lavage when acid contamination is suspected. In many forms of respiratory disease, particularly asthma, swelling of the mucosa and bronchoconstriction are important features. Bronchoconstriction may be induced by histamine, parasympatho-mimetic drugs or anticholinesterases, particularly some of the nerve gases. Certain anaesthetic agents including thiopentone are believed to render the patient more liable to bronchoconstriction. *d*-Tubocurarine, with its reputation for histamine release, has been suspected as a potential bronchoconstrictor, but Gerbershagen and Bergman (1967) found no significant change of airway resistance when large doses of *d*-tubocurarine were administered to a series of anaesthetized patients.

A number of agents will dilate the bronchioles. Atropine in dosage of 1·0 mg. increases the anatomical dead space by about 20 ml. (Nunn and Bergman, 1964). Aminophylline (200 mg.) is a popular therapeutic agent but probably not as effective as a beta-sympathomimetic agent such as isoprenaline. Since this agent may also cause cardiac arrhythmias, it is usually given by droplet inhalation, although the intravenous administration of 1–2μg. may be used in emergencies.

Obstruction by pressure from outside the lumen remains perhaps the most important cause of lower airway obstruction. It is usually the least amenable to treatment. The air passages are held open by the following two mechanisms.

(1) *Structural rigidity* is relatively more important in the cartilaginous tubes (*see Table 1*).

(2) *Transmural pressure gradient* is the sole factor maintaining the patency of the smaller non-cartilaginous tubes. The intraluminar pressure is normally close to atmospheric while the surrounding intrathoracic pressure tends to be subatmospheric. The transmural pressure gradient is the difference between the two pressures and depends on the elastic recoil of the lungs (*Figure 13*).

During a forced expiration (*Figure 28*) the intrathoracic and alveolar pressures are raised considerably above atmospheric. This results in a rapid outflow of gas and, since part of the resistance lies in the smaller air passages, a pressure drop will occur between the alveoli and the main bronchi. Under these circumstances the intrathoracic pressure rises considerably above the pressure within the main bronchi. Collapse will occur if this reversed pressure gradient is sufficiently high to overcome the structural rigidity of these tubes. In fact, such collapse is know to occur in the normal subject during a maximal forced expiration and it is responsible for the associated wheeze (Dekker, Defares and Heemstra, 1958). This effect is particularly prominent in bronchi with a posterior membranous sheath which appears to invaginate into the lumen.

The limitation of air flow rate by bronchial collapse is much more marked in emphysematous patients. The resistance in the small bronchi of these patients

is higher and, therefore, the pressure drop from the alveoli to the larger bronchi is greater. During a forced expiration, the adverse pressure gradient across the walls of the bronchi will thus tend to be greater. To make matters worse, the bronchi of the emphysematous patient are much less able to withstand collapse than those of the normal subject (Macklem, Fraser and Bates, 1963). These factors combine to render the emphysematous patient particularly liable to bronchial collapse during a forced expiration, and Macklem has demonstrated

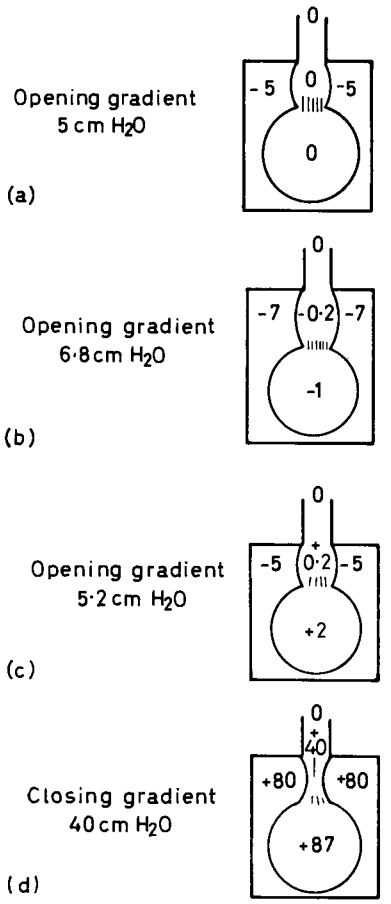


Figure 28. Typical transmural pressure gradients of the intrathoracic air passages under various conditions of ventilation. Note the pressure drop occurring in the smallest air passages, leading to a pressure difference between the alveoli and the larger air passages. (a) Static pressures at the end of expiration (upright, conscious subject). (b) Pressures at the middle of a normal inspiration. Note the increased favourable transmural pressure gradient of the intrathoracic airway. (c) Pressures at the middle of a normal expiration. Note the decreased (but still favourable) transmural pressure gradient of the intrathoracic airway. (d) Typical pressures during a forced expiration. Note the unfavourable transmural pressure gradient of the intrathoracic airway—leading to collapse

this clearly by cinebronchography. Limitation of air flow rate by this mechanism is an important factor in reducing the effectiveness of coughing, and may play a part in the impairment of ventilatory capacity. It is fortunate that bronchial collapse is immediately reversed at the next inspiration.

A similar mechanism of airway closure operates in asthmatic patients, but the critical zone of closure is probably the smaller bronchi. Collapse is again caused by an adverse transmural pressure gradient which reaches a high level because of resistance between the alveoli and the site of collapse. In the

asthmatic patient this resistance is due to bronchiolar spasm and mucosal oedema, and usually responds to therapy.

The alveolar duct is structurally the weakest part of the air passages and collapse at this site is of the greatest importance. It differs quantitatively from collapse at the two sites mentioned above, since the obstruction tends to be complete, causing *trapping* of the alveolar gas. Clinically, trapping is demonstrated by asking the patient to make a forced expiration into a spirometer. The expiratory spirogram is then compared with a trace obtained during a slow expiration and trapping is indicated by the forced expiration being the slower, often arresting at a lung volume above the functional residual capacity (*Figure 29*). It is generally assumed that the obstruction occurs at the level of the alveolar duct, although this cannot be confirmed by direct observation and it is difficult to exclude the possiblity of obstruction at the bronchiolar level. Trapping reduces both ventilatory capacity and air flow rate during coughing.

It was shown in Chapter 3 that closure of small airways occurs spontaneously towards the end of a maximal expiration, since the calibre of these passages varies with the lung volume (*Figure 13*). This important effect is shown as an increase in airway resistance as expiration proceeds into the expiratory reserve (Cheng, Godfrey and Shepard, 1959) and there is evidence that, as residual volume is approached, there is total airway closure in the dependent parts of the lung (Milic-Emili and his colleagues, 1966). The role of this effect in the limitation of a maximal expiration has been discussed in Chapter 3 (page 52).

In the normal patient the patency of the alveolar duct is maintained by the retraction of the alveolar septa in the surrounding lung parenchyma. This force is thought to be largely due to surface tension at the alveolar lining fluid/gas interface. *Figure 29a* shows a hypothetical transverse section of an alveolar duct showing how the surrounding septa act like the guy ropes of a tent. Destruction of septa in emphysema will thus render the alveolar ducts more liable to closure. Expiratory obstruction from this cause is perhaps the most important feature of the disease. Studies by Campbell, Martin and Riley (1957) have shown that maximal expiratory flow rate occurs with intrathoracic pressures of only 9 cm H_2O in emphysematous patients, compared with 26 cm H_2O in asthmatic patients, and 45 cm H_2O in normal subjects. The resultant peak expiratory flow rate was of the same order in both the emphysematous and asthmatic patients.

Although the patient with obstructive airway disease often has some bronchiolar constriction, which may be reversible by therapy, the changes leading to trapping are irreversible and usually progressive. Three factors are important for the maintenance of such ventilation as the pathology permits. Firstly, the F.R.C. usually increases giving rise to the familiar barrel chest. This is a normal response to expiratory resistance from any cause and confers the double advantage of increasing the calibre of the ducts and also raising the alveolar transmural pressure gradient, both changes helping to reduce the tendency towards alveolar duct collapse. Secondly, the patient learns to raise the expiratory resistance of his upper airway by grunting or pursed-lip breathing. *Figure 29b* shows how this alters the pressure gradients along the respiratory tract in his favour. Thirdly, the patient tries to avoid making forced expirations although this is, of course, essential for coughing. Failure of effective coughing is often more distressing than the limitation of ventilatory capacity.

These considerations offer some guidance in the anaesthetic management of patients with obstructive airway disease. The avoidance of trapping is clearly

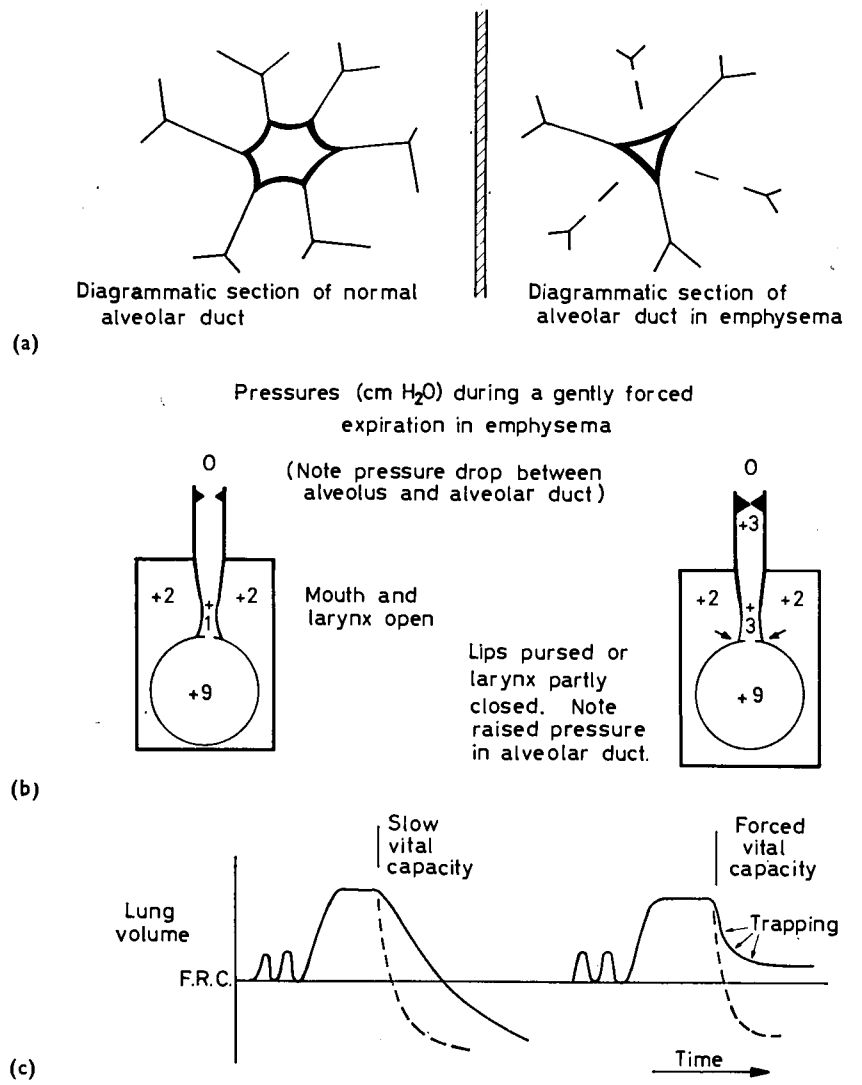


Figure 29. Mechanism of trapping in the alveolar duct. (a) Hypothetical transverse sections of the alveolar duct showing loss of 'guy rope' action in emphysema. (b) On the left is shown the development of an unfavourable transmural pressure gradient across the alveolar duct during a gently forced expiration. On the right, pursing of the lips tends to maintain the pressure in the alveolar duct. (c) Spirogram of slow and forced vital capacity in a patient with trapping. Normal expirations are shown by the dotted lines

important, both for the maintenance of ventilation and also for minimizing the elevation of the mean intrathoracic pressure with its unfavourable effects upon venous return. The first principle is the avoidance of a reduction in the F.R.C.

or, perhaps, the maintenance of a slightly increased F.R.C. Butler (1957) showed that an increase in F.R.C. of 500 ml. caused a very marked reduction of expiratory resistance in a group of anaesthetized patients, over the age of 35, who complained of cough (although they had normal chests on clinical and x-ray examination). The second principle is the avoidance of excessive expiratory

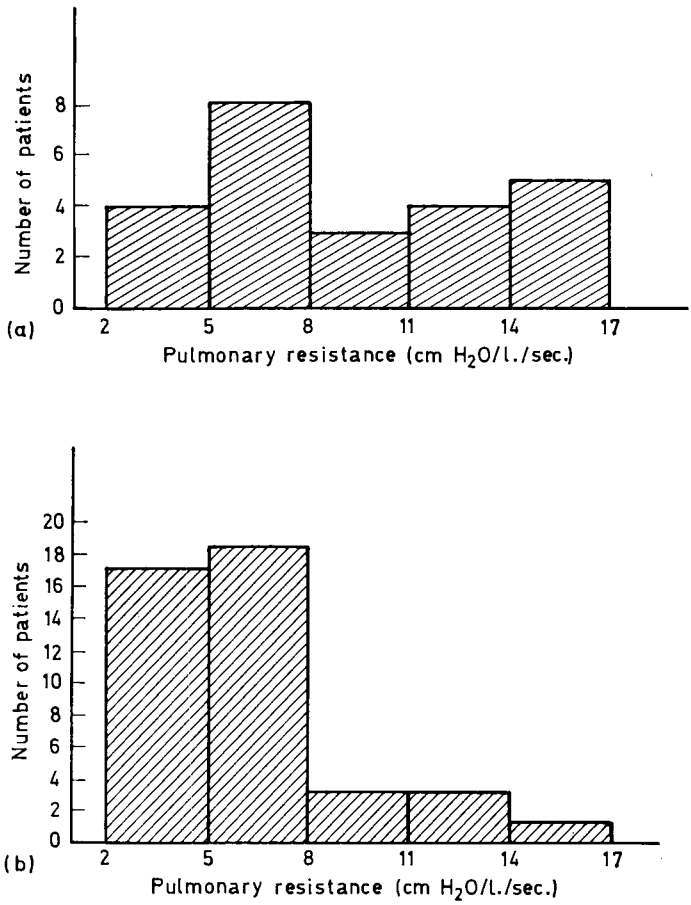


Figure 30. Histograms of measured resistance to breathing in anaesthetized patients. (a) All patients were over 53 years and undergoing urological surgery (most with impaired ventilatory function) (Bodman, 1963). (b) Pooled data of three series of anaesthetized patients without impairment of ventilatory function. Data from the series of patients in (b) have been pooled, as the results of each study showed a similar distribution of values. These studies contrast sharply with the patients in (a), most of whom showed pre-operative evidence of obstructive airway disease

muscular activity, which checks expiration so markedly in the conscious emphysematous patient. In the paralysed patient, the use of a subatmospheric pressure phase is analogous to a forced expiration in the conscious subject, and a 'negative phase' may set up the same adverse pressure gradients and so cause trapping.

There are strong theoretical objections to the use of a subatmospheric pressure in patients with obstructive airway disease. Both the forced expiration and the reduction of F.R.C. would appear to be potent causes of trapping and this is confirmed by the work of Butler (1957). It would even seem likely that the use of an external expiratory resistor might prove helpful. Nevertheless, Jaques (1957) and Siebecker and Curtis (1957) have described beneficial effects of subatmospheric pressures and so perhaps the matter does not have the clinical significance that theoretical considerations would suggest. Further research is needed.

There have been comparatively few studies of the resistance of the lower respiratory tract of anaesthetized human patients. Butler (1957) found that the total pressure swing required to achieve a ventilation of 10 l./min. in young paralysed patients was approximately double the value predicted from data of conscious patients and considerably higher values were obtained in older patients. Changes in compliance would not account for this difference, and thus it appeared that resistance to gas flow was increased. Bodman (1963) reported measurements of expiratory flow resistance in a series of paralysed patients undergoing urological surgery, many of the older patients having some impairment of respiratory function. He obtained normal values (within the range 1·2–3·2 cm H_2O/l./sec.) in 3 patients below the age of 36. However, in 24 patients above the age of 53, values were widely scattered and ranged as high as 16 cm H_2O/l./sec. (excluding the resistance of the endotracheal tube, connector, catheter mount, etc., which ranged from 4·8–9·2 cm H_2O/l./sec.). Bodman's values for older patients are displayed as a histogram in *Figure 30a* where they contrast with considerably lower values obtained in three series of rather younger anaesthetized patients, not showing evidence of impaired ventilatory function. There is a remarkable degree of uniformity in the results of these studies and they all report a mean respiratory resistance of about 6 cm H_2O/l./sec.

Newman, Campbell and Dinnick (1959) reported a few 'specimen results' in connection with the description of a technique for measurement of resistance which, in fact, formed the basis of the method used by Bodman (1963). They expressed their results as the pressure drop at a flow rate of 0·5 l./sec., and the values ranged from 0·5 to 3·0 cm H_2O in a series of 8 healthy patients whose ages were not recorded. In 5 patients they were able to show that expiratory resistance was almost double the inspiratory resistance.

From these few studies, it seems that, during anaesthesia, the resistance to gas flow offered by the lower air passages is about double the resistance offered by the whole respiratory tract of the conscious subject. Expiratory resistance is higher than inspiratory, particularly in the older 'chesty' patient. Expiratory resistances up to 20 cm H_2O/l./sec. must be expected in the older routine surgical patients.

THE EFFECTS OF INCREASED RESISTANCE TO BREATHING

The Relationship between Peak Flow Rate, Mean Flow Rate and Minute Volume

Some of the more important effects of increased resistance to breathing are due to the abnormal pressure gradients resulting from the tidal flow of gas past the elevated resistance. It is, therefore, important to appreciate the relationship

between the instantaneous rate of gas flow and the minute volume. In the examples below, the minute volume is assumed to be 7 l./min.

Triangular waveform.—If inspiration and expiration have equal duration and constant gas flow rates without any pauses, it follows that the peak flow rates

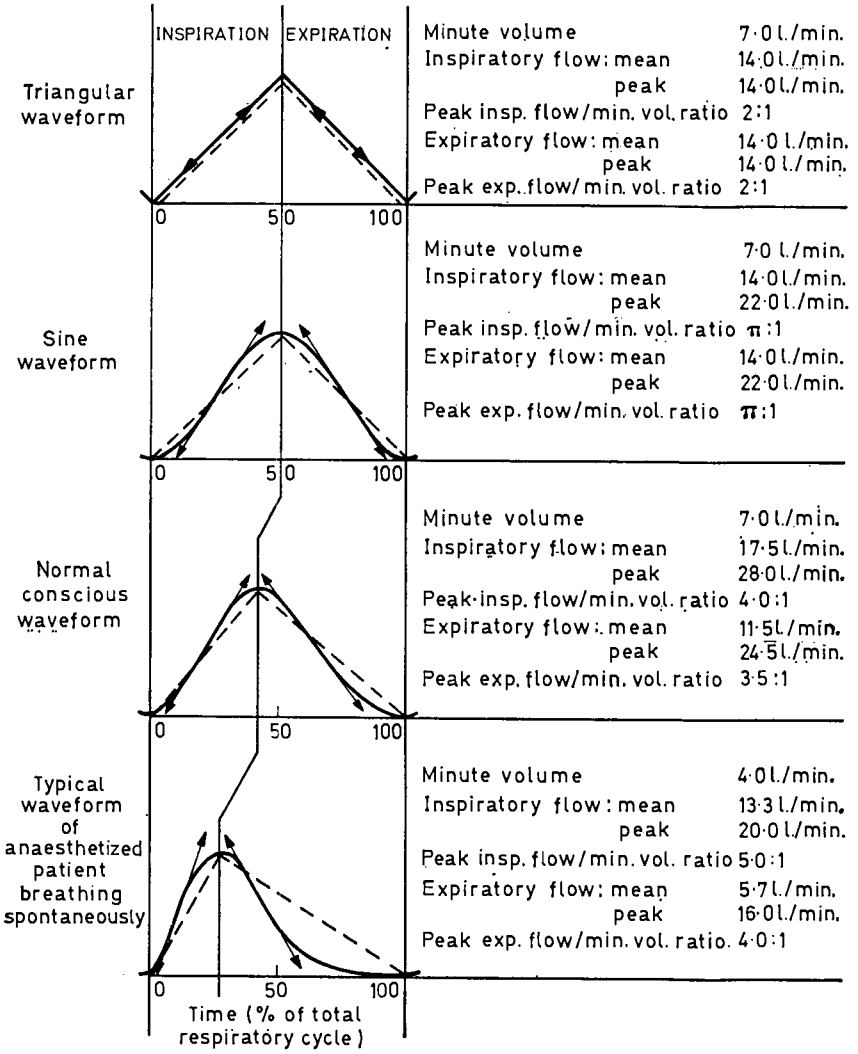


Figure 31. Respiratory waveforms showing the relationship between minute volume, mean flow rates (broken lines) and peak flow rates (indicated by arrows). The normal conscious waveform is taken from Cain and Otis (1949). The waveform of the anaesthetized patient is derived from 44 spirograms of patients during surgery

will equal the mean inspiratory and expiratory flow rates which must be twice the minute volume or 14 l./min. (*Figure 31*). This peak flow/minute volume

ratio of two is the lowest which can be attained and would be appropriate for breathing through a very high resistance.

Sine wave.—The triangular waveform is seldom found in respiration but a sine waveform is closely approximated during spontaneous hyperventilation. Like the triangular pattern, there are no pauses and the durations of inspiration and expiration are equal (*Figure 31*). Therefore, the *mean* inspiratory and expiratory flow rates again equal twice the minute volume. However, the peak flow in each direction will exceed the mean flow rate when the flow rate reaches a maximum at the middle of inspiration and expiration. It may be shown that the peak flow is in fact equal to π times the minute volume. Thus, if the minute volume is 7 l./min., the peak flow rate will be about 22 l./min.

The normal respiratory waveform does not conform to a sine wave. The inspiratory phase is usually less than half the duration of the total respiratory cycle, and the peak inspiratory flow rate is reasonably constant with a value of about 4 times the minute volume. Expiration lasts about half the cycle, but reaches its peak flow early, thereafter declining exponentially into the post-expiratory pause (*Figure 31*).

Nunn and Ezi-Ashi (1962) studied the respiratory waveforms of 44 anaesthetized patients breathing spontaneously and found that post-expiratory pauses tended to be longer with lower minute volumes.

Thus as minute volume fell, the peak flow/minute volume ratio tended to rise and the peak flow rates remained roughly constant within the range 15–30 l./min. (*Table 6*). These values were derived from a spirometer trace which tends to overlook some of the more transient peaks of high flow rate; nevertheless, 15–30 l./min. seems a reasonable range of peak flow rates as a basis for consideration of the effects of resistance to breathing during anaesthesia with spontaneous respiration.

Table 6

Relationship between peak flows and minute volume of anaesthetized patients breathing spontaneously with various post-expiratory pauses

Mean minute volume (l./min.)	*Duration of post-expiratory pause (sec.)*	*Peak flow/min. vol. ratio*	*Peak flow rate (l./min.)*
6·2	Less than 0·5	4–5 (insp.) 2–3 (exp.)	25–31 (insp.) 12–19 (exp.)
4·0	0·5–2·0	4·5–6	18–24
2·9	2·0–4·0	5·5–7	16–20

During artificial ventilation, the anaesthetist may impose any peak flow rate he chooses up to a limit of about 120 l./min. In practice, the highest level usually encountered is about 75 l./min. associated with a minute volume of the order of 20 l./min.

The Effects of Resistance on Intrathoracic Pressure

Expiratory resistance alone will result in an increase of intrathoracic pressures

during expiration, but a fall during inspiration (*see* Mechanism of compensation, page 101). The *mean* pressure will rise since expiration lasts longer than inspiration. These changes occur during spontaneous or artificial ventilation by intermittent positive pressure without a 'negative phase'.

Inspiratory resistance alone will result in a decrease of both intra-alveolar and intrathoracic pressures during inspiration. Mean pressure will also fall since expiratory pressures are unchanged. The fall of pressure during inspiration can only be produced by the inspiratory muscles or by a cabinet respirator. No reduction can occur during artificial ventilation by intermittent positive pressure.

A combination of inspiratory and expiratory resistances will result in a change of intrathoracic pressure, the direction of which will depend upon the relative magnitude of inspiratory and expiratory resistance and peak flow rates. It is possible that alveolar and intrathoracic mean pressures may be unchanged if the swings in each direction are of equal duration and magnitude.

Changes in intrathoracic pressure can often be seen at the bedside. Elevation of intrathoracic pressure may be detected by observation of the level of blood in the external jugular vein while reduction of pressure may cause indrawing of suprasternal space, intercostal space or subcostal margin.

The effects of changes in the intrathoracic pressure are usually considered in relation to the *mean* pressure with respect to time. The mean pressure may be determined graphically from a record of the instantaneous pressure, by construction of a rectangle of area equal to that under the curve and length equal to a respiratory cycle. The height of the rectangle will then indicate the mean pressure (*Figure 32*). This technique is the same as that used for determination of the mean arterial blood pressure. Alternatively, the mean pressure can be measured directly by using a manometer, which is so damped that it cannot respond to the rapid changes in pressure (*Figure 32*). Consideration of these methods of measurement will make it clear that the mean pressure depends upon the duration as much as the actual level of the pressure transients.

The Effects of Changes in Mean Intrathoracic Pressure

The most important effect of raised intrathoracic pressure is the increase in central venous pressure. The response is fundamentally similar whether caused by expiratory resistance, positive pressure breathing, artificial ventilation with intermittent positive pressure, or the Valsalva manœuvre.

Comparatively little attention has been given to the increase in lung volume which results from expiratory resistance. Mention has already been made of the reduction in trapping which occurs (Butler, 1957), and it seems there would be less likelihood of pulmonary collapse. Prolongation of the inspiratory phase during artificial ventilation produces similar changes in the intrathoracic pressure, and this has been shown to improve the relative distribution of inspired gas and pulmonary blood flow (Watson, 1962b, Bergman, 1963a). This matter is discussed in Chapter 7, but in general it may be said that there are respiratory advantages and circulatory disadvantages to be obtained from the increased lung volume associated with a raised mean intra-alveolar pressure. It should be remembered that the F.R.C. in the supine position is about one litre less than in the upright position.

A reduction of intrathoracic pressure as a result of inspiratory resistance is seen classically in laryngeal obstruction. It is rarer during anaesthesia but can result from the use of a non-rebreathing gas circuit (with unidirectional valves) when the fresh gas supply is inadequate. Reduction of intrathoracic pressure improves the venous return, but there would be a danger of pulmonary oedema if the pulmonary capillary pressure were not able to fall sufficiently to keep the capillary/alveolar pressure difference less than the osmotic pressure of the plasma proteins.

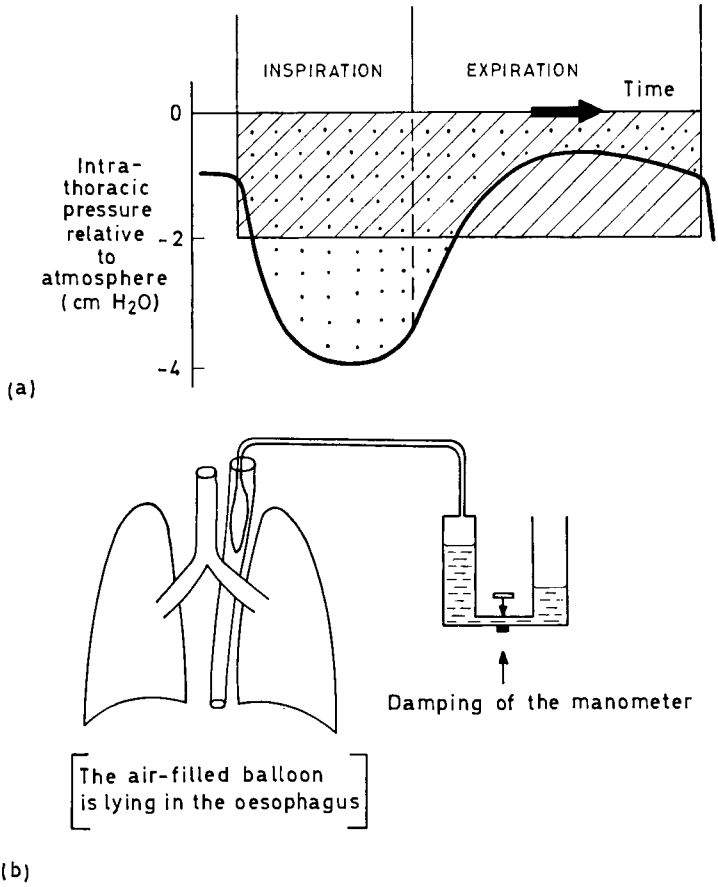


Figure 32. Measurement of the mean intrathoracic pressure. (a) The mean pressure is derived from the instantaneous pressure by construction of a rectangle (shaded) equal in area to that (dotted) above the instantaneous pressure curve. The height of the rectangle then indicates the mean intrathoracic pressure (2 cm H_2O below atmospheric). (b) A simple manometer is used which cannot follow individual breaths. If suitably damped, it will indicate the mean intrathoracic pressure

Probably the most serious effect of diminished alveolar pressure is reduction of lung volume. The expiratory reserve volume is less than one litre in the supine subject (Whitfield, Waterhouse and Arnott, 1950) and, therefore, a small reduction in F.R.C. renders the patient liable to trapping and possibly

collapse. Butler and Smith (1957) found that an alveolar pressure of only 5 cm H_2O below atmospheric was sufficient to cause a reversal of the normal

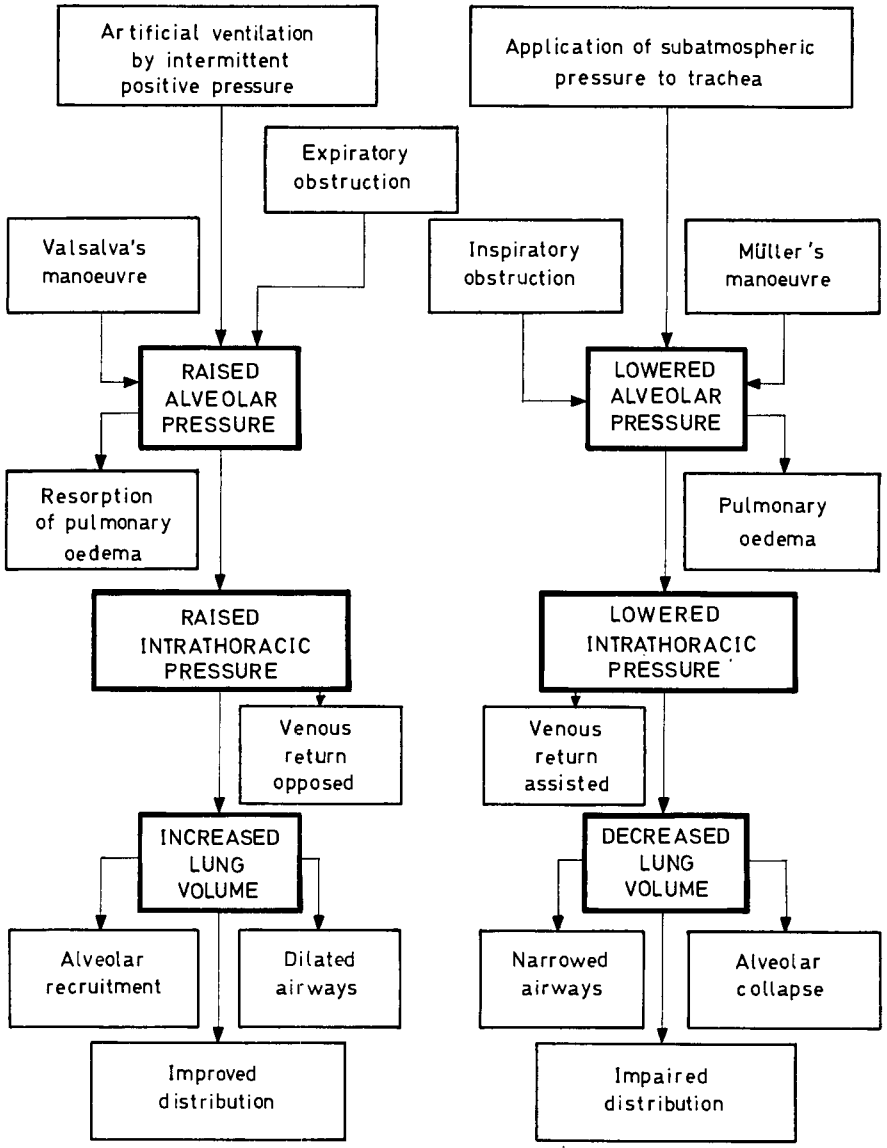


Figure 33. Causes and effects of changes in intrathoracic pressure. In general, a raised intrathoracic pressure has circulatory disadvantages but respiratory advantages. A lowered intrathoracic pressure has respiratory disadvantages with possible circulatory advantages

pulmonary transmural pressure gradient in anaesthetized patients, indicating widespread airway obstruction. This is clearly a most undesirable state, and

similar considerations apply to reduction of the lung volume by injudicious use of a subatmospheric pressure during the expiratory phase of artificial ventilation. In contrast with the effects of raised intrathoracic pressure, it may be said that there are respiratory disadvantages and possible circulatory advantages to be obtained from the decreased lung volume associated with a lowered mean intra-alveolar pressure.

The causes and effects of altered alveolar pressures are summarized in *Figure 33.*

The Respiratory Response to Increased Resistance to Breathing

The normal response to *inspiratory resistance* is an increased inspiratory effort with little change in the F.R.C. (Fink, Ngai and Holaday, 1958). Accessory

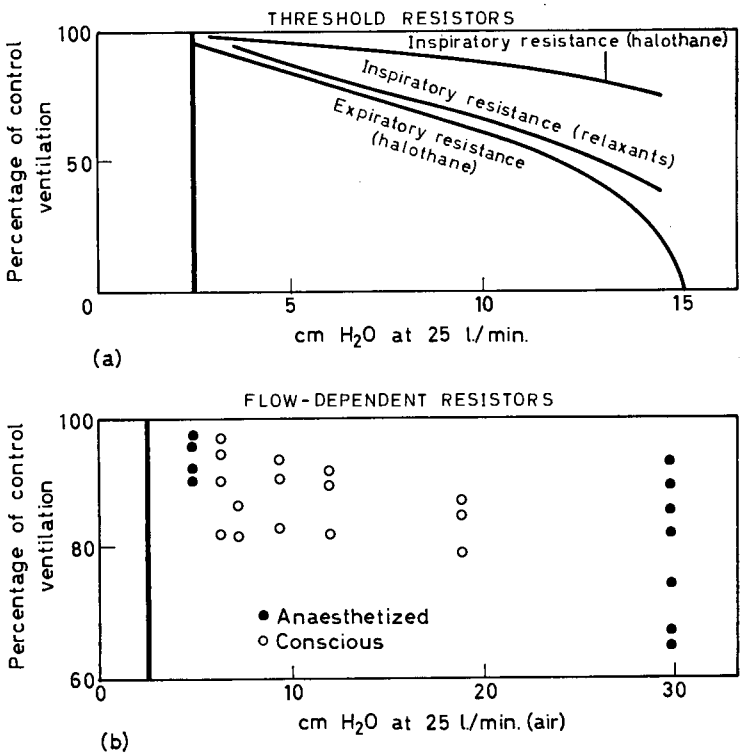


Figure 34. Ventilatory response to added resistance to breathing. (a) The response of anaesthetized patients to threshold resistors (Nunn and Ezi-Ashi, 1961). (b) The response of anaesthetized patients is compared with the published results in conscious subjects (McIlroy and his colleagues, 1956; Zechman, Hall and Hull, 1957). The conscious subjects breathed air through resistors with laminar flow. The anaesthetized patients breathed 70 per cent N_2O/30 per cent O_2 through tubular resistors with predominantly turbulent flow. In both diagrams the heavy vertical line indicates the author's suggested upper limit of acceptable resistance for an anaesthetized patient

muscles are brought into play according to the degree of resistance. There is considerable individual variation in the ability of subjects to compensate for the added resistance, and ventilation is diminished or even abolished if the

resistance is sufficiently high. Maximal voluntary inspiratory effort at the F.R.C. will attain an alveolar pressure about 90 cm H_2O below atmospheric (Rahn and his colleagues, 1946b). Campbell (1958, p. 79) has pointed out that the inspiratory muscles are not contracting maximally at this level, and appear to be subject to reflex inhibition. He added that pressures of 90 cm H_2O below atmospheric would result in a tendency for gases to be drawn out of solution in the tissues.

The respiratory response of the anaesthetized patient to inspiratory resistance was studied by Nunn and Ezi-Ashi (1961), who found a remarkable ability of patients to compensate for an inspiratory threshold resistor (*Figure 34*). Patients who had received relaxants responded rather less favourably than those anaesthetized with halothane, who suffered only a 15 per cent reduction of ventilation against an inspiratory threshold resistor of 10 cm H_2O (a level which is distinctly unpleasant to the conscious subject).

Asthmatic patients also show a remarkable capacity to compensate for increased airway resistance. Twenty patients in status asthmaticus studied by Palmer and Diament (1967) were found to have a mean P_{CO_2} in the lower reaches of the normal range. Isoprenaline aerosols give symptomatic relief from dyspnoea but may cause little change in P_{CO_2}. Hypercapnia in the asthmatic patient is a sign of serious deterioration.

Mechanism of compensation.—There is a twofold mechanism for the augmentation of inspiratory effort in the face of resistance. The first mechanism operates immediately and even during the first breath in which the resistance is applied. It seems probable that the muscle spindles indicate that the inspiratory muscles have failed to shorten by the intended amount, and their afferents augment the activity of the motor neurone pool. The resemblance of the inspiratory muscle control to a servo-mechanism has already been described in Chapter 2 (page 22). It is of interest that the conscious subject is able to detect very small increments in external resistance, and it is clear that the afferent pathway of the reflex is in existence (Campbell and his colleagues, 1961). A second compensatory mechanism develops over about 90 seconds and overacts for a similar period when the resistance is removed (Nunn and Ezi-Ashi, 1961). It is probable that this delayed response depends upon elevation of the arterial P_{CO_2}, which is an inevitable consequence of under-ventilation. After the resistance is removed, hyperventilation continues until the P_{CO_2} returns to normal.

A similar two-phase response to inspiratory obstruction was demonstrated in dogs (Bendixen and Bunker, 1962). The first breath after obstruction developed a subatmospheric pressure of about 15 cm H_2O, which corresponds to a much greater tension in the inspiratory muscles than would be present during normal unobstructed respiration. Thereafter the dogs further augmented their inspiratory tension during the 50 seconds of the observation period.

Expiration against pressures of 10 cm H_2O results in no contraction of the abdominal muscles or rise of intragastric pressure. Above this pressure, expiratory muscles are brought increasingly into play, up to pressures of 17·5 cm H_2O at which level their use is invariable.

At expiratory pressures below 10 cm H_2O, the additional work of expiration is performed entirely during inspiration by a most remarkable mechanism, in

which *inspiration* is augmented until the lung volume is increased to a point at which the elastic recoil is sufficient to overcome the expiratory resistance Campbell, 1957). The increase in lung volume, divided by the expiratory pressure to be overcome, is, in fact, a measure of the total static compliance of the subject. A spirogram of this change is shown in *Figure 12* in relation to factors influencing the F.R.C. The same mechanism is found in anaesthetized patients (Campbell, Howell and Peckett, 1957; Nunn and Ezi-Ashi, 1961). The latter workers found that expiratory resistance tended to diminish the pulmonary ventilation rather more than did the same level of inspiratory resistance. There was, furthermore, a rather sharp cut-off of ventilation with expiratory pressures in excess of 15 cm H_2O (*Figure 34*).

It will be noticed that the response to expiratory resistance runs counter to what might be expected from demonstration of the Hering–Breuer inflation reflex in animals. In Chapter 2 it has been explained that in man this reflex is extremely weak in response to pressures of less than about 12 cm H_2O (page 38).

The actual mechanism of the increased inspiratory effort is rather complicated and seems likely to depend on the ability of the intrafusal fibres of the inspiratory muscle spindles to accommodate themselves to the altered F.R.C. brought about by the impairment of expiration. This resets the developed inspiratory tension in accord with the increased F.R.C. (Nunn and Ezi-Ashi, 1961). It should be noted that, in spite of the lack of expiratory muscular activity, the increased lung volume results in an increase of intrathoracic pressure which will act adversely on the venous return. Taking an example from the idealized patient represented in *Figure 19*, an expiratory pressure of 10 cm H_2O above atmospheric would increase the lung volume by 850 ml. (compliance times pressure difference). At this lung volume, the end-expiratory intrathoracic pressure would have risen from 3 cm H_2O *below* atmospheric to about 1·5 cm H_2O above atmospheric.

Perhaps of greater importance is the response of the patient to the *combination of inspiratory and expiratory resistance.* Nunn and Ezi-Ashi (1961) found that a combined inspiratory and expiratory threshold resistor produced much the same decrease of minute volume as was obtained with the same expiratory threshold resistor alone. They also studied the effect of two tubular resistors through which the flow was largely turbulent. The resistance of the larger was equivalent to a 6 mm. endotracheal tube, and the smaller to a 3.5 mm. endotracheal tube (*Figure 27*), both being well above the external resistance considered acceptable for an anaesthetized patient. These resistors caused no measurable change in F.R.C., and less decrease of ventilation than was caused by comparable pressure gradients produced by the threshold resistors. The larger tubular resistor reduced the mean ventilation by 7 per cent, and the smaller by 21 per cent (*Figure 34*). It is unlikely that a 7 per cent reduction would be of clinical significance.

Studies of the response of the conscious subject to external resistance to breathing have been reported by Davies, Haldane and Priestley (1919), Killick (1935), Cain and Otis (1949), McIlroy and his colleagues (1956), and by Zechman, Hall and Hull (1957). In *Figure 34b*, some of their results are shown (open circles) for comparison with results obtained during anaesthesia with tubular resistors (solid circles). It is surprising that anaesthetized patients

seem able to compensate for the added load just as well as conscious subjects, although their control minute volumes (without resistance) were substantially less than those of the conscious subjects. On a cautionary note, it should be mentioned that these experiments have all been acute and there are no data on the ability of an anaesthetized patient to tolerate longstanding resistance to breathing.

The good ventilatory response of the anaesthetized patient to resistance joins an interesting list of previously unsuspected factors which help anaesthetized patients to survive some of the insults to which they are, at times, subjected. Many other factors appear in this book.

PRINCIPLES OF MEASUREMENT OF FLOW RESISTANCE

Resistance to respiratory gas flow is determined by the simultaneous measurement of gas flow rate and the appropriate pressure gradient, as outlined in *Figure 21.* Measurement of gas flow rate usually presents no insuperable problem, and the difficulties centre around the measurement of the pressure gradient. Methods of presentation of results are described earlier in this chapter.

Apparatus Resistance

Continuous flow of gas offers the simplest method of measurement of airway resistance. The pressure difference is then static and may be measured by simple methods such as liquid U-tube manometers.

Reciprocating flow has the advantage of testing the apparatus under the actual conditions of use, but requires manometers of rapid response. Cooper (1961) has shown that it is generally possible to use data derived from continuous flow studies to deduce the resistance offered to reciprocating flow.

Nasal Resistance

The resistance of the nose can easily be determined by measuring the mouth-to-atmosphere pressure difference, while the subject breathes through his nose, with the mouth closed around the tube leading to the manometer. Either continuous or reciprocating flow can be used, powered either by the patient's respiratory muscles or by some external device (Seebohm and Hamilton, 1958; Butler, 1960).

Airway Resistance

Simultaneous measurement of air flow rate and mouth-to-intrathoracic pressure gradient.— In Chapter 3, it was shown how simultaneous measurement of tidal volume and intrathoracic pressure yielded the dynamic compliance of the lung (*Figure 20*). For this purpose pressures were selected at the moments of zero air flow when pressures were uninfluenced by air flow resistance. The same experimental arrangement may be used for the determination of flow resistance, but for this purpose, steps are taken to eliminate the component of pressure which is produced by the elastic forces. *Figure 35* shows a suitable experimental arrangement in which a pneumotachograph is used to measure the instantaneous flow

rate which may then be integrated to give respired volumes. A second differential manometer measures the difference between mouth and intrathoracic pressure.

From the flow trace it is easy to select the points of zero flow at which the pressure gradient is opposed only by elastic forces. It is then possible to construct the dotted line in the pressure trace (*Figure 35*), which shows the pressure

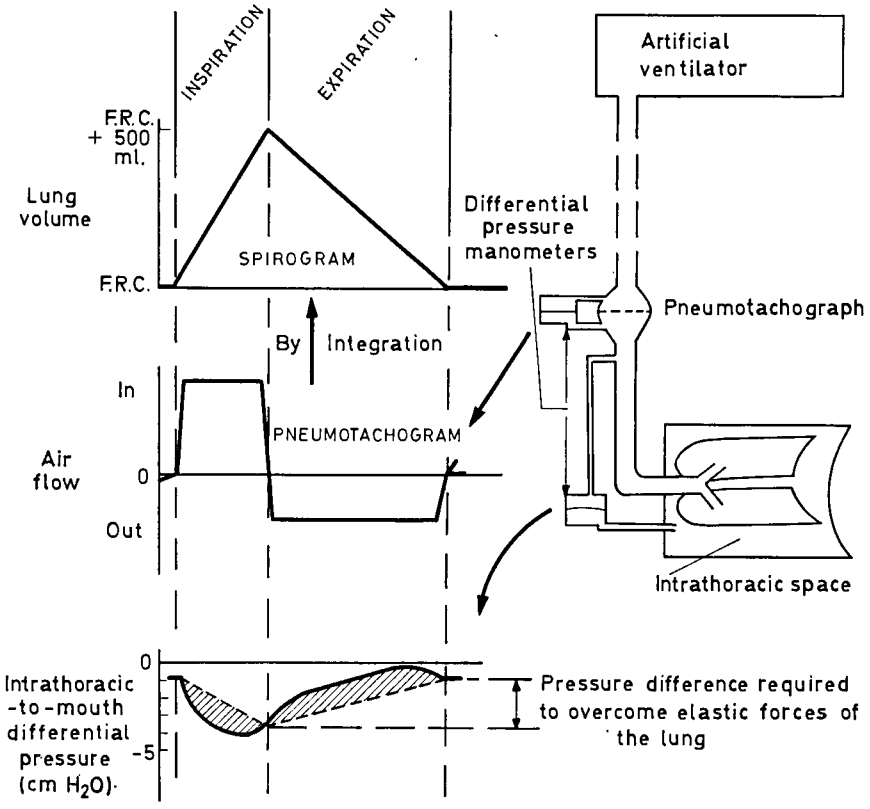


Figure 35. The measurement of pulmonary resistance and dynamic compliance by simultaneous measurement of air flow and intrathoracic-to-mouth differential pressure (Neergaard and Wirz, 1927b). The spirogram is conveniently obtained by integration of the pneumotachogram. In the pressure trace, the dotted line shows the pressure changes which would be expected in a hypothetical patient with no pulmonary resistance. Compliance is derived as shown in Figure 20. Pulmonary resistance is derived as the difference between the measured pressure differential and that which is required for elastic forces (shaded area) compared with the flow rate shown in the pneumotachogram. Note that the pneumotachogram is a much more sensitive indication of the no-flow points than the spirogram

changes which would be seen in a hypothetical patient with zero resistance to gas flow, and in whom pressure gradients would relate only to elastic forces. The difference between this and the observed pressure gradient (shaded zone) is the component due to flow resistance. It is then a simple matter to read off the flow resistance component of the pressure gradient for different flow rates as given by the pneumotachogram above it. A flow rate/pressure gradient plot

may then be derived, or else the resistance may be expressed according to any of the mathematical conventions discussed earlier in this chapter.

Alternatively, the mouth-to-intrathoracic pressure gradient and respired volume may be plotted as X and Y co-ordinates to give a loop. *Figure 20* showed how dynamic compliance could be derived from the no-flow points of such a loop. In our hypothetical patient with zero resistance to gas flow, the 'loop' would consist of a straight line (*Figure 36a*). The greater the resistance, the

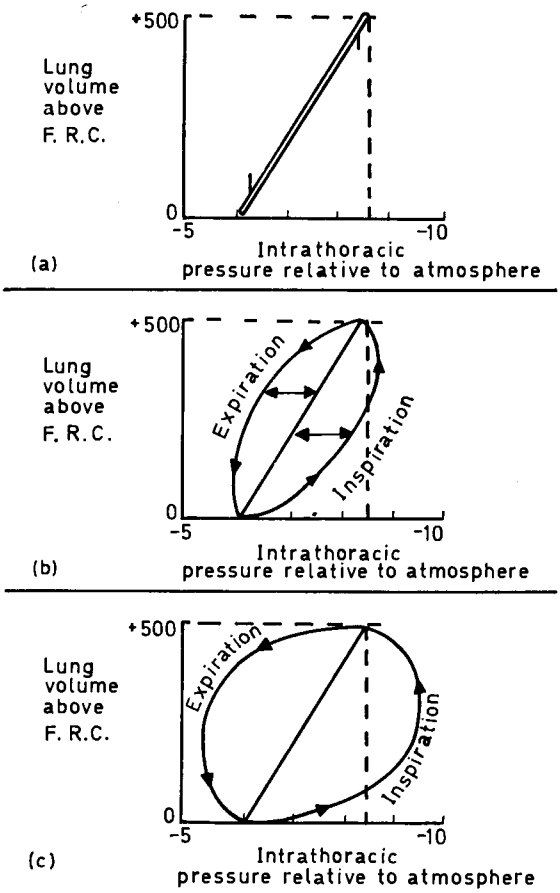


Figure 36. Dynamic pressure/volume loops obtained in conscious upright subjects with varying degrees of pulmonary resistance. It is not possible to determine the actual resistance from a loop, but the area of the loop indicates the amount of work done in overcoming pulmonary resistance. The diagonals joining the no-flow points of the loop lie about 1 cm H_2O to the right of the transmural pressure curve in Figure 18. (a) A hypothetical subject with zero pulmonary resistance; pressure changes solely in accord with elastic forces:

$$\text{compliance} = \frac{\text{volume change}}{\text{pressure change}} = \frac{500}{2{\cdot}5} = 200 \text{ ml./cm } H_2O$$

(b) Subject with normal pulmonary resistance; horizontal displacement of points from the diagonal (shown by arrows) indicates pressure required to overcome pulmonary resistance. (c) Subject with excessive pulmonary resistance; the higher the resistance, the fatter the loop becomes. (Pressure cannot rise above 3·5 cm H_2O below atmospheric without use of expiratory muscles)

fatter the loop becomes, with the horizontal deflections of the points from the 'no resistance' line indicating the pressure gradient required for gas flow at that particular flow rate. Elegant though this method of display may be, it is not possible to derive the actual instantaneous gas flow rate from the loop and, therefore, the resistance cannot be quantified according to the methods described above. Nevertheless, we shall see in Chapter 6 that the work required to overcome the flow resistance corresponds to the area of the loop.

The interrupter technique.—A single manometer may be used to measure both the mouth and the alveolar pressure if the air passages distal to the manometer

are momentarily interrupted with a shutter. The method is based on the assumption that, while the airway is interrupted, the mouth pressure comes to equal the alveolar pressure, a concept open to some doubt. Flow resistance may thus be derived from the difference between the alveolar pressure (measured during interruption) and the mouth pressure (measured immediately before and after interruption). Both this and the preceding methods were first described in the classic paper of Neergaard and Wirz in 1927b.

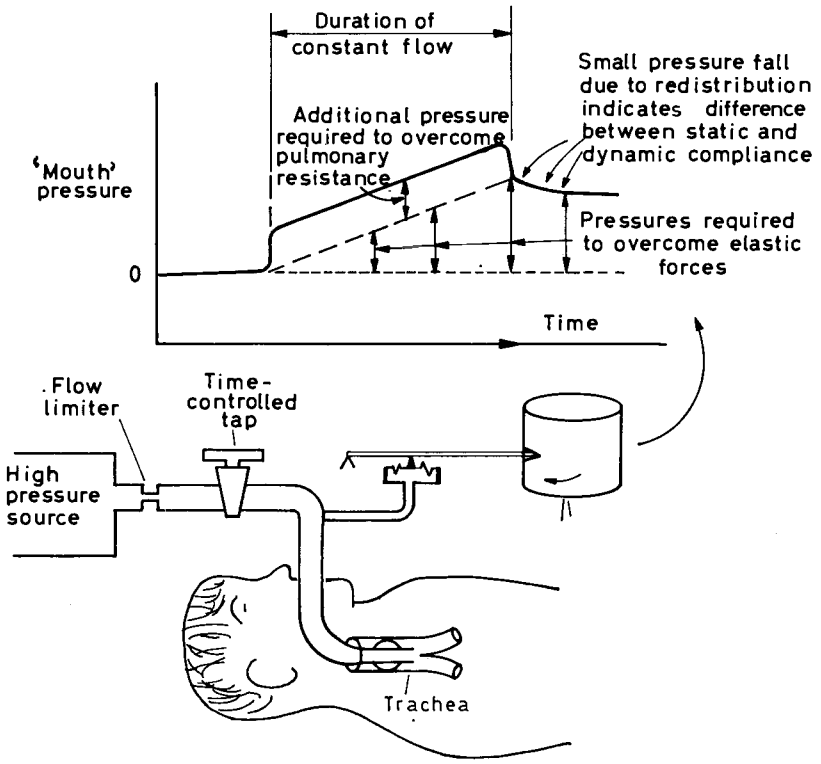


Figure 37. Measurement of compliance and resistance with the Pufflator. With this simple device a constant flow rate of gas is passed into the patient for a pre-set time interval. The broken line on the pressure trace indicates the pressure which would be required for a hypothetical patient with no pulmonary resistance. The difference between this and the actual pressure is the pressure required to overcome pulmonary resistance. In this example it is constant throughout the inflation.

$$\textit{Tidal volume} = \underset{(\textit{pre-set})}{\textit{constant flow rate}} \times \underset{(\textit{pre-set})}{\textit{duration of flow}}$$

$$\textit{Static compliance} = \frac{\textit{tidal volume}}{\textit{static end-inflation pressure}}$$

$$\textit{Pulmonary resistance} = \frac{\textit{additional pressure required to overcome pulmonary resistance}}{\textit{constant flow rate (pre-set)}}$$

The Pufflator.—This simple device for the measurement of inspiratory resistance of the paralysed patient was described by Don and Robson (1965). A constant-flow generator is used to inflate the lungs of a patient for a known period of

time, after which the flow abruptly ceases, the mouth or tracheal pressure being measured throughout this process. The static pressure after flow ceases is the elastic component for that particular tidal volume, and the appropriate fraction of this elastic pressure may then be subtracted from the dynamic pressure during inflation to indicate the pressure required to overcome flow resistance (*Figure 37*). The technique thus yields compliance (lungs and chest wall) and resistance.

The body plethysmograph.—If the hypothetical patient with zero resistance to gas flow were to sit in a sealed box and inhale, there would clearly be no change in the pressure within the box. However, if he had appreciable airway resistance, the pressure of the alveolar gas would fall below ambient during inspiration and the thorax would expand in accord with Boyle's law. The increased displacement of the thorax would then increase the pressure in the box in accord with the airway resistance (DuBois, Botelho and Comroe, 1956). It is possible to obtain a direct plot of pressure gradient against respiratory flow rate on a cathode ray oscilloscope or *X–Y* plotter. A patient may be studied without instrumentation in a few minutes and functional residual capacity may be measured at the same time. The body plethysmograph measures only the *airway resistance*, in contrast to other methods which measure the *pulmonary resistance* (equal to airway plus pulmonary tissue resistance).

Analysis of the passive spirogram.—Perhaps the simplest method of assessment of resistance is the study of the slope of a passive spirogram—either a passive expiration into an ordinary spirometer (Comroe, Nissell and Nims, 1954), or the discharge of a weighted spirometer into a relaxed patient (Newman, Campbell and Dinnick, 1959). Both methods are suitable only for paralysed patients. The first stage in the analysis of the result is to determine the static compliance, which is given by the volume change divided by the pressure change. The resistance to flow may then be derived by a number of different methods.

(1) Spirograms obtained by this method appear to approximate closely to simple exponential functions and, therefore, a time constant may be derived (*Figure 38*). Assuming that resistance remains constant throughout the breath, the resistance may be derived from the equation:

$$\text{resistance} \times \text{compliance} = \text{time constant}$$

The concept of the time constant is discussed more fully in the following chapter and in Appendix D. During expiration it seems feasible that the resistance (in the sense of pressure divided by flow) may remain constant. Initially the flow rate is high but increased tendency to turbulence is probably offset by the wider calibre of the air passages.

(2) The initial pressure gradient is known and the tangent to the first part of the curve will indicate the flow rate at that point (*Figure 38*).

(3) At any point of the curve, the flow rate may be derived as the tangent to the curve. The mouth pressure is known (assumed equal to the pressure within the spirometer), and the alveolar pressure may be derived from its initial pressure and final pressure (assumed equal to the pressure within the

spirometer) assuming that the alveolar pressure changes in proportion to the volume change (indicated by the spirometer).

Clinical Tests of Resistance to Breathing

It is rather unusual to carry out a formal measurement of airway resistance in the clinical investigation of a patient. The more usual procedure is to measure the ventilatory (or more specifically the expiratory) capacity of the patient. In most cases this approach is satisfactory as it is usually obvious when ventilatory

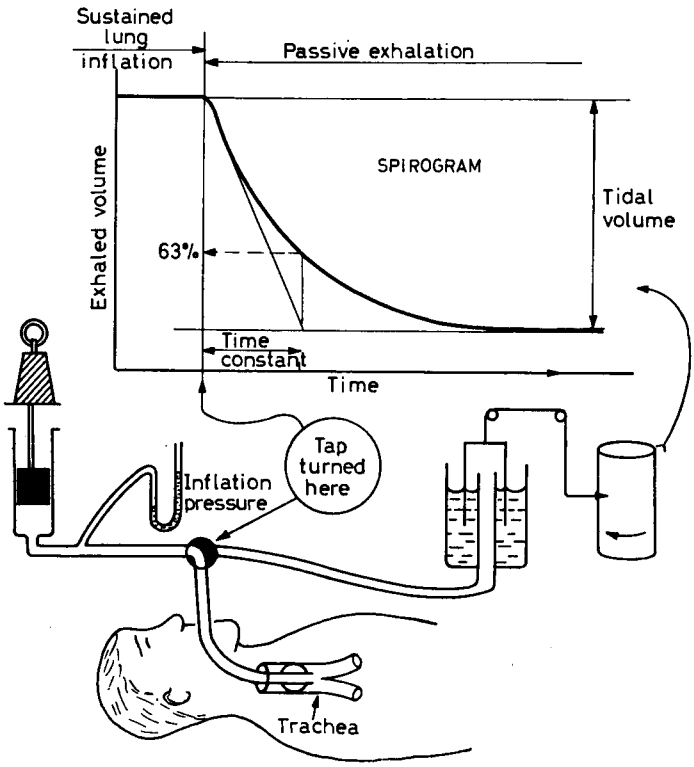


Figure 38. Measurement of resistance and compliance by analysis of the passive spirogram. This method is only applicable to the paralysed patient. Only a water manometer and a spirometer are required.

$$\textit{Static compliance} = \frac{\textit{tidal volume}}{\textit{inflation pressure}}$$

$$\textit{Compliance} \times \textit{resistance} = \textit{time constant}$$

$$\textit{Initial resistance} = \frac{\textit{initial pressure gradient}}{\textit{initial flow rate}} = \frac{\textit{inflation pressure}}{\textit{tidal vol./time constant}}$$

capacity is impaired by increased resistance to breathing. However, there are many other possible causes of reduction of ventilatory capacity (*Figure 52* and page 156) and it is important to distinguish increased resistance from such conditions as restriction of lung volume, diminished force of contraction of respiratory muscles and lesions of the lower motor neurone.

Formerly the standard test of ventilatory function was to measure the maximal breathing capacity (M.B.C.). This test consisted of urging the patient to breathe maximally in and out of a lightweight spirometer for a period of 15 seconds. The ventilation over this period was then multiplied by four to give the value which would be obtained if ventilation had been sustained for a full minute. Normal values depend upon body size, age and sex, the range being 47–259 l./min. for men and 48–177 l./min. for women (Cotes, 1965). The average young adult male should have a value of about 170 l./min. It is difficult to obtain repeatable results with this test, which may be quite exhausting for the patient. It has therefore become more usual to assess the ventilatory capacity of a patient indirectly by study of a forced expiration. This carries the assumption that the major component of the resistance is operative during expiration, and this is true in most patients with obstructive airway disease of the type which typically occurs in emphysema.

The forced expiration may be quantified in many ways but the commonest are measurement of the peak flow rate or the forced expiratory volume (one second). The former may be measured by three methods: as the slope of a spirometer trace, with a peak flowmeter (Wright and McKerrow, 1959), or by observation of the pneumotachogram. Normal values will depend upon the method since the spirometer method overlooks transients of very high flow rate while the pneumotachogram method is particularly sensitive to these transients. The peak flowmeter is intermediate (page 171). The peak flow measured by the Wright peak flowmeter tends to be about four times the M.B.C.

Forced expiratory volume (F.E.V.) is measured by instructing the patient to take a maximal inflation and then to exhale maximally into a spirometer of low inertia. The volume expired in the first second is measured and designated the $F.E.V._{1.0}$. Some prefer to measure over three-quarters or half a second. The $F.E.V._{1.0}$ is a valid measurement of expiratory capacity, but some find it easier to derive the indirect M.B.C. which equals:

$$35 \times F.E.V._{1.0}$$

Water spirometers are inconvenient and lack portability. Much ingenuity is currently being devoted to the design of suitable dry spirometers.

A reduction of M.B.C. or $F.E.V._{1.0}$ below the predicted value for the patient may provide valuable information about the ventilatory capacity of the patient but does not indicate the cause of the impairment. Further light may be shed by taking the following steps.

(1) The investigator should satisfy himself that the patient's ability to exhale is not being curtailed by failure to develop the appropriate tension in the expiratory muscles. This may be due to a wide range of conditions including poliomyelitis, muscular dystrophies and abdominal pain. Without appreciation of this point, a reduced F.E.V. could be erroneously interpreted as indicating increased airway resistance.

(2) Restrictive disease of the chest (e.g. kyphoscoliosis) will also give a reduction of the F.E.V. which might be confused with increased airway resistance. The distinction may be made by comparison with the vital capacity which is reduced more in restrictive disease than in obstructive disease. $F.E.V._{1.0}$ may with advantage be expressed as a percentage of the vital

capacity, with values below 85 per cent indicating an abnormal airway resistance.

(3) Bronchoconstriction may be distinguished from structural causes of increased airway resistance by repeating measurement of the $F.E.V._{1.0}$ or peak flow after the use of a bronchodilator aerosol spray (e.g. isoprenaline). No change of a reduced F.E.V. which is less than 85 per cent of vital capacity is usually indicative of increased airway resistance caused by structural changes leading to trapping.

For further information on these tests and data for prediction of normal values, the reader is referred to Comroe and his colleagues (1962) and Cotes (1965). Techniques for measurement of gas volumes and flow rates are described in Chapter 6 (pages 168 et seq.).

CHAPTER 5

MECHANISMS OF PULMONARY VENTILATION

The previous chapters have described the various structures, factors and mechanisms which play a part in pulmonary ventilation. This chapter is concerned with the tidal exchange resulting from the interaction of the factors already considered.

The flow of respiratory gases may always be considered as secondary to the development of a pressure gradient between the mouth* and the alveoli. Inspiration may result either from raising the mouth pressure (e.g. artificial ventilation by intermittent positive pressure—I.P.P.), or from lowering the alveolar pressure (e.g. spontaneous breathing). In either case, the pressure gradient is developed in the same direction and the resultant gas flow is roughly similar.

Apart from normal breathing, there are many alternative methods of achieving adequate tidal ventilation of the lungs. This chapter considers the various methods in two groups. The first part of the chapter discusses methods of ventilation in which gas flow results from a change in gas pressure induced by external means (e.g. artificial ventilation by I.P.P.). The second part of the chapter considers methods of ventilation in which the driving pressure gradient is secondary to forces acting directly on the boundaries of the thoracic cavity. Although this group includes normal spontaneous respiration, it is considered later as the fundamental principles of ventilation are clearer when ventilation results directly from changes in mouth pressure.

PART I. TIDAL EXCHANGE PRODUCED BY THE DEVELOPMENT OF A PRESSURE GRADIENT BETWEEN THE MOUTH AND THE AIR SURROUNDING THE TRUNK

The cumbersome title of the first part of this chapter represents an attempt to consider together techniques which are similar from the physiological point of view. Artificial ventilation by I.P.P. is, from the clinical standpoint, quite different from artificial ventilation by means of a cabinet respirator. However, the two methods are almost identical in terms of pressure gradients and the resultant gas flow. Furthermore, the similarity extends to the effects upon the venous return.

PHASES OF THE RESPIRATORY CYCLE

Inspiration

During artificial ventilation by I.P.P., the mouth pressure is intermittently

* Throughout this chapter, 'mouth' should be taken to read 'tracheal' when the mouth is bypassed by a tracheostomy or endotracheal tube.

raised above ambient. When a cabinet respirator is used (with subatmospheric pressures only), the ambient pressure around the trunk is rhythmically lowered below the mouth pressure. In each case, a mouth-to-ambient pressure gradient is developed during inspiration, and then allowed to decay at the start of expiration. From the point of view of ventilation, the two techniques seem to be identical. They are compared in *Figure 39*, and it will be seen that the various pressure gradients are the same although actual pressures, particularly intrathoracic, differ between the two methods.

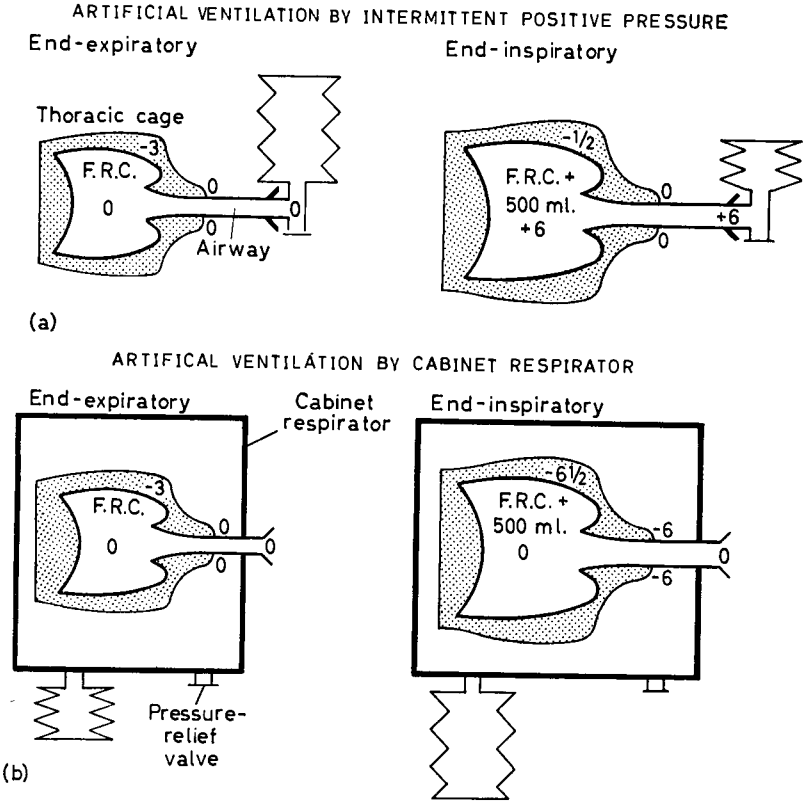


Figure 39. Comparison of artificial ventilation by (a) intermittent positive pressure (I.P.P.) and (b) cabinet respirator (subatmospheric pressures only). The actual pressures differ in the two techniques, but the following pressure gradients are the same in both cases: mouth-to-ambient; alveolar-to-intrathoracic (transmural); intrathoracic-to-ambient. Ambient pressure refers to the pressure surrounding the trunk and is therefore cabinet pressure in the latter case. Static values for supine anaesthetized patient: lung compliance, 150 ml./cm H_2O; thoracic cage compliance, 200 ml./cm H_2O; total compliance, 85 ml./cm H_2O. (Intrathoracic space is shown stippled.) Figures indicate pressures relative to atmosphere (cm H_2O)

If inspiration is slow, inspired air will be distributed according to the compliance of the different parts of the lungs and chest wall, the most compliant parts receiving the largest quantity of inspired air. If, however, there are regional variations in airway resistance and inspiration is completed fairly

quickly, distribution will be influenced by the tendency of gas to take the paths of least airway resistance. This problem has already been mentioned in Chapter 3 in connection with the distinction between static and dynamic compliance (page 53). It will be discussed in greater detail in Chapter 7 which is devoted to problems of distribution of inspired gas.

Expiration

During I.P.P. ventilation, it is usual to allow a passive expiration by letting the mouth pressure fall to atmospheric. With the cabinet respirator, the equivalent procedure is to allow cabinet pressure to rise to atmospheric. In terms of pressure differentials, the two are identical.

With either technique, expiration may be assisted in a manner analogous to the use of expiratory muscles during spontaneous respiration. During I.P.P. ventilation, the mouth pressure may be reduced below atmospheric—the so-called 'negative phase'. With the cabinet respirator, the equivalent technique is the raising of the cabinet pressure above atmospheric during expiration. Formerly, this was common practice and pressure swings as much as 15 cm H_2O on either side of atmospheric were usual.

The use of subatmospheric pressure with I.P.P. or the use of raised pressure in the cabinet will both tend to reduce the lung volume below the F.R.C. We have seen in Chapter 4 that this may increase airway resistance and cause pulmonary collapse, although the systemic venous return may be improved. When the lung volume falls below the F.R.C. in this manner, pressure volume relationships follow the extrapolation of the curves in *Figures 18 and 19* downwards and to the left. The picture is, however, complicated by alveolar collapse and airway trapping.

VENTILATION BY INTERMITTENT STEP INCREASES IN MOUTH PRESSURE (CONSTANT PRESSURE GENERATORS)

The subject of time relations is best approached by considering the type of I.P.P. ventilation in which the mouth pressure is suddenly raised to a level which is maintained throughout inspiration. At the end of inspiration, the pressure is allowed to fall immediately to atmospheric, where it remains until the start of the next inspiration. This type of pressure profile is known as 'square wave' (*Figure 40*), and may be produced by many commercially available ventilators such as the Manley, the Bird (with air entrainment) or the Barnet, and is approached by many others including the Radcliffe. If the inflating pressure is maintained for several seconds, the tidal volume will be indicated by the following relationship:

$$\text{tidal volume} = \text{sustained inflation pressure} \times \text{total compliance}$$

When the mouth pressure is raised during inspiration, it is opposed by the two forms of resistance which have already been considered; the elastic resistance of lungs and chest wall, and the frictional (non-elastic) pulmonary resistance.*

* Pulmonary resistance = airway resistance + pulmonary tissue resistance (page 85).

At any instant, the inflation pressure equals the sum of the pressures required to overcome these two forms of resistance:

$$\text{inflation pressure} = \text{pressure required to overcome elastic resistance} + \text{pressure required to overcome pulmonary resistance}$$

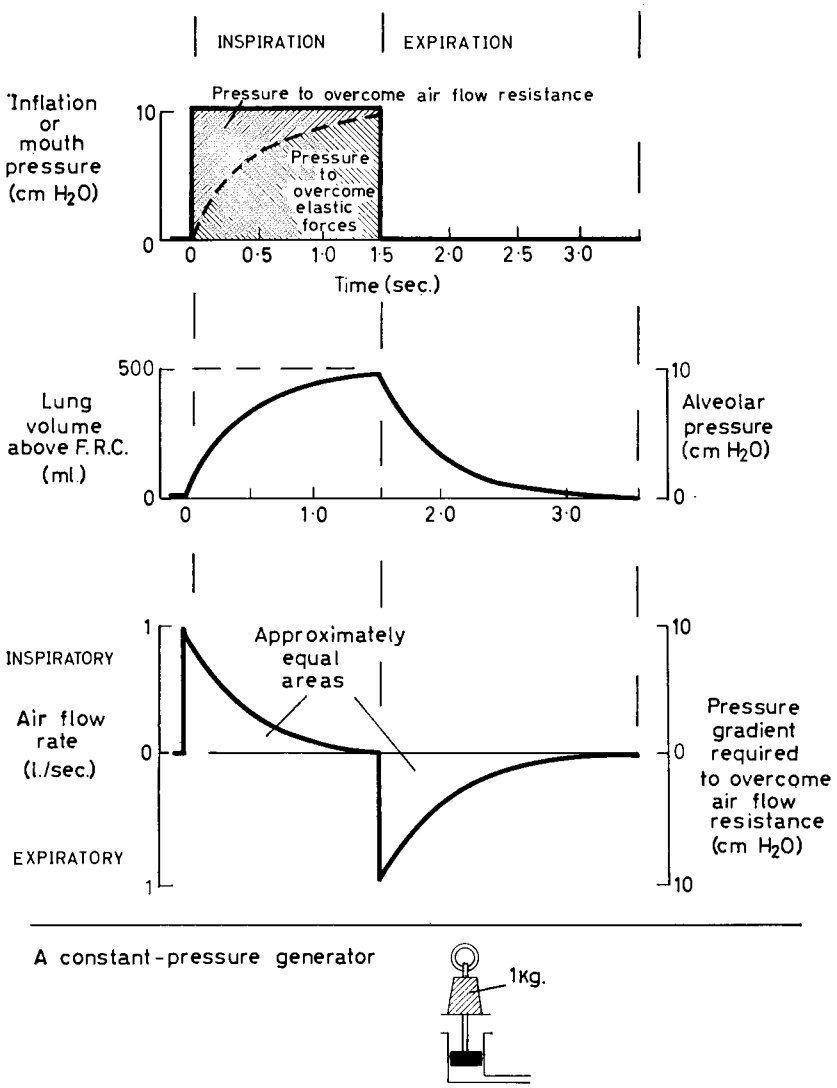


Figure 40. Artificial ventilation by intermittent application of a constant pressure (square wave). Passive expiration. Inspiratory and expiratory flow rates are both exponential. Assuming that air flow resistance is constant, it follows that flow rate and pressure gradient required to overcome resistance may be shown on the same graph. Lung volume and alveolar pressure may be shown on the same graph if compliance is constant. Values are typical for an anaesthetized supine paralysed patient: total dynamic compliance, 50 ml./cm H_2O; pulmonary resistance, 3 cm H_2O/l./sec.; apparatus resistance, 7 cm H_2O/l./sec.; total resistance, 10 cm H_2O/l./sec.; time constant, 0·5 sec.

The pressure required to overcome elastic resistance equals the lung volume above F.R.C. divided by the total compliance, while the pressure required to overcome the pulmonary resistance equals the pulmonary resistance multiplied by the instantaneous air flow rate (assuming for the moment that the air flow is entirely laminar).

The equation may now be rewritten:

$$\begin{matrix}\text{inflation}\\ \text{pressure}\end{matrix} = \left(\frac{\text{lung volume above F.R.C.}}{\text{compliance}}\right) + \left(\begin{matrix}\text{instantaneous}\\ \text{air flow rate}\end{matrix} \times \begin{matrix}\text{pulmonary}\\ \text{resistance}\end{matrix}\right)$$

The equation can be elaborated to allow for dynamic (as opposed to static) compliance and for the turbulent component of gas flow, but this simplified form is sufficient for the present.

The right-hand side of the equation has two terms, one of which is directly related to lung volume and the other to rate of gas flow. When the lung volume is equal to the F.R.C. (e.g. at the start of inspiration) the first term is zero, and inflation pressure is acting solely against the pulmonary resistance to gas flow. When gas flow ceases (at the end of inspiration) the second term is zero and inflation pressure is acting solely against elastic recoil. At the end of a normal expiration when the lung volume equals the F.R.C. and gas flow ceases, both terms are zero.

During inspiration both terms have finite values. *Figure 40* shows how the two components of the inflation pressure vary during inspiration while their sum remains constant. The component opposed by elastic forces (which equals the alveolar pressure) increases in proportion to the lung volume, while the component opposed by air flow resistance is proportional to the instantaneous air flow rate (which equals the slope of the plot of the lung volume against time). With a square pressure wave, flow is maximal at first and then declines exponentially. Therefore, the component of the inflation pressure opposed by airway resistance is maximal at first and also declines exponentially.

If expiration is passive and mouth pressure remains at ambient, the driving force is the elevation of the alveolar pressure above atmosphere, caused by elastic recoil of the lungs and chest wall. This pressure is dissipated in overcoming the airway resistance during expiration. In *Figure 40*, it will be seen that during expiration, the alveolar pressure (proportional to lung volume above F.R.C.) is directly proportional to the expiratory flow rate.

Time Relations

In the example shown in *Figure 40*, typical values for the anaesthetized patient were chosen as follows: total compliance, 50 ml./cm H_2O; pulmonary plus apparatus resistance, 10 cm H_2O/l./sec. (flow assumed laminar). These two quantities alone determine the rate of inflation and deflation for any particular inflation pressure. Assuming that compliance and resistance remain constant, all the curves shown in *Figure 40* are *exponential*. Changes of this type are of great importance in anaesthesia, and Appendix D describes some of the practical aspects of exponential functions as they concern anaesthetists.

During inflation with a constant mouth pressure, the lung volume follows a typical exponential 'wash-in' curve (shown in *Figure 126* of Appendix D). The expiratory curve is a classical example of a 'wash-out' curve and also features in Appendix D (*Figure 125*).

Exponential changes may be relatively fast or slow and their rate may be quantified by the *half-life* or the *time constant*. The former is preferred for measuring the rate of radioactive decay but the latter is more convenient for biological systems. Factors determining the time constant are considered in Appendix D, and for the example shown in *Figure 40* the relationship is as follows:

$$\text{time constant} = \text{compliance} \times \text{resistance}$$

$$= \frac{50}{\text{ml./cm } H_2O^*} \times \frac{10}{\text{cm } H_2O/\text{l./sec.}} = 0{\cdot}5 \text{ sec.}$$

Table 44 (Appendix D) provides the necessary information for calculating the changes in lung volume for any time during inspiration or expiration. Only two quantities need be known. The first is the time constant (0·5 sec. in this example) and the second is the equilibrium tidal volume, which would be attained if inspiration were maintained for several seconds. The latter equals inflation pressure multiplied by compliance (10 × 50 = 500 ml. in this example). We may now tabulate the changes occurring during inspiration (wash-in) as in *Table 7*.

Table 7

Duration of inflation		*Lung volume increase*	
sec.	*time constants*	*Percentage of final value*	*ml.*
0·35	0·69 (half-life)	50	250
0·5	1	63	315
1·0	2	86½	433
1·5	3	95	475
2·0	4	98	490
2·5	5	99	495
Infinity		100	500

Once we know the change in lung volume for any duration of inspiration, we also know the alveolar pressure (equal to volume above F.R.C. divided by compliance). This is the pressure opposing elastic recoil forces, and the balance of the inflation pressure opposes resistance to air flow (*see Table 8*).

Table 8

Time	*Pressure opposed by elastic recoil*	+	*Pressure opposed by air flow resistance*	=	*Total inflation pressure*
At start of inspiration	0	+	10	=	10
After 0·35 sec.	5	+	5	=	10
After 0·5 sec.	6·3	+	3·7	=	10
After 1·0 sec.	8·7	+	1·3	=	10
After 1·5 sec.	9·5	+	0·5	=	10
Infinite duration	10	+	0	=	10

* For compatibility of units the compliance should be expressed as 0·050 l./cm H_2O.

Pressure opposed by air flow resistance is directly proportional to air flow rate in our example, for which laminar flow was specified. Note that, at the beginning of inspiration, the whole inflation pressure is available to overcome air flow resistance. In this example, the inflation pressure of 10 cm H_2O is sufficient to produce a flow rate of 1,000 ml./sec. If this rate were maintained, a tidal volume of 500 ml. would be attained in 0·5 sec.—one time constant.

Time relations during expiration may be derived in a similar fashion using the values for rate of decay in a wash-out exponential curve (*Table 44*, Appendix D), as in *Table 9.*

Table 9

Duration of expiration		*Lung volume remaining above F.R.C.*		*Alveolar pressure remaining to overcome flow resistance*
sec.	*Time constants*	*Percentage of tidal volume*	*ml.*	
0	0	100	500	10
0·35	0·69 (half-life)	50	250	5·0
0·5	1	37	185	3·7
1·0	2	13½	67	1·3
1·5	3	5	25	0·5
2·0	4	2	10	0·2
2·5	5	1	5	0·1
Infinity		0	0	0

The flow rate of gas falls exponentially during expiration in proportion to the alveolar pressure.

The Effect of Changes in Inflation Pressure, Resistance and Compliance

Changes in *inflation pressure* do not alter the time constant but directly influence the amount of air introduced into the lungs in a given number of time constants. In our example, an inflation pressure of 10 cm H_2O introduced 433 ml. gas into the lungs in 1 second (2 time constants). A pressure of 20 cm H_2O would have introduced 866 ml.

Changes in *compliance* directly influence the tidal volume obtained if the same inflation pressure is maintained indefinitely. Compliance also directly affects the time constant.

Changes in flow *resistance* cannot by themselves alter the tidal volume obtained if inflation is maintained indefinitely (unless the resistance becomes total). However, the time constant increases in proportion to the resistance. Proportional increases in either compliance or resistance cause identical increases in time constant. These effects are illustrated in *Figure 41.*

Overpressure

If the duration of inflation is limited, the inflation pressure required for a particular tidal volume cannot be derived simply from the equation:

$$\text{inflation pressure} = \frac{\text{required tidal volume}}{\text{compliance}}$$

This relationship takes no account of time and is only true after the passage of infinite time. It is true that 98 per cent of inspiration is complete in 4 time constants. However, with a time constant of 0·5 seconds, this corresponds to an

inspiration of 2 seconds which may be too long. To minimize mean intrathoracic pressure, expiration should last about half as long again as inspiration, and therefore we would be faced with a total of 5 seconds per breath and a maximum respiratory rate of 12 breaths per minute. Means must therefore be found of inflating the lungs more quickly.

The solution to the problem requires no knowledge of mathematics, and is soon discovered by all who are responsible for ventilating paralysed patients.

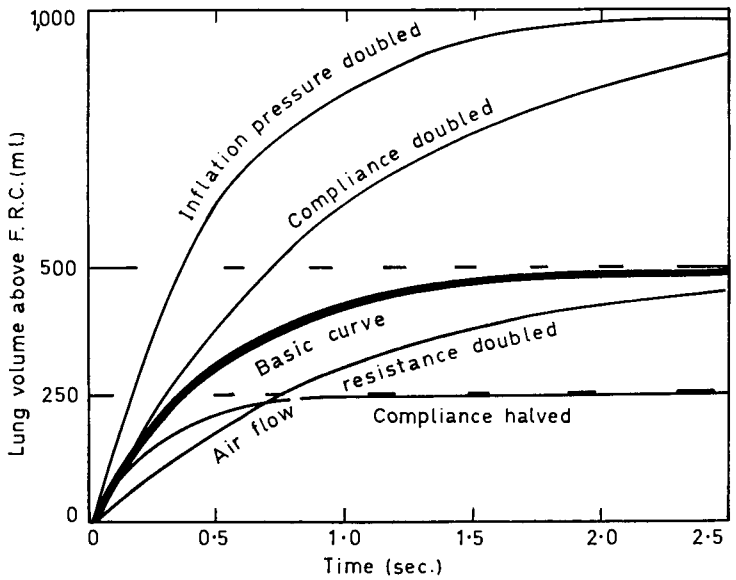


Figure 41. Effect of changes in various factors on inflation of the lungs. Fixed relationships: ultimate tidal volume = inflation pressure × compliance; time constant = compliance × resistance. (See also Table 10)

63% of inflation completed in 1 time constant
86½% of inflation completed in 2 time constants
95% of inflation completed in 3 time constants
98% of inflation completed in 4 time constants
99% of inflation completed in 5 time constants

Table 10

	Basic curve	*Air flow resistance doubled*	*Inflation pressure doubled*	*Compliance doubled*	*Compliance halved*
Inflation pressure (cm H_2O)	10	10	20	10	10
Compliance (ml./cm H_2O)	50	50	50	100	25
Ultimate tidal volume (ml.)	500	500	1,000	1,000	250
Air flow resistance (cm H_2O/l./sec.)	10	20	10	10	10
Time constant (sec.)	0·5	1·0	0·5	1·0	0·25

The principle is called *overpressure*, and is especially important to the anaesthetist as it is analogous to speeding the induction of inhalational anaesthesia by the use of higher concentrations of the agent at the start of induction.

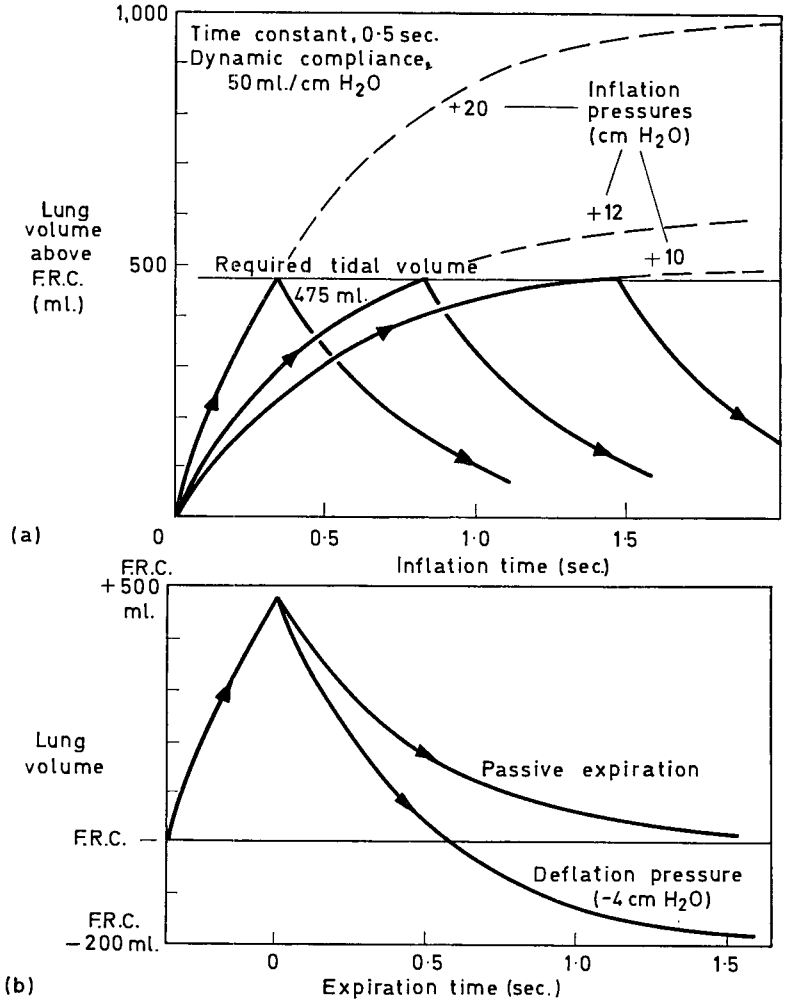


Figure 42. (a) Shows how the duration of inflation may be shortened by the use of overpressure. Inflation curves are shown for + 20 cm H_2O (equilibrium 1,000 ml.), + 12 cm H_2O (equilibrium 600 ml.) and + 10 cm H_2O (equilibrium 500 ml.). With a required tidal volume of 475 ml. note the big reduction in duration of inflation needed when the inflation pressure is increased from 10 to 12 cm H_2O. (b) shows how expiration is influenced by the use of a subatmospheric pressure or 'negative phase'. Expiration may be terminated at the F.R.C. after 0·6 seconds, or may be prolonged, in which case the lung volume will fall to 200 ml. below the F.R.C.

If resistance and compliance are fixed, there is nothing which can be done to alter the time constant. However, the introduction of a certain volume of gas into the lungs can be hastened by employment of a higher pressure and a

shorter duration of inflation. In effect one *aims* at a higher tidal volume but cuts short the inflationary phase while gas is still entering the chest at a fast rate. In this way one avoids the tedious creep up to equilibrium between 2 and 5 time constants and only the first part of the exponential wash-in is used, over the first 1 or 2 time constants. This process is shown in *Figure 42*. It will be seen that quite a small increase in inflation pressure results in a considerable reduction of duration of inspiration. The effects of various increases in inflation pressure can be calculated from the data in *Table 44* (Appendix D).

The shortening of the required duration of inspiration is very striking when the required tidal volume is close to the equilibrium volume. *Table 11* has been prepared for a tidal volume of 495 ml., for a patient with the same compliance and time constant as in *Figure 42*. Trivial increases in inflation pressure above 10 cm H_2O cause a marked reduction in required duration of inspiration.

Table 11

Inflation pressure		*Time required for inflation of 495 ml.*	
cm H_2O	*Increase (%)*	*Time constants*	*Seconds*
10·0	0	5	2·5
10·1	+1	4	2·0
10·4	+4	3	1·5
11·4	+14	2	1·0
15·7	+57	1	0·5
25·2	+152	0·5	0·25

It is important to remember that, if overpressure is inadvertently sustained, the lung volume and alveolar pressure will be increased more than was intended. The greater the degree of overpressure employed, the greater will be the danger of lung distension in the event of failure of the mechanism which terminates the inflation phase. The risk of rupture of the lung is real in infants. Unfortunately, a safety valve cannot be effectively used as the development of the high pressure is essential for the shortening of inspiration. Unless the resistance to air flow is pathologically high, it is probably wise to restrict the inflation pressure to no more than double the inflation pressure given by the equation:

$$\text{inflation pressure} = \frac{\text{required tidal volume}}{\text{compliance}}$$

Possible failure of the mechanism to terminate inflation (e.g. sticking of a valve) will then only result in double the intended tidal volume. In most cases this would be harmless.

The use of a subatmospheric pressure during expiration (the 'negative phase') speeds up expiration in exactly the same way as overpressure speeds inflation (*Figure 42*). This may be useful if the patient is exhaling through narrow-bore tubes. As in the case of inflation, much depends on how long the subatmospheric pressure is maintained. If it is cut short, then expiration is hastened, the lung volume does not necessarily fall below the F.R.C., and the intrathoracic pressure does not fall below the normal end-expiratory value. If, however, the

subatmospheric pressure is maintained for several seconds, the lung volume must fall below the F.R.C. and the intrathoracic pressure will fall below its normal end-expiratory value.

VARIABLE OR FLOW-LIMITED PRESSURE GENERATORS

The application of a constant or 'square' pressure wave has been considered first because it is easier to consider the relationship between pressure and flow when the first variable is held constant. We must now consider artificial ventilation by I.P.P. when the flow of gas from the apparatus to the patient is regulated in such a way that the mouth pressure is not constant throughout inspiration. Such devices have been classified as 'flow generators' (Mapleson, 1962) which implies that the intended flow is produced under all circumstances. However, a reduced compliance or a raised airway resistance may reduce the flow below the intended rate and it is probably better to consider the inspiratory flow rate as governed by the mouth pressure which itself is dependent on the flow generated by the apparatus.

The simplest pattern of flow generation is a constant flow rate throughout the inspiratory phase. This has already been considered in *Figure 37*, for the measurement of air flow resistance and compliance with the Pufflator. When constant flow is used for artificial ventilation it is usual to commence the expiratory phase as soon as inflation is complete and, therefore, the pressure and volume changes are cut short compared with those obtained during measurement of compliance and resistance with the Pufflator. *Figure 43* shows the changes which may be expected with constant-flow generators such as the Blease Pulmoflator or Bird respirators (the latter used without air entrainment).

The other common pattern of flow is sine wave. This is the flow pattern which is developed by a cylinder and piston, driven from a rotating crank with a long connecting rod. It may also be obtained by the use of an eccentric or a Yorkshire coupling (*Figure 44*). The first type of linkage is used in the Starling 'Ideal' pump (intended for laboratory animals), and the Mörch III Piston ventilator. An eccentric drive is used in the Beaver ventilator, while the Smith-Clark ventilator uses a Yorkshire coupling. The Engström ventilator is fundamentally a sine-wave generator with a piston and connecting rod, but the beginning and end of the inspiratory piston stroke are cut off, leaving only the middle of the stroke which approximates to constant flow. The volume and pressure changes with sine-wave flow are difficult to analyse, and vary in a complex manner with changes in the characteristics of the patient (*Figure 44*). Cabinet respirators usually have sine-waveform.

Between the extremes of constant flow and sine-wave flow lie an infinite variety of devices for artificial ventilation. Consideration of their individual characteristics must lie outside the scope of this book, and the reader is referred to *Automatic Ventilation of the Lungs* by Mushin and his colleagues (1959). Manual ventilation still remains the commonest method of artificial ventilation, and may be regarded as flow generation. The pattern of flow is usually intermediate between constant flow and sine wave, depending mainly on the habits of the individual anaesthetist.

Expired Air Resuscitation

This is a special form of I.P.P. ventilation with flow limitation in which the donor exhales into the respiratory tract of the patient. The recipient is then allowed to exhale to atmosphere while the donor inhales ready for the next breath. The technique is suggested in a number of passages in the Bible and,

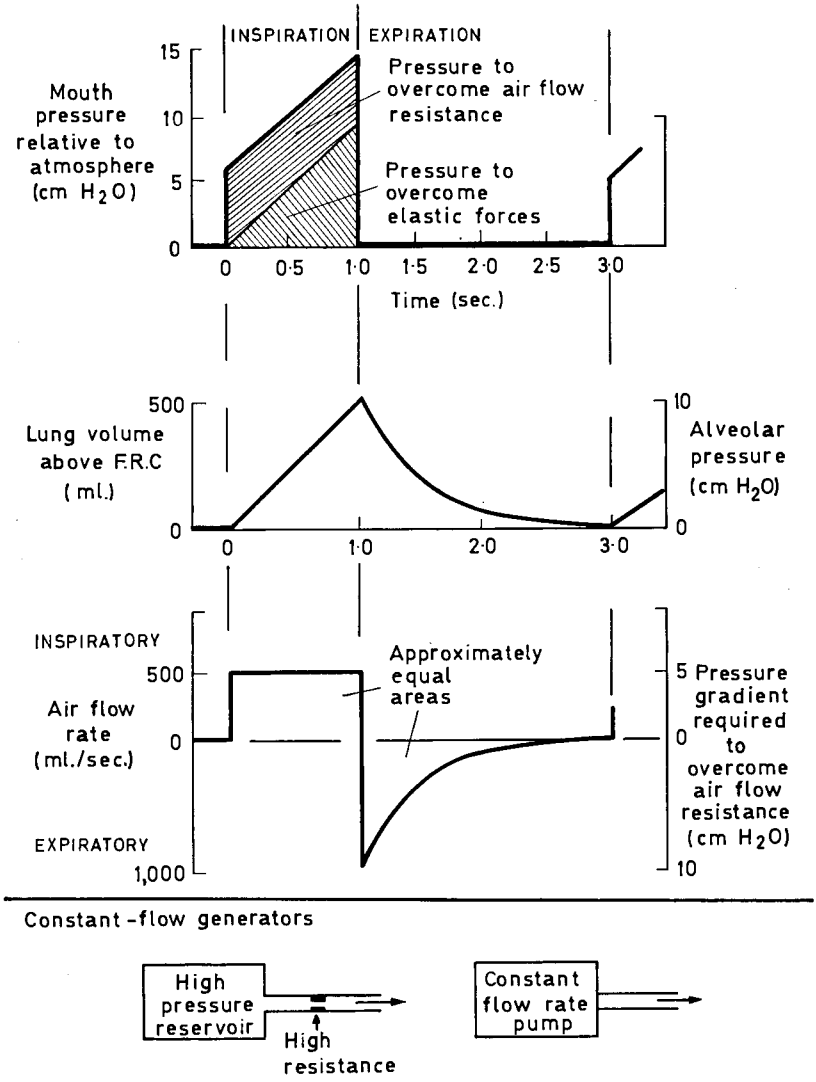


Figure 43. Artificial ventilation by intermittent application of a constant-flow generator with passive expiration. Note that inspiratory flow rate is constant. Assuming that air flow resistance is constant, it follows that a constant amount of the inflation pressure is required to overcome flow resistance. Lung volume and alveolar pressure may be shown on the same graph if compliance is constant. Values are typical of an anaesthetized supine paralysed patient: total dynamic compliance, 50 ml./cm H_2O; pulmonary resistance, 3 cm H_2O/l./sec.; apparatus resistance, 7 cm H_2O/l./sec.; total resistance, 10 cm H_2O/l./sec.; time constant, 0·5 sec.

without doubt, its origin is lost in the distant past. The first clear account of expired air resuscitation is in a manual for the rescue of people, apparently drowned, published in Holland in the eighteenth century (Herholdt and Rafn, 1796).

At first sight, it might appear that expired air, being 'vitiated', would not constitute a suitable inspired air for the recipient. However, if the donor doubles his ventilation, he is able to 'breathe for two'. If neither party had any respiratory dead space, the simple relationship shown in *Table 12* would apply.

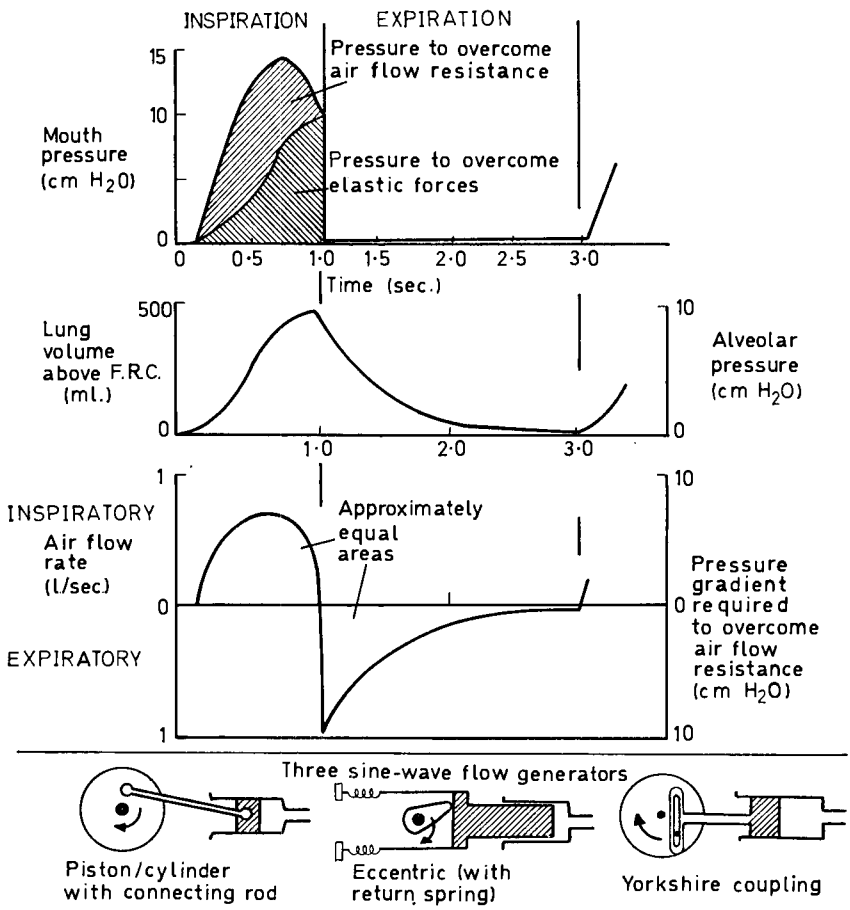


Figure 44. Artificial ventilation with inspiratory gas flow conforming to a sine wave. Passive expiration. Note that inspiratory gas flow rate is out of phase with the change in lung volume. (The latter conforms to a sine wave and the former to the differential of the sine which is the cosine.) Assuming that air flow resistance is constant, it follows that flow rate and pressure gradient required to overcome resistance may be shown on the same graph. Lung volume and alveolar pressure may be shown on the same graph if compliance is constant. Peak inspiratory flow rate equals π times the minute volume times 1·5. (The factor 1·5 is inserted because in this example inspiration does not last half the respiratory cycle. Values are typical of an anaesthetized supine paralysed patient: total dynamic compliance, 50 ml./cm H_2O; pulmonary resistance, 3 cm H_2O/l./sec.; apparatus resistance, 7 cm H_2O/l./sec.; total resistance, 10 cm H_2O/l./sec.; time constant, 0·5 sec.)

In fact the existence of the donor's respiratory dead space makes the situation more favourable. The donor's dead space is filled with fresh air at the end of his inspiration, and this is the first gas to be delivered to the recipient. An increased dead space will, therefore, improve the freshness of the gas the patient receives and also helps to prevent hypocapnia in the donor. The beneficial effect of dead space is exploited in certain instrumental aids to the technique which add an external apparatus dead space to the donor (Elam, 1962).

Table 12

	Normal ventilation	*Doubled ventilation*	
		Donor	*Recipient*
Alveolar CO_2	6%	3%	6%
Alveolar O_2	15%	18%	15%

(Doubling the donor's ventilation increases the alveolar O_2 concentration to a value midway between the normal alveolar oxygen concentration and that of room air.)

Within the last few years, expired air resuscitation has been widely accepted as superior to the manual methods of artificial respiration which are discussed below. The success of the technique rests upon the following considerations.

(1) Safar (1959) has demonstrated that airway obstruction is usual in unconscious patients, and cannot easily be cleared without the continuous use of the hands of the rescuer. In contrast to the manual methods of artificial respiration, expired air resuscitation leaves the rescuer's hands free to control the victim's airway.

(2) During expired air resuscitation, information is fed back to the rescuer who can see the chest expansion, hear any airway obstruction and sense the tidal exchange by means of his proprioceptive receptors.

(3) The donor is usually able to ventilate the victim adequately with only 20 per cent of his total ventilatory capacity (Elam and Greene, 1962). There is thus seldom difficulty in obtaining adequate ventilation, which may be maintained for long periods without fatigue (Greene and his colleagues, 1957; Cox, Woolmer and Thomas, 1960).

(4) The method is extremely adaptable. It may, for example, be used before drowning persons have been removed from the water, and by linesmen electrocuted whilst working on pylons (Elam and Greene, 1962).

(5) The method appears to be 'natural', and many rescuers have achieved success after the minimum of instruction.

Expired air resuscitation has been extensively reviewed by Elam and Greene (1962), and by Elam (1962). Essential features of the technique are as follows.

(1) The airway must be cleared, firstly by removal of foreign matter and, secondly, by opening the pharynx either by extension of the atlanto-occipital junction or by protrusion of the mandible (page 139).

(2) The rescuer should employ a tidal volume about double normal. Most rescuers appear to do so intuitively.

(3) The first few breaths should be delivered at the fastest possible rate; thereafter a normal respiratory rate should be employed.

(4) Alternative variants of the technique should be learned as no one

method can be applicable to all situations. For example mouth-to-nose may be required when trismus precludes the use of mouth-to-mouth.

(5) No potential rescuer should be led to believe that success is dependent on the use of ancillary apparatus (discussed by Elam, 1962). A rescue is such a rare event in the life of most of us, that there is little chance of having apparatus to hand.

Glossopharyngeal Respiration (frog breathing)

This remarkable technique is suitable for patients who have paresis of the respiratory muscles but retain the use of the muscles used in swallowing. Gulps of air are taken into the mouth and passed into the lungs, which are thus inflated stepwise. After a number of swallows, a passive expiration takes place and the cycle starts again (Dail, Affeldt and Collier, 1955). Not everyone can master the technique, but it is often useful for supplementing weakened breathing, and for taking an extra large breath before a cough.

CHOICE OF MANNER OF ARTIFICIAL VENTILATION BY INTERMITTENT POSITIVE PRESSURE

There are many types of machine capable of artificial ventilation by I.P.P. and yet many anaesthetists still prefer to ventilate patients by manual compression of a reservoir bag. This indicates that there is no general agreement on the precise requirements for a ventilator, and numerous investigations have failed to detect any obvious bearing of the precise manner of ventilation on the gross function of the respiratory or circulatory systems of reasonably healthy anaesthetized patients. Until there is agreement on the optimal P_{CO_2}, even the minute volume of ventilation must remain largely a matter of personal opinion and P_{O_2} can be easily adjusted by appropriate enrichment of the inspired gas with oxygen (page 154).

Mean intrathoracic pressure is invariably elevated during I.P.P. ventilation unless a subatmospheric pressure is used during expiration. Raised intrathoracic pressure results in a raised central venous pressure and this would reduce the venous return unless the peripheral venous pressure were able to rise and so maintain the peripheral-to-central gradient. In fact, this compensation seems to occur in healthy anaesthetized patients, in whom it has been shown that an elevation of intrathoracic pressure during I.P.P. does not reduce the cardiac output (Maloney and his colleagues, 1953; Prys-Roberts and his colleagues, 1967a). However, the former group demonstrated adverse changes in patients with 'circulatory inadequacy'. Impairment of venous return and cardiac output is to be expected in patients who are unable to raise their peripheral venous pressure in response to a rise of central venous pressure. This would result from any failure to contract capacitance vessels, which might be due to either of the following groups of causes.

(1) Capacitance vessels being already fully contracted (e.g. in hypovolaemic hypotension).

(2) Paralysis of vasomotor system (e.g. due to polyneuritis or ganglion block).

There has probably been an overstatement of the importance of the waveform of ventilation. Although both compliance and physiological dead space

are influenced by the duration of ventilation (*see* page 130), these factors are seldom critical and the actual waveform seems to be of very minor importance.

Having belittled the clinical significance of the choice of manner of artificial ventilation, we may nevertheless proceed to consider certain factors which are of some theoretical interest and may be important in certain problem patients.

Pressure versus *Flow Generation*

Constant-pressure generators give the most rapid initial flow rate for any particular inflation pressure. They are, therefore, suited to obtaining the minimum duration of inspiration. Whether or not this is desirable is discussed below.

At first sight, flow generators would seem preferable to pressure generators in the event of a reduction of compliance, or an increase in air flow resistance. However, the effect of changed characteristics of the patient is dependent on the manner of cycling of the ventilator which may be:

time-cycled (inspiration terminated after a pre-set time);
volume-cycled (inspiration terminated after passage of a pre-set volume);
pressure-cycled (inspiration terminated after a pre-set pressure is attained at the mouth or elsewhere in the apparatus).

Various combinations of these cycling mechanisms are also to be found.

If inspiration is limited to a pre-set time (*time-cycled*), a pressure generator will deliver a smaller volume in the face of increased resistance. A true flow generator will deliver almost the correct volume provided the raised mouth pressure does not exceed the setting of the safety valve. If compliance is diminished the flow generator should again deliver almost the correct volume, while the pressure generator would deliver a reduced tidal volume in proportion to the reduction in compliance.

If inspiration is terminated by the passage of the intended volume (*volume-cycled*), a flow generator should deliver the correct tidal volume in the normal time (unless the developed mouth pressure exceeds the setting of the safety valve). The minute volume should thus be independent of moderate changes in compliance or resistance. The response of a constant-pressure generator is a little more complicated. If air flow resistance is increased, the time constant will be increased proportionately and more time will be needed for inflation (*Figure 41*). Even if tidal volume remains normal, respiratory frequency will fall, and so the minute volume will be diminished. If the compliance is decreased, the time constant of inflation will be decreased. However, the tidal volume produced by the inflation pressure will also fall, and it is then possible that the volume required for cycling would never be attained and the ventilator would stop cycling.

The third group of ventilators terminate the inflation phase after the development of a pre-set mouth pressure (*pressure-cycled*). Only flow generators can be pressure-cycled and a constant-pressure generator must be cycled either by time or volume, the latter being unusual but possible. Cycling by pressure carries the disadvantage that, should resistance increase or compliance decrease, the mouth pressure will reach the critical level at a smaller tidal volume than with normal respiratory function. The apparatus may thus appear to be

functioning normally although an unsuspected change of lung characteristics has occurred and tidal volume is substantially reduced. It is, however, possible that the duration of inspiration will be sufficiently reduced to increase the respiratory frequency enough to maintain a normal minute volume.

The danger of a ventilator clicking rhythmically with no one aware of a reduction of ventilation is much reduced if there is some moving part which bears a relation to the volume of gas passed into the lung. The Blease Pulmoflator, for example, cycles when a predetermined pressure has been reached. However, the movements of the gas reservoir give some indication of the tidal exchange.

This account of ventilator performance in the face of changed parameters in the patient is necessarily very condensed and largely theoretical. In practice, the subject is extremely complex, largely because a precise definition of a ventilator's function is seldom possible, and Mushin and his colleagues (1959) repeatedly refer to 'hybrid types' and to 'qualifications and reservations' about the mode of operation of individual ventilators. Frequently more than one method of cycling is included in one apparatus. Mapleson (1962) has presented a more detailed account of the effect of changes in the pulmonary characteristics of the patient.

It is not possible to formulate hard and fast rules for the selection and operation of ventilators. A rational approach may be made along the following lines.

(1) Understand the physiology of artificial ventilation.

(2) Choose a ventilator with care, taking due account of:

- (*a*) the staff who will operate it;
- (*b*) the circumstances under which it will be used;
- (*c*) its reliability and servicing facilities;
- (*d*) its versatility;
- (*e*) its size and storage requirements;
- (*f*) its cost.

(3) Learn everything you can about its operation and its response to changed characteristics of the patient's respiratory system.

(4) Become thoroughly familiar with its use on a model lung.

(5) When an unfamiliar ventilator is first used on patients, monitor ventilation and mouth pressure until you are quite confident of your ability to maintain these variables at reasonable values. *Ideally*, they should always be monitored.

The choice of a particular ventilator is generally far less important than having a full understanding of the operation of the one you use.

Choice of Duration of Inspiration and Expiration

The first step is to select an appropriate respiratory frequency and then to decide what proportion of the cycle should be devoted to inspiration.

Normal adult respiratory frequency is 15 breaths per minute (B.P.M.) but

if we wish to impose a minute volume of 15 l./min. on an adult, we may select an infinite number of combinations of tidal volume and frequency. For convenience of operation our choice will probably lie between 300 ml. tidal volume at 50 B.P.M. and 1,500 ml. tidal volume at 10 B.P.M.

Characteristics of the artificial ventilator may further limit the choice, but otherwise the following considerations apply.

(1) *Age of the patient.* The normal adult range is 10–20 B.P.M. In children the rate rises as age falls, to 50 B.P.M. in neonates.

(2) *Minimum work.* For any particular combination of compliance and resistance there is a respiratory frequency which gives the minimum work of breathing for a particular minute volume (page 166). This frequency is usually selected reflexly by the spontaneously breathing subject, and it seems sensible to adopt the same frequency when the patient is paralysed. It will require the minimum work by the respirator, and the development of the lowest mean mouth pressures. *High airflow resistance requires a low respiratory frequency. Low compliance requires a high respiratory frequency.*

(3) *Anatomical dead space.* Formerly, great emphasis was laid on the increased ventilation of the anatomical dead space as respiratory frequency was increased. Often quoted was the example of a tidal volume of 151 ml. with an anatomical dead space of 150 ml. giving an effective alveolar ventilation of 1 ml. per breath. It is now known that the effective volume of the anatomical dead space is not constant under such conditions, and the anatomical dead space tends to fall with decreasing tidal volume (Rohrer, 1915; Briscoe, Forster and Comroe, 1954; Nunn and Hill, 1960). Similar considerations probably apply to apparatus dead space (Kain, Panday and Nunn, 1969). These matters are discussed in greater detail in Chapter 7.

In practice, quite a wide range of frequencies seems to be employed, and the author (1958a) found frequencies ranging from 8 to 24 B.P.M. during manual ventilation of patients for routine surgery. There is no evidence of harm resulting from the extremes of this range.

In recent years, ideas on the optimum duration of inspiration have changed. During the 1950's it was generally felt that duration of inspiration should be as short as possible to ensure the minimum mean intrathoracic pressure and, therefore, minimum interference with venous return. The shortest possible duration of inflation was obtainable with a square pressure wave such as that produced by the Radcliffe ventilators.

It is now realized that interference with the venous return is seldom of significance (*see* page 126) but, on the other hand, attention has been drawn to the improved distribution of inspired air if a reasonably long time is permitted for inspiration. This problem was mentioned briefly in Chapter 3 (*Figure 14*) in connection with the difference between static and dynamic compliance. It will also be discussed in greater detail in Chapter 7. For the moment we may note the following advantages in allowing more than the minimum time for inspiration.

(1) *Reduced compliance.* Where there are imperfections of distribution of the type shown in *Figure 14*, a certain inflation pressure will produce a significantly

larger tidal volume if the inflation phase is slightly prolonged. Watson (1962a) has elegantly demonstrated an increase in compliance, as follows:

Duration of inspiration	*Total compliance*
0·5 sec.	35 ml./cm H_2O
1·0 sec.	50 ml./cm H_2O
3·0 sec.	60 ml./cm H_2O

(2) *Physiological dead space.* The physiological dead space tends to be increased when the duration of inspiration is very short. It is likely to be the alveolar rather than the anatomical component of the physiological dead space which is changed, since maldistribution results in an excessive part of the inspired gas being delivered to alveoli with minimal circulation; this gas cannot therefore take effective part in gas exchange. Watson (1962b) and Bergman (1967) found physiological dead space/tidal volume ratios (V_D/V_T ratio) markedly related to duration of inspiration during artificial ventilation of paralysed patients. Mean values in Watson's study were as follows:

Duration of inspiration	V_D/V_T *ratio*
0·5 sec.	50%
1·0 sec.	30%
1·5 sec.	25%
2·5 sec.	20%

Thus the use of a very high respiratory frequency is likely to result in excessive dead space ventilation, but *not* solely because of the repetitive ventilation of the anatomical dead space as was formerly believed.

(3) *Alveolar/arterial* P_{O_2} *difference.* The use of the alveolar/arterial P_{O_2} difference as an index of maldistribution of pulmonary blood flow relative to inspired gas is discussed in Chapter 9 (page 251). Bergman (1963a) found lower P_{O_2} gradients (i.e. better distribution) when inspiration was prolonged and mean mouth pressure was highest. This was in a study of artificially ventilated dogs but no significant changes were found in a similar study of anaesthetized man (Bergman, 1967).

The efficiency of ventilation is thus increased as the inspiration is prolonged. There is considerable improvement with an extension of inspiration from 0·5 second to 1·0 second, but thereafter the improvement is less marked. In fact, if inspiration is unduly prolonged, the respiratory frequency becomes limited and very large tidal volumes must be employed. This causes excessive intrathoracic pressures (Watson, Smith and Spalding, 1962), and may interfere with venous return in certain patients. A compromise is, therefore, required between respiratory and circulatory considerations. Spalding and Smith (1963) have suggested 1·3 seconds as a reasonable duration of inspiration for the adult.

When expiration is unassisted by subatmospheric pressures, we have seen that it follows a wash-out exponential curve of time constant equal to the

product of compliance and resistance. Expiratory air flow resistance is higher than inspiratory, and therefore the time constant will be slightly longer. Values for resistance may be as high as 20 cm H_2O/l./sec., and compliance 100 ml./cm H_2O. The time constant may therefore be as much as 2·0 seconds and 95 per cent of the return to F.R.C. will then take 6·0 seconds (3 time constants). If sufficient time is not available during expiration, the next inspiration will start before the lung volume has returned to F.R.C. and the succeeding inspiration will enter the inspiratory reserve. The process is usually self-limiting as the elastic recoil is increased and the air passages will be dilated. The next expiration therefore proceeds more rapidly, and a compromise end-expiratory level is attained somewhere above the F.R.C.

A moderate increase in lung volume is not necessarily a bad thing. It is true that the mean intrathoracic pressure will be raised and the venous return may be significantly hampered in a small number of patients. On the other hand, the increased lung volume tends to prevent collapse and, during anaesthesia, the lung seems to function rather better than at normal volume. Nevertheless, it is clearly undesirable to have pronounced increases in lung volume which, apart from other considerations, may hamper the surgeon working in the chest or upper abdomen. It is therefore customary to allow a fairly long time for expiration, at least three time constants whenever this is possible. In the normal patient, expiration should therefore last at least 1·5 seconds, and in the presence of increased resistance it may be necessary to allow as long as 6·0 seconds.

We may summarize with typical phase durations for the normal adult:

Duration of inspiration	1·5 seconds
Duration of expiration	2·25 seconds
Total duration of cycle	3·75 seconds
Respiratory frequency 60 ÷ 3·75 =	16 breaths per minute
Ratio inspiration/expiration	1/1·5

Choice of Waveform

Few workers have attempted the extraordinarily difficult task of evaluating the efficiency of different waveforms (apart from considerations of phase duration). Watson (1962b) and Bergman (1963a and 1967) were unable to detect any significant differences in lung function with different waveforms, although they could show differences associated with duration of the inspiratory phase.

When venous return is critical and it is important to maintain a minimum intrathoracic pressure, it is probably preferable to use a square pressure waveform, which minimizes the duration of inspiration. However, a subatmospheric pressure used during expiration is generally a more effective method of lowering the mean intrathoracic pressure.

Manual versus *Automatic Ventilation*

Manual ventilation has advantages in simplicity and reliability. It also ensures that the anaesthetist remains in close contact with the patient. The 'educated hand of the anaesthetist' has been claimed to be sensitive to changes in resistance to inflation, and to be able to make the required adjustments to

maintain ventilation in the face of changing lung characteristics. Unfortunately, this has not been borne out by experimental studies.

Robinson (1968), using a model system, found that anaesthetists had difficulty in detecting even gross changes in compliance of the model patient and were not much more successful in detecting changes of airway resistance. Egbert and Bisno (1967), also using a model system, found most anaesthetists unable to maintain a constant ventilation in the face of changing characteristics of the model lung. It has, however, been claimed that the irregularity of manual ventilation may prevent collapse (Bendixen, Hedley-Whyte and Laver, 1963) and ventilation may also be modified to accommodate particular activities of the surgeon.

Against these advantages, mechanical ventilation wins the day when paralysis is prolonged. It is tedious and therefore difficult to maintain adequate manual ventilation for more than a few hours. Mechanical ventilation is also advantageous for the single-handed anaesthetist who has to attend to other tasks such as transfusion, monitoring, record keeping and resuscitation.

It is difficult to avoid the conclusion that, in practice, the choice of the manner of artificial ventilation is largely a matter of personal preference, convenience and cost. On these considerations, some ventilators seem more suitable for use in operating theatres while others are preferable for long-term ventilation of patients with respiratory inadequacy. Due attention must always be paid to reliability, motive power, ease of sterilization and safety. In the light of present knowledge such considerations seem to outweigh the subtleties of waveform. Subatmospheric pressure for use during expiration and patient triggering are features which should be included when possible.

PART II. Tidal Exchange Produced by Forces Acting Directly on the Boundaries of the Thoracic Cavity

The first part of this chapter has considered artificial ventilation produced by the development of a pressure gradient between the mouth and the air surrounding the chest. The second part considers tidal exchange produced by forces acting directly on the boundaries of the thoracic cavity. These boundaries may be moved by contraction of the subject's own muscles or by external forces applied by a second person (e.g. in the manual methods of artificial ventilation) or by a machine (e.g. cuirass respirator or electrophrenic respiration). It is a common feature of all these forms of ventilation that the geometric pattern of expansion of the thorax is partly dependent upon the action of local forces, and does not depend solely on the response of the regional elasticity to the development of a pressure gradient as in the forms of ventilation discussed in the first part of the chapter.

SPONTANEOUS RESPIRATION

The muscular pattern of contraction during normal breathing has been the subject of controversy for many years. Elucidation has been hampered by the difficulty in detecting contraction of many of the muscle groups concerned. It is difficult to detect active contraction of the diaphragm and also to distinguish

active movement from passive movement secondary to displacement of the abdominal viscera by the abdominal muscles. Even greater difficulty is encountered in demonstrating the localization of contraction within the intercostal group of muscles. The most effective methods of study have proved to be electromyography, measurement of pressures within the thorax and abdomen, and studies (particularly radiographic) of the change in shape of the thorax. These methods are usually correlated with spirometric demonstration of the respiratory phase.

Electromyography is the only method of demonstrating contraction in muscles such as pectoralis minor and the internal intercostals, which are covered by other muscles and which produce no skeletal movement that could not be attributed to other muscles. Nevertheless, the technique is difficult to apply in these circumstances and it is not possible to separate the actions of different layers of the intercostals by accurate placing of the electrodes. Electromyography of the diaphragm is difficult but may be accomplished with a bipolar oesophageal lead (Agostoni, Sant'Ambrogio and Carrasco, 1960; Agostoni, 1962).

The measurement of pressures within the thorax and abdomen is particularly valuable as evidence of contraction of expiratory muscles. Effective contraction of the abdominal muscles cannot take place without the appearance of characteristic peaks of oesophageal and intragastric pressure.

Radiographic and stethographic methods will show changes in shape of the confines of the thorax but will not necessarily indicate the muscle groups responsible. Ribs may be elevated, for example, either by contraction of the intercostals or by contraction of the diaphragm. For a detailed account of the muscles of breathing the reader is referred to *The Respiratory Muscles* by Campbell (1958). This monograph contains an extensive bibliography of the classical and more recent work in the field.

The diaphragm is the most important inspiratory muscle. During contraction, the origin and insertion are approximated, resulting both in descent of the domes and in elevation and rotation of the lower ribs (*Figure 45*). The normal excursion of the domes is 1·5 cm., increasing to 6–7 cm. during deep breathing (Wade and Gilson, 1951). Although the diaphragm plays the major part in inspiration, there is a large reserve of function in the other inspiratory muscles. Thus unilateral paralysis of the diaphragm causes little reduction of ventilatory capacity, while even bilateral phrenic interruption is compatible with reasonably good ventilatory function (Dowman, 1927).

The intercostal muscles acting alone are able to maintain a high level of ventilation (Otis, Fenn and Rahn, 1950), and contract during inspiration in most, but not all, subjects (Campbell, 1955). Inspiratory activity is less in the higher than in the lower intercostal spaces. Campbell (1955) was unable to demonstrate in man the expiratory activity which has been reported in animals. Other muscles, particularly the scaleni, may occasionally be found to contract during normal quiet breathing.

Expiration is passive in the normal resting subject but active when making expulsive efforts, talking, breathing against high expiratory resistance or when

the minute volume is greater than about 40 l./min. There is normally no myographic or manometric evidence of contraction of abdominal or intercostal muscles during quiet breathing provided that these muscles are not in sustained contraction for the maintenance of posture. However, the contraction of the inspiratory muscles is not suddenly terminated at the start of expiration. Instead, there appears to be a gradual 'let-down' of tone so that expiration starts slowly. Only after the expiration of about a quarter of the tidal volume does inspiratory tone finally disappear, and expiration of the remaining part of the tidal volume proceeds according to a wash-out exponential function (*Figure 40*). In this respect expiration differs between spontaneous respiration and artificial ventilation by I.P.P. In the latter, the whole of expiration usually proceeds according to the simple exponential process shown in *Figure 40*, while in the former, the expiratory spirogram follows the rather complex S-shaped

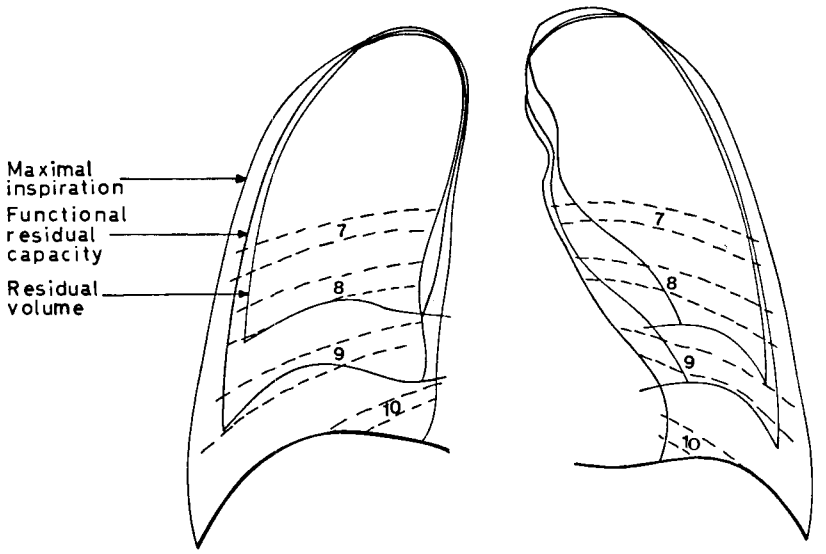


Figure 45. Outlines of chest radiographs of a normal subject at various levels of lung inflation. The numbers refer to ribs as seen in the position of maximal inspiration. (I am indebted to Dr. R. L. Marks who was the subject)

curve shown in *Figure 31*. Modifications of the pattern of spontaneous respiration occurring during anaesthesia are described on page 97.

Active Hyperventilation

As ventilation is increased, the inspiratory muscles contract more vigorously and accessory muscles are recruited. The first group to be recruited is usually the scaleni, and considerable hyperventilation (about 50 l./min.) is attained before the sternomastoids and extensors of the vertebral column are brought into use (Campbell, 1958). Extreme hyperventilation (as during the measurement of the maximum breathing capacity) requires the use of a great many different muscle groups. The pectorals, for example, reverse their usual origin/insertion and help to expand the chest when the arms are fixed by grasping a

suitable support. During voluntary hyperventilation, expiratory muscle activity remains absent until a minute volume of about 40 l./min. is attained (Campbell, 1952). Thereafter, it plays an increasingly important role as respiration progressively assumes the quasi sine-wave push-pull pattern of extreme hyperventilation (Cooper, 1961).

Effect of Posture

Throughout this book, the effect of posture is stressed, since so many studies of normal human physiology relate to standing or seated subjects. The anaesthetist, on the other hand, is concerned almost exclusively with supine patients, and must constantly be mindful of the differences consequent on change of posture. In fact, the simplified account above of the action of the respiratory muscles refers primarily to supine subjects. An important difference in the upright position is the tonic contraction of the postural (anti-gravity) muscles. Many of these, including the abdominal muscles, show a variation in tone according to the respiratory phase.

In the supine position the diaphragm is some 4 cm. higher in the chest (Wade and Gilson, 1951) and this accords with the reduction of F.R.C. (*Figure 11*). The dimensions of the rib cage are probably little altered. Although the reduction of F.R.C. is undesirable from the point of view of airway and alveolar closure (page 51), the diaphragm is able to contract more effectively the higher it is forced into the chest.

In the lateral position (*Figure 46*), the lower dome of the diaphragm is pushed higher into the chest while the upper dome is flattened. It follows that the lower dome can contract more effectively than the upper, and the ventilation of the lower lung is found to be about twice that of the upper lung. This is fortunate since gravity causes a somewhat similar discrepancy between the blood flow of the two lungs. Thus the ventilation/perfusion ratio of each lung remains approximately constant, regardless of position (Svanberg, 1957).

Effect of Anaesthesia

Comparatively little is known of the pattern of contraction of the respiratory muscles during spontaneous respiration of the anaesthetized patient. Much has been written of the change from thoracic to abdominal respiration with deepening respiration, but this describes a pattern of spatial change which cannot readily be interpreted as changes in the pattern of contraction of muscles. Miller (1938) used two pneumographs (around the chest and abdomen) to demonstrate the rather sharp cut-off of thoracic movements as anaesthesia passes from the second into the third plane of the third stage. The suggestion that this is due to intercostal paralysis is probably naïve since the diaphragm is able to expand the chest without the assistance of the intercostals. 'Abdominal breathing' is usually associated with a short duration of inspiration during which the sharp descent of the diaphragm is too rapid to allow the normal inflow of gas into the chest. The pressure of gas within the lungs then falls sharply and the chest wall is either actively indrawn or at least does not expand as usual. The condition is thus similar to subcostal, intercostal and suprasternal retraction seen with severe inspiratory obstruction. The tendency towards

shortening of inspiration is clearly shown in the spirogram of the anaesthetized patient in *Figure 31*, in which inspiration lasts only 30 per cent of the total respiratory cycle compared with 40 per cent in the normal respiratory waveform shown in the same diagram.

Certain special patterns of inspiration may be seen during anaesthesia. Sighing appears to be more common under ether anaesthesia and during the administration of nitrous oxide supplemented with pethidine than under halothane. It has been suggested that the sigh is useful to re-expand collapsed areas

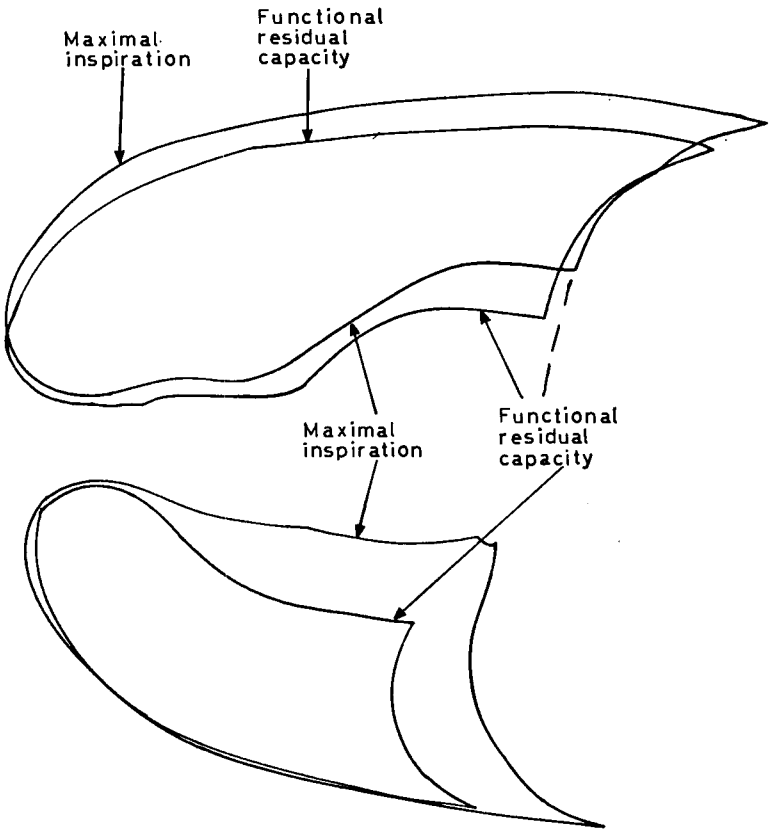


Figure 46. Radiographic outlines of the lungs at two levels of lung volume in a conscious subject during spontaneous breathing in the lateral position (right side down). This is the same subject as in Figure 45: comparison will show that, in the lateral position at F.R.C., the lower lung is close to residual volume while the upper lung is close to inspiratory capacity. The diaphragm therefore lies much higher in the lower half of the chest. Both these factors contribute to the greater volume changes which occur in the lower lung during inspiration. The mediastinum seems to rest on a pneumatic cushion at F.R.C. and rises during inspiration

of lung (page 375). A most curious pattern occasionally seen is the double inspiration, producing a spirogram like the outline of a Bactrian camel. The significance of the double inspiration is not known, but it is unlikely to be a particularly effective method of ventilation. Reversed rhythm has been described as a feature of profound anaesthesia; the pause is said to occur at the

end of inspiration instead of at the end of expiration. It is certainly rare and has never been observed by the author.

It has long been thought that expiratory muscle activity occurs during anaesthesia. An electromyographic study by Freund, Roos and Dodd (1964) showed that expiratory activity in the abdominal muscles is, in fact, an invariable feature of anaesthesia and is not related to any particular technique. In particular, it occurs even in the absence of an endotracheal tube or pharyngeal airway and cannot therefore be regarded as a modified cough in resentment of mechanical irritation.

Every surgeon knows that expiratory muscle tone diminishes as anaesthesia deepens. When anaesthesia lightens, contraction of the expiratory muscles becomes apparent in one of the following ways.

(1) Detection by the surgeon during abdominal surgery.
(2) Observation of the abdomen by the anaesthetist.
(3) Detection of an 'expiratory push' visible in the reservoir bag.

The expiratory push is one of the most sensitive indices of lightening anaesthesia and is noticed instinctively by the experienced anaesthetist. An excellent demonstration of the return of expiratory muscle activity may be made by connection of a simple manometer to a balloon in the oesophagus. Pronounced peaks of pressure may be seen at the same time as the appearance of the expiratory push. The reason for the enhanced expiratory muscle activity of the anaesthetized patient is unknown.

Deep anaesthesia and carbon dioxide retention are sometimes associated with a characteristic phenomenon known as tracheal tug. During inspiration, the larynx and lower jaw are jerked downwards and this movement is usually attributed to traction from the diaphragm transmitted through the mediastinum to the trachea. Mitchinson and Yoffey (1947) suggested that downward movement of the larynx was normally prevented by a stabilizing contraction of the elevators of the larynx; it is postulated that tracheal tug develops when the stabilizing muscles are paralysed while the diaphragm is still contracting vigorously. Observations in hypercapnic dogs (unpublished) have led the author to believe that contraction of the infrahyoid and hyomandibular muscles may make some contribution to the development of tracheal tug.

We shall see in later chapters that there is ample evidence to suggest that the distribution of inspired air relative to pulmonary blood flow is defective during anaesthesia. This *could* be explained by a spatial maldistribution of inspired gas due to abnormal functioning of the ventilatory mechanism as a result of anaesthesia. In fact, this is extraordinarily difficult to demonstrate and no one has succeeded in doing so up to the present time.

Comparison between Spontaneous Respiration and I.P.P. Ventilation

I.P.P. ventilation results in a spatial pattern of distribution of inspired gas which is determined solely by the regional variations in compliance, except in so far as regional variations in airway resistance may influence distribution if inflation is fairly rapid. It is still not clear to what extent similar considerations apply to the distribution of inspired gas during spontaneous respiration. It used

to be taught that the diaphragm descended in inspiration, creating a 'vacuum' in the pleural cavities, and that gas then entered the lungs because 'nature abhors a vacuum'. This facile explanation overlooks the fact that the pleural space does not exist and the lungs cannot, therefore, freely expand into the space after the manner of the familiar bag-in-a-bottle 'model' of the respiratory system. In fact, the lungs remain firmly in contact with the parietal pleura, although the two layers slide over one another to a certain extent. Thus the lungs must follow the changes in the shape of the confines of the thorax and the spatial pattern of distribution of inspired gas must be influenced by the pattern of change of shape of the confines of the thorax. It may then be argued that it could only be coincidental if this pattern were identical to the pattern obtained with I.P.P. ventilation.

Although the *geometrical outline of the lungs as a whole* must follow the movements of the chest wall, it does not follow that the entry of air into specific lobes and lobules is so influenced. The boundaries between the lobes and lobules have considerable freedom of movement so that the fraction of the tidal air admitted to a particular lobule may well be largely independent of the spatial pattern of expansion of the confines of the thorax. If, for example, the left dome of the diaphragm were paralysed and respiratory movement on that side were confined to expansion of the upper ribs, the radiological appearance would show distribution of inspired gas in favour of the upper parts of the lungs. However, inspiration would be associated with ascent of the interlobar fissure, so that the lower lobe would be better ventilated than radiological appearances might suggest. Bergman (1963b) has demonstrated identical patterns of nitrogen wash-out with spontaneous and artificial ventilation. The interpretation of this finding is difficult but it probably supports the belief that there are no differences of spatial pattern of distribution of inspired air which are of practical importance.

Reference has already been made to the differences in expiratory waveforms. Artificial ventilation by I.P.P. is usually associated with a passive expiration conforming to a simple exponential wash-out. During spontaneous respiration, this is modified by the initial slow let-down of inspiratory muscle tone while, during anaesthesia, there is active expiratory muscle activity.

ARTIFICIAL VENTILATION PRODUCED BY FORCES ACTING DIRECTLY ON THE THORAX

This section is concerned largely with manual methods of artificial ventilation of the type used in first aid. Their importance is now greatly reduced following the recognition of the superiority of expired air resuscitation (page 123).

Shortly after World War II, the advent of nerve gases stimulated interest in simple methods of artificial ventilation. Attention was first directed to the manual methods, and the December 1951 issue of the *Journal of Applied Physiology* (vol. 4, no. 6) was devoted to comparative studies of the various methods. Unfortunately, these studies employed either conscious non-apnoeic subjects or else anaesthetized volunteers who had been paralysed and intubated. In neither case was there airway obstruction and this vitally important factor was overlooked.

It was not until 1959 that the iconoclastic paper of Safar showed that airway obstruction was almost always present in the unconscious subject and could not be satisfactorily cleared by the use of an oropharyngeal airway or by placing the patient in the prone position. Effective ventilation by the manual methods was shown to be ineffective unless the trachea was intubated. A subsequent paper by Safar, Escarraga and Chang (1959) demonstrated the nature of the pharyngeal obstruction and showed that the pharyngeal airway was most effectively cleared either by extension of the atlanto-occipital joint or by protrusion of the mandible (*Figure 47*). These manœuvres are now regarded as essential adjuncts to the manual methods of artificial respiration (Karpovich, 1962) but, unfortunately, either two rescuers are required, or else a single rescuer uses his legs to maintain the victim's head in a favourable position. In either event the procedure is complicated, tiring and difficult to teach.

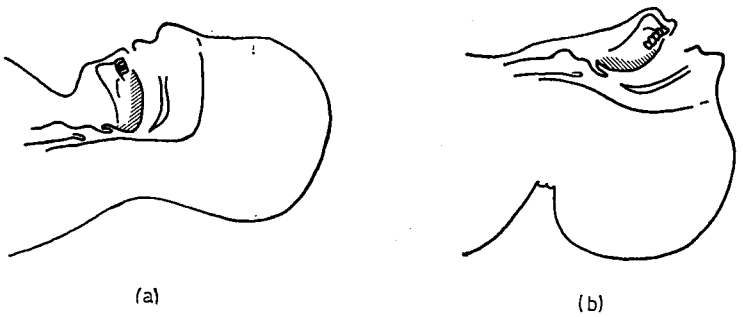


Figure 47. Clearance of airway by extension of the atlanto-occipital joint. (a) The outline of the pharynx in the unconscious patient. Turning into the prone position does little to improve the obstruction between the base of the tongue and the posterior pharyngeal wall. This may be cleared by maximal extension of the atlanto-occipital joint (b). The airway may also be cleared by protrusion of the mandible in the manœuvre familiar to all anaesthetists

Nevertheless, it should be remembered that the manual methods have saved lives in the past. Although normal ventilatory exchange is desirable, life may be sustained on an alveolar ventilation which is only half the normal value.

Some manual methods of artificial ventilation employ an active expiratory phase with passive inspiration. This is the exact opposite of spontaneous respiration or artificial ventilation by I.P.P. Other methods employ an active inspiratory phase which is intended to simulate spontaneous respiration. A third group has both active inspiration and active expiration. These methods are known as 'push-pull' and are analogous to spontaneous respiration with expiratory muscle activity, or to I.P.P. ventilation with a subatmospheric pressure phase during expiration.

Group I—Active Expiratory Phase Only

Generally speaking these techniques are unsatisfactory. They operate within the patient's expiratory reserve (*see Table 13*), which is appreciably

reduced in the supine or prone position. (The figures in *Table 13* are taken from Whitfield, Waterhouse and Arnott (1950).)

Table 13

Number of subjects	*Expiratory reserve volume (ml.) (A.T.P.S.)*	
	Mean	*Range*
Male: 64 sitting	1,269	270–2,540
41 lying	1,005	200–2,600
Female: 32 sitting	884	300–1,580
16 lying	663	170–1,120

The normal airway resistance rises very sharply as the residual volume is approached and, in practice, it is doubtful if effective use can be made of more than half of the expiratory reserve volume. Therefore, an active expiratory phase alone is unlikely to produce effective tidal exchange. The following are the more important methods employing an active expiratory phase alone.

Belt respirator (Paul Bragg Pneumobelt).—This device consists of an intermittently inflated belt which surrounds the lower chest and abdomen. It cannot be relied upon to produce an effective tidal exchange in the totally paralysed patient, but finds some use for assisting breathing in the *partly* paralysed patient.

Back pressure (Schafer's method, 1904).—Intermittent pressure is applied to the lower ribs with the patient in the prone position. Even with a clear airway, the tidal exchange seldom approaches normal. Gordon and his colleagues (1951b) reported a mean tidal volume of 238 ml. in apnoeic intubated subjects but this was increased to 469 ml. by 'spring-off' at the end of the patient's expiratory phase. Karpovich, Hale and Bailey (1951) obtained a mean exchange of 451 ml. in conscious volunteers simulating apnoeic victims. It is, however, unlikely that conscious volunteers are able to relax completely and they probably tend to supplement their ventilation; such studies almost always indicate higher tidal volumes than are found with paralysed patients.

Epigastric compression.—Pinkerton (1957) has suggested that ventilation may be maintained during bronchoscopy by intermittent pressure applied to the patient's epigastrium with an anaesthetic reservoir bag secured with a binder and attached in place of a mask to a conventional anaesthetic gas circuit. Intermittent inflation of the bag can then be produced by manual compression of a second bag within the circuit. Tidal exchanges of the order of 250 ml. may be produced by this method.

External cardiac massage.—All concerned with resuscitation should understand clearly that external cardiac massage is most unlikely to achieve an effective tidal exchange. In healthy, intubated curarized patients, Safar and his colleagues (1961) recorded a mean tidal volume of 156 ml. during external cardiac massage. However, in 12 victims of cardiac arrest, they were unable to detect any tidal exchange in spite of tracheal intubation. Cardiac massage must be supplemented by artificial ventilation and, when single handed, the

rescuer should alternate 15 strokes of cardiac massage with 2 breaths of expired air, repeated as rapidly as possible.

Group II—Active Inspiratory Phase Only

These methods operate within the inspiratory capacity, which is approximately three times the expiratory reserve when the patient is lying down (Whitfield, Waterhouse and Arnott, 1950). However, this advantage is largely offset by the mechanical difficulty of expanding the thorax by manual means. The more important inspiratory methods are as follows.

Rocking bed.—This technique closely simulates the normal movements of the diaphragm. Active contraction is replaced by varying the gravitational load of the abdominal viscera on its lower surface. However, the pattern of thoracic expansion differs from normal since passive descent of the diaphragm does not expand the rib cage, which therefore tends to move paradoxically. When the feet are lowered from the horizontal, the lung volume increases in proportion to the sine of the angle of tilt (Colville, Shugg and Ferris, 1956). There is little change when the feet are elevated, and the most effective range of rocking is between horizontal and 20 degrees, feet down (Radford and Whittenberger, 1962). The method is most effective in tall adults in whom it is generally possible to obtain adequate ventilation.

Hip lift and hip roll (Gordon and his colleagues, 1951a).—The victim lies prone while the rescuer lifts the hips with or without rolling them to one side over his thigh. This manœuvre extends the spine and allows the abdominal viscera to fall. This produces inspiration and tidal exchange occurs above the F.R.C. In conscious volunteers, Karpovich, Hale and Bailey (1951) obtained a mean tidal volume of 888 ml., but less satisfactory results would be expected when airway obstruction complicated the picture.

Cuirass respirators.—Cuirass respirators exert an intermittent subatmospheric pressure over the lower part of the chest. The area of application varies from the epigastrium (shell cuirasses) to the greater part of the trunk (Tunnicliffe jacket). The greater the area of application the more efficient is the ventilation although at the cost of convenience of application. With a large area of application the efficiency and general effects approach those of a cabinet respirator. The smaller cuirasses, however, tend to hamper movement of the chest and are, therefore, chiefly suitable for the reinforcement of ventilation in patients with partial respiratory paralysis.

Group III—Both Active Inspiratory and Expiratory Phases (push-pull)

These techniques are now accepted as the most efficient of the manual methods of artificial respiration. Tidal exchange occurs above and below the F.R.C. The following methods are in use.

Rocking stretcher (Eve, 1932).—This method differs from the rocking bed in the range of tilt which is much greater. The patient must be secured to the stretcher which is commonly tilted about 40 degrees on either side of horizontal. Tidal exchange occurs above and below the F.R.C. measured in the horizontal position. Comroe and Dripps (1946) found the method greatly superior to Schafer's method.

Arm lift, back pressure (Holger Nielsen method, 1932).—The victim lies prone. The rescuer kneels at the head of the victim and produces inspiration by drawing the elbows towards the head. Expiration is produced by back pressure as in Schafer's method. Both phases are active, and tidal exchange takes place above and below the F.R.C. In curarized intubated subjects, Gordon and his colleagues (1951b) obtained a mean tidal volume of 957 ml., most of the exchange occurring below the F.R.C. (i.e. in the expiratory reserve). Safar (1959) reported an exchange of only 619 ml. under similar circumstances. Karpovich, Hale and Bailey (1951) obtained a mean tidal volume of 938 ml. in conscious volunteers.

Arm lift, chest pressure (Silvester's method, 1857).—The victim lies supine. The rescuer kneels at the head of the victim and produces inspiration by raising the victim's arms above his head. Expiration is produced by laying the victim's arms on his chest and exerting pressure. Both phases are active and tidal exchange takes place above and below the F.R.C. Karpovich, Hale and Bailey (1951) obtained a mean tidal volume of 1,068 ml. in conscious volunteers, but Safar (1959) obtained an exchange of only 503 ml. in intubated curarized subjects.

Hip roll, back pressure.—Studies of this combination have given results broadly similar to those of Silvester's method and the Holger Nielsen technique. Gordon and his colleagues (1951b) reported mean tidal exchanges of 1,057 ml. (hip lift) and 903 ml. (hip roll). Karpovich, Hale and Bailey (1951) obtained a mean tidal exchange of 1,015 ml.

All the push-pull manual methods of Group III are capable of producing an adequate tidal exchange if the airway is perfectly clear. Unfortunately, this is seldom the case and the data of Safar (1959) given in *Table 14* clearly demonstrate the significance of this factor.

Table 14

Curarized anaesthetized patients—artificial respiration by back pressure, arm lift method (Holger Nielsen method, 1932)

Airway	*Mean tidal volume (ml.)*	*Percentage of patients with tidal volume less than dead space*
Natural (head in flexion)	126	75
Oropharyngeal airway (head in flexion)	178	71
Natural (head in extension)	328	31
Oropharyngeal airway (head in extension)	351	20
Endotracheal tube	619	0

Finally, it must be stressed that the production of a normal tidal volume does not necessarily guarantee normal arterial blood gas levels. Gordon and his colleagues (1951c) found a marked degree of desaturation during artificial respiration with Schafer's method, which could not be entirely explained by

hypoventilation. It is likely that reduction of the lung volume below the F.R.C. resulted in sufficient airway closure to cause appreciable shunting, and this accords with the study of Nunn and his colleagues (1965b) in which shunting was caused by normal subjects breathing within their expiratory reserve. There is no doubt that shunting might be considerably aggravated by inhalation of foreign material in many situations confronting the first aid worker.

CHAPTER 6

THE MINUTE VOLUME OF PULMONARY VENTILATION

So far, most of this book has been concerned with mechanisms and factors related to the tidal flow of gas into and out of the lungs. The present chapter considers what ventilatory exchange may be regarded as adequate and classifies the causes of failure of ventilation. The work and energy cost of breathing are discussed and finally, the principles of measurement of ventilation are presented.

There is a close analogy between the minute volume of ventilation and the urinary flow rate. Each process removes catabolites in an amount equal to the product of the flow rate of the carrier and the concentration of the catabolite in the carrier:

$$\begin{matrix}\text{urea cleared} \\ \text{per day}\end{matrix} = \begin{matrix}\text{volume of urine} \\ \text{passed per day}\end{matrix} \times \begin{matrix}\text{concentration of urea} \\ \text{in the urine}\end{matrix}$$

$$\begin{matrix}\text{carbon dioxide} \\ \text{cleared per min.}\end{matrix} = \begin{matrix}\text{minute volume} \\ \text{of ventilation}\end{matrix} \times \begin{matrix}\text{concentration of } CO_2 \\ \text{in mixed expired air}\end{matrix}$$

The clearance of urea is generally easier to understand and measure because the flow of urine is fluvial in contrast to ventilation which is tidal. Clearance of carbon dioxide is therefore influenced by the composition of the inspired air and by the dead space, factors which have no counterpart in the clearance of urea.

Further difficulties in the study of pulmonary ventilation arise from the fact that gases are less easy to handle, measure and sample than are liquids. Thus nurses have, for many years, been trained to measure and record the flow of urine, while the bedside measurement of pulmonary ventilation is still considered to be outside the scope of ordinary medical care. We may note in passing that charting the respiratory frequency on the temperature chart is almost useless as an indication of the adequacy of ventilation.

DEFINITION OF ADEQUACY OF VENTILATION

It is the function of the respiratory system to ensure normal levels of oxygen and carbon dioxide in the arterial blood. It is then the function of the circulatory system to transport the arterial blood to the tissues. An adequate minute volume of ventilation may be defined as follows.

> The respiratory minute volume which will ensure satisfactory levels of both oxygen and carbon dioxide in the arterial blood, under prevailing conditions of barometric pressure, composition of the inspired gas, dead space, distribution, shunting, diffusing capacity and metabolic activity of the patient.

A minute volume which is adequate for a healthy resting subject at sea level will not be adequate if the subject is on the top of Mount Everest, is exercising,

is breathing 9 per cent oxygen or if he has developed diseases such as emphysema which impair pulmonary function.

Our definition hinges on what is considered a satisfactory level of oxygen and carbon dioxide in the arterial blood. The P_{CO_2} is the more important consideration in defining the adequacy of ventilation under hospital conditions, since the P_{O_2} can easily be altered by changes in the concentration of oxygen in the inspired gas and is, therefore, less dependent on the minute volume. For example, a patient with a grossly inadequate minute volume (as regards P_{CO_2}) may have a normal or elevated P_{O_2} if the concentration of oxygen in the inspired gas is increased by the appropriate amount.

There is no consensus of opinion on the optimum P_{CO_2} during anaesthesia. Whereas it might appear reasonable to keep the P_{CO_2} within the normal range (36–44 mm Hg), many anaesthetists feel it is preferable to hyperventilate the patient and so reduce the P_{CO_2} to levels within the range 20–30 mm Hg (Gray and Rees, 1952; Geddes and Gray, 1959). The following advantages have been claimed.

(1) In cases of doubt, it is better to err on the side of overventilation rather than underventilation.

(2) The chances of pulmonary collapse are minimized by a large tidal volume.

(3) Apnoea is considered by many to be a desirable feature of an anaesthetic and this may be maintained by the reduction of P_{CO_2} (page 31). It is now thought to be unlikely that stimulation of the Breuer–Hering reflex plays a part in causing apnoea (page 38).

(4) Hypocapnia with alkalosis causes changes in distribution and duration of action of certain drugs, and such changes have been considered desirable (Dundee, 1952; Utting, 1963).

(5) There are a number of situations in which cardiac arrhythmias are less likely to arise if the P_{CO_2} is reduced (page 318).

There seems little doubt that patients remain quiet and relaxed on the operating table with smaller doses of relaxants and anaesthetics if they are passively hyperventilated. Whatever their motives, most anaesthetists employ hyperventilation with hypocapnia during the conduct of an anaesthetic with paralysing doses of relaxants (Nunn, 1958a). Opposition to this practice is based principally on the reduction of cardiac output and cerebral blood flow which results from hypocapnia (pages 314 and 317).

During operations in which patients are allowed to breathe spontaneously, there is usually a rise in P_{CO_2} (Nunn, 1958a). Anaesthetists vary in the extent to which they will permit this to occur. Elevation as far as about 75 mm Hg seems to be commonplace even during operations not requiring much relaxation. However, during laparotomy with spontaneous respiration, levels as high as 150 mm Hg have been reported (Birt and Cole, 1965).

Against this wide spectrum of P_{CO_2} values, the cynic argues that the exact level is unlikely to be very important. For the healthy patient this may well be true, but the skill of an anaesthetist is also measured by his ability to carry bad risk patients through extensive surgical procedures with the minimum mortality. Under such conditions, the maintenance of P_{CO_2} at the optimum level may be critically important, and the next section of this chapter considers how this

may be accomplished. This is linked to a consideration of the influence of ventilation on P_{O_2} in those situations where the anaesthetist cannot or does not wish to adjust the concentration of oxygen in the inspired gas. If, for example, he is relying upon nitrous oxide to keep the patient unconscious, it is not possible to raise the inspired oxygen concentration much above 30 per cent.

The Relationship between Ventilation and Alveolar Gas Tensions during Anaesthesia

Once it is decided what levels of the arterial P_{CO_2} and P_{O_2} should be regarded as optimal, there are two approaches towards ensuring that these levels are maintained:

(1) we may make direct (or indirect) measurements of the arterial blood gas levels and then adjust ventilation accordingly;

OR

(2) from observations made on other patients under similar circumstances, we may ventilate the patient so that we may *expect* the arterial blood gas levels to remain within the required range.

The first course is a counsel of perfection since, at present, the measurements are too troublesome for routine use. While measurement may be essential to the management of really difficult clinical problems, it will probably not be feasible during routine anaesthesia for a great many years. Fortunately it is seldom essential and, in the vast majority of cases, it is satisfactory to rely on observations made on other patients under similar circumstances. We may then consciously or subconsciously estimate what will be a reasonable ventilation for a particular patient.

At this stage it is necessary to consider oxygen and carbon dioxide separately. It is usual to consider carbon dioxide homeostasis first, in spite of oxygen being more important. This is because the problems of oxygenation are more complicated and include a number of factors which do not matter in the case of carbon dioxide. This approach, however convenient, carries the danger that we may be so concerned with carbon dioxide as to ignore oxygen. There is even a tendency to think that, if the arterial P_{CO_2} is within normal limits, the arterial P_{O_2} must also be normal. This does not necessarily follow. Shunting through atelectatic lung is just one example of conditions in which a normal P_{CO_2} may be associated with appreciable desaturation. Our approach then, is firstly to calculate a minute volume which will ensure a normal P_{CO_2} and secondly to consider whether or not this will ensure adequate oxygenation. If not, we may then raise the inspired oxygen concentration which, in appropriate degree, will overcome most of the barriers to adequate oxygenation.

Calculation of Ventilation required for CO_2 *Homeostasis*

Certain simplifying assumptions are usually made, based on typical conditions during uncomplicated anaesthesia. Appropriate corrections can be applied later if they are required.

(1) Barometric pressure is 760 mm Hg. Water vapour pressure at 37°C is

47 mm Hg, and so the dry barometric pressure of alveolar gas is 760 − 47 = 713 mm Hg.

(2) The inspired gas is free of carbon dioxide.

(3) The patient's metabolic activity is basal on the English Standard (Robertson and Reid, 1952), or about 15 per cent below basal on the American Standard (Aub and DuBois, 1917; Boothby and Sandiford, 1924) (*see Table 15*).

(4) The respiratory exchange ratio (R.Q.) is 0·8

Table 15

Predicted values for oxygen consumption and carbon dioxide output during uncomplicated anaesthesia (ml./min.) (S.T.P.D.)

Age	*Oxygen consumption*			*Carbon dioxide output*		
	Small patient	*Average patient*	*Large patient*	*Small patient*	*Average patient*	*Large patient*
Male						
14–15		190			152	
16–17		200			160	
18–19	168	210	252	134	168	202
20–29	162	203	243	130	162	194
30–39	162	203	243	130	162	194
40–49	158	198	237	126	158	190
50–59	155	194	233	124	155	186
60–69	150	187	224	120	150	179
Female						
14–15		174			139	
16–17		188			150	
18–19	156	194	233	125	155	186
20–29	152	190	228	122	152	182
30–39	150	187	224	120	150	179
40–49	148	184	221	118	147	177
50–59	144	180	216	115	144	173
60–69	140	175	210	112	140	168

Values for CO_2 output will only apply in a steady respiratory state.
Values are probably about 6 per cent lower during artificial ventilation.
Figures are based on 85 per cent of basal according to data of Aub and DuBois (1917) and Boothby and Sandiford (1924).

(5) The physiological dead space and distribution have the values known to apply to healthy anaesthetized patients. General considerations commonly exclude apparatus dead space, allowance for which is postponed until consideration of an individual patient.

Charts and nomograms for prediction of correct ventilation are all based on the following axiomatic relationship:

$$\text{volume of } CO_2 \text{ eliminated in one minute} = \text{alveolar ventilation} \times \text{concentration of } CO_2 \text{ in alveolar gas}$$

Therefore:

$$\text{alveolar ventilation} = \frac{\text{volume of } CO_2 \text{ eliminated per minute}}{\text{concentration of } CO_2 \text{ in alveolar gas}}$$

$$= \frac{\text{volume of } CO_2 \text{ eliminated per minute}}{\text{alveolar } P_{CO_2} \div 713}$$

For all practical purposes,

$$\text{arterial } P_{CO_2} = \text{alveolar } P_{CO_2}$$

Therefore:

$$\text{alveolar ventilation} = \frac{\text{volume of } CO_2 \text{ eliminated per minute}}{\text{arterial } P_{CO_2} \div 713}$$

So far these equations make no assumptions which are likely to be invalid. Unfortunately, they are of little practical use until alveolar ventilation (which cannot be measured) is related to minute volume of respiration (which can be measured). This relationship depends upon the physiological dead space which approximates to one-third of the tidal volume in healthy, anaesthetized, intubated patients (Nunn and Hill, 1960). Therefore the alveolar ventilation will approximate to two-thirds of the minute volume.

However, it is important to remember that the dead space is increased under certain circumstances, and that the alveolar ventilation will then be less than two-thirds of the minute volume. The most important causes of an increase of dead space are certain respiratory diseases, pulmonary embolus and conditions associated with a reduction of pulmonary blood flow (pages 184 et seq.). In addition, during anaesthesia, the total dead space usually includes apparatus dead space which will vary widely with different gas circuits and is often an important factor. For example, a value of 100 ml., at a respiratory frequency of 20 breaths per minute, will cause a reduction in alveolar ventilation of 100 times 20 ml., equals 2 litres per minute. Not without significance is the difference in total dead space between intubated and non-intubated patients. Kain, Panday and Nunn (1969) found the total dead space to be about 85 ml. greater in unintubated patients breathing from a face mask.

If we confine our attention to healthy intubated patients and ignore, for the moment, apparatus dead space, the following relationship applies:

$$\text{required minute volume} = \frac{\text{predicted oxygen consumption} \times \text{R.Q.}}{\text{required arterial } P_{CO_2} \div 713} \times 1{\cdot}5$$

where the factor 1·5 represents the ratio of minute volume to alveolar ventilation.

However, minute volume is normally expressed under conditions of body temperature (B.T.P.S.), while oxygen consumption is expressed under conditions of standard temperature and pressure, dry (S.T.P.D.). To convert gas volumes at S.T.P.D. to B.T.P.S. the factor is approximately 1·2 (*see* Appendix B). Also, oxygen consumption is usually expressed in millilitres per minute and a factor of 0·001 is required to convert this to litres per minute, which is the customary unit for expression of minute volume.

Allowing a value of 0·8 for the R.Q., the equation may now be written as follows:

$$\text{required minute volume} = \frac{\text{predicted oxygen consumption}}{\text{required arterial } P_{CO_2}} \times 0{\cdot}8 \times 1{\cdot}2 \times 1{\cdot}5 \times 0{\cdot}001 \times 713$$

It so happens that the product of the numbers on the right is very close to 1·0 and therefore as a reasonable approximation:

$$\text{*required minute volume (l./min.)} = \frac{\text{predicted oxygen consumption (ml./min.)}}{\text{required arterial } P_{CO_2} \text{ (mm Hg)}}$$

* The apparent inconsistency of the dimensions in this equation is explained by the omission of the constant 1·0 which has the dimensions of pressure.

This equation forms the basis of the charts of Nunn (1960a), subsequently presented in the form of a slide rule (Nunn, 1962a), shown in *Figure 48.* These approaches pass through a stage of predicting the patient's carbon dioxide

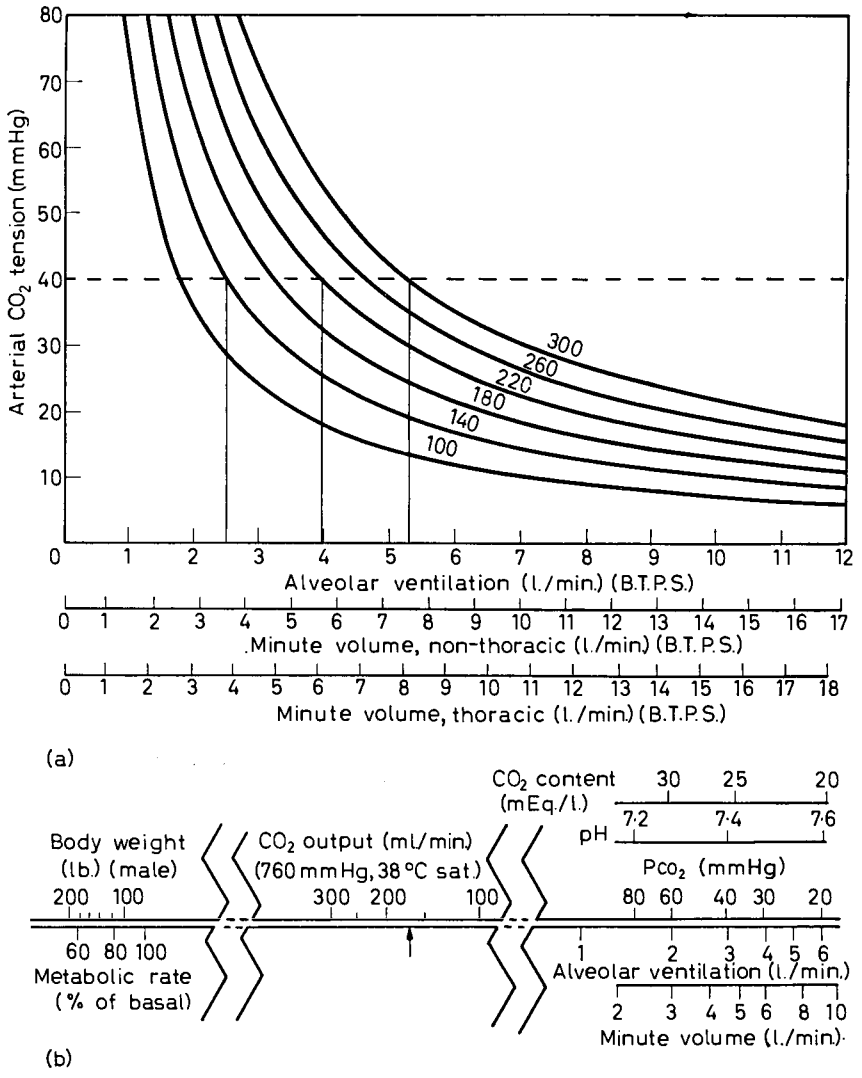


Figure 48. Prediction of relationship between P_{CO_2} *and ventilation. (a) shows the graph relating* P_{CO_2} *and ventilation for different values of* CO_2 *output (Table 15). (b) shows the relationship presented in the form of a slide rule (Nunn, 1962a). The other side of the slide rule gives the relationship between* P_{CO_2}*, inspired oxygen concentration and alveolar* P_{O_2}*. (Reproduced from Nunn (1960a; 1962a) by courtesy of the Editor of* Anaesthesia)

output, but this is bypassed in the simplified equation above. Radford's nomogram (1955) employs the same basic equation but assumes a fixed dead space related to the weight of the patient (*Figure 49*). Both methods give

reasonable results during steady artificial ventilation, when the calculated minute volume usually gives an arterial P_{CO_2} within the range 34–46 mm Hg (Scurr, 1956). However, predicted relationships are far less accurate during anaesthesia with spontaneous respiration, when ventilation tends to fluctuate from minute to minute, in response to surgical stimulus (Nunn, 1960a).

Adequacy of Oxygenation when Ventilation has been Adjusted to Maintain CO_2 *Homeostasis*

When efforts are made to calculate the 'correct' ventilation for an anaesthetized patient, they are usually based on an attempt to attain an arterial

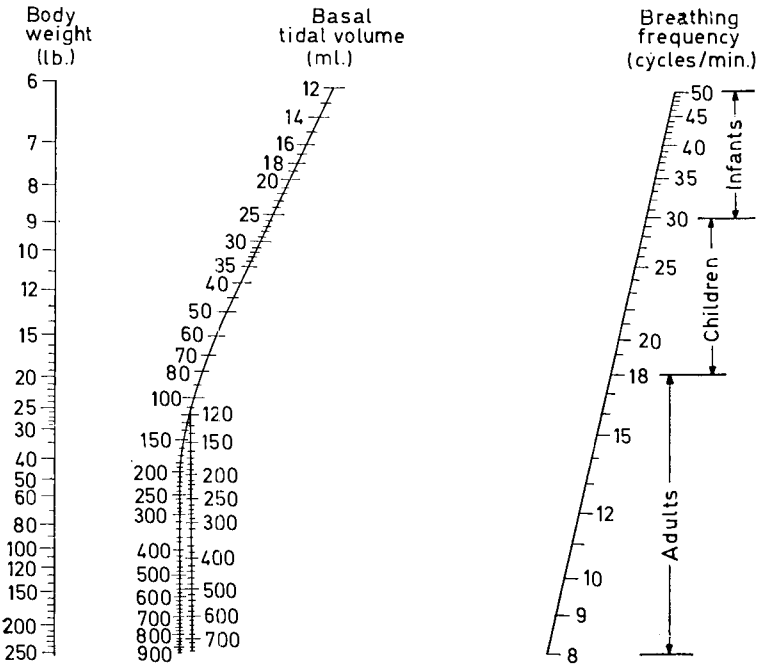


Figure 49. Radford's (1955) ventilation nomogram. (Reproduced by courtesy of the author and the Editor of the Journal of Applied Physiology)

P_{CO_2} of the desired level. For a patient breathing air, the attainment of a normal P_{CO_2} ensures that the *alveolar* P_{O_2} will also be normal. However, during anaesthesia it does not follow that a normal *alveolar* P_{O_2} results in a normal *arterial* P_{O_2}. There is a tendency to think that the appearance of cyanosis will give adequate warning of any appreciable degree of hypoxaemia. However, this is not true and patients may have an arterial P_{O_2} as low as 40 mm Hg without the appearance of cyanosis. Therefore we must accept that mere observation of the patient cannot give any assurance of avoiding hypoxia. The author has reached the conclusion that the only practicable safeguard is to understand the factors which influence arterial P_{O_2} and to so conduct an

anaesthetic that hypoxia is unlikely to occur. It is, of course, possible that a monitoring device for detecting arterial desaturation will one day become available, but it presents serious practical problems and its development seems improbable at the present time.

The level of oxygen in the arterial blood is influenced by two important factors which do not significantly affect the level of carbon dioxide. The first is the concentration of oxygen in the inspired gas; the second is the degree of admixture of venous blood with arterial blood, a condition which seems to be

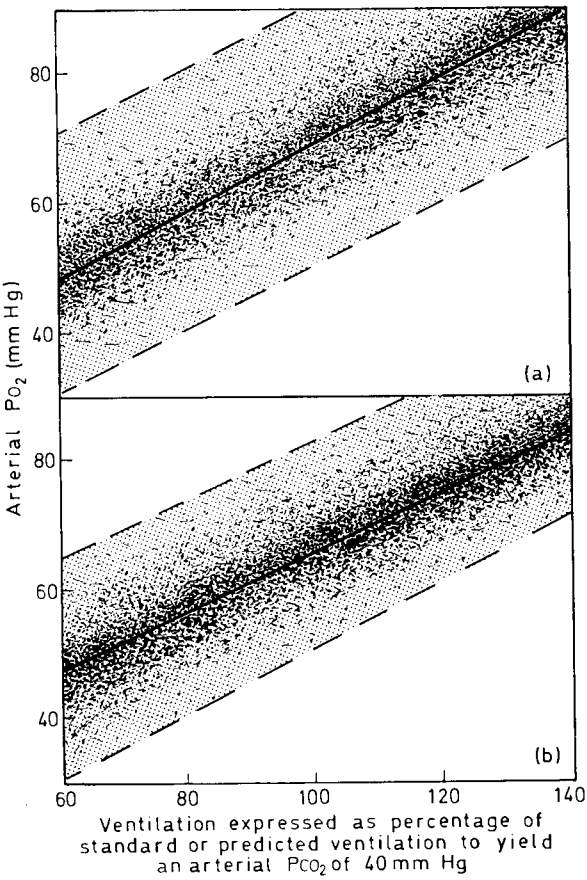


Figure 50. Measured arterial P_{O_2} *in relation to ventilation while inhaling 21 per cent oxygen. (a) Anaesthesia with spontaneous respiration (Nunn, 1964). (b) Anaesthesia with artificial ventilation (Wakai, 1963). In both cases the continuous line indicates the mean relationship, while the broken lines indicate the approximate range of observations made*

almost always present during anaesthesia. Oxygen enrichment of the inspired gas will compensate for a considerable degree of venous admixture, and it is important for the anaesthetist to grasp the quantitative aspects of this difficult and markedly non-linear relationship.

If we consider the case of anaesthetized patients breathing 21 per cent oxygen, we may wonder whether 'standard' or normal ventilation is sufficient to ensure normal arterial oxygenation. *Figure 50* shows the findings of Wakai

(1963) during artificial ventilation, and of Nunn (1964) during spontaneous respiration. The results of the two studies are not greatly different and show unequivocally that a ventilation calculated to result in an arterial P_{CO_2} of 40 mm Hg will not produce a normal arterial P_{O_2}. With double the 'standard' ventilation, normal values of arterial P_{O_2} have been obtained during anaesthesia with concentrations of oxygen in the inspired gas ranging from 21 to 24 per cent (Nunn, Bergman and Coleman, 1965).

There seems little doubt that the defect in arterial oxygenation is due mainly to shunting, although it may be due in some part to maldistribution. These changes are discussed in detail in Chapter 9, where we shall see that the malfunction during the inhalation of 21 per cent oxygen may be expressed conveniently as a difference between alveolar and arterial P_{O_2} of the order of 35 mm Hg* (compared with a normal value of less than 10 mm Hg):

mean alveolar P_{O_2} with standard ventilation	105 mm Hg
mean arterial P_{O_2} (observed)	70 mm Hg
alveolar-to-arterial P_{O_2} difference	35 mm Hg

Arterial P_{O_2} may be restored to the normal value of 100 mm Hg by increasing the alveolar P_{O_2} to approximately 150 mm Hg.

Table 16

Inspired oxygen concentrations required for maintenance of normal arterial P_{O_2} *in the majority of intubated, anaesthetized patients at sea level*

Minute volume of respiration (l./min.) (B.T.P.S.)	*Inspired oxygen concentration* (%)
Infinity	28
20	29·5
10	31·5
7	32·5
6	33·5
5	34·5
4	36·5
3	39
2	44·5
1	61

Values for minute volume below about 5 l./min. will usually be associated with carbon dioxide retention which will be severe when the minute volume is less than 3 l./min. Enrichment of the inspired gas mixture with oxygen will not prevent carbon dioxide retention.

This may be achieved by increasing the concentration of oxygen in the inspired gas mixture, and an increase to 30 per cent is sufficient in the average patient. A greater increase will be needed in certain patients with larger shunts and, of course, if the ventilation is less than standard. *Table 16* gives an approximate indication of the concentration of oxygen in the inspired gas which is required

* The alveolar-to-arterial P_{O_2} difference in a particular patient varies with the actual P_{O_2} (*see* page 340). The difference noted here only applies to an alveolar P_{O_2} close to 100 mm Hg.

to ensure a normal arterial P_{O_2} at different levels of ventilation in the healthy, intubated, anaesthetized patient.

THE EFFECT OF DIFFERENT LEVELS OF VENTILATION ON ALVEOLAR GAS TENSIONS*

As ventilation increases, the composition of the alveolar gas tends to approach that of the inspired gas. The difference between inspired and alveolar concentrations of a gas is equal to the ratio of the output (or uptake) of the gas, to the alveolar ventilation.

$$\begin{matrix}\text{alveolar}\\ \text{concentration}\\ \text{of gas } X\end{matrix} = \begin{matrix}\text{inspired}\\ \text{concentration}\\ \text{of gas } X\end{matrix} + (\text{or} -) \left(\frac{\text{output (or uptake) of gas } X}{\text{alveolar ventilation}}\right)$$

Note: (1) Concentrations are here expressed as fractions and must be multiplied by 100 to give percentages.

(2) The equation does not correct for any difference in the inspired and expired minute volumes and, in the case of oxygen, is usually subject to a slight error which may be avoided by the use of a small correction factor which may be ignored for general clinical purposes.

(3) The sign on the right-hand side is + for output and − for uptake.

(4) Tension of a gas X may be obtained by multiplying both sides of the equation by the dry barometric pressure (barometric pressure *minus* water vapour pressure at body temperature).

(5) The figures for gas exchange and alveolar ventilation must both be expressed under the same conditions of temperature and pressure. B.T.P.S. is used for the examples given below.

In the case of carbon dioxide:

$$\text{alveolar } P_{CO_2} = \text{dry barometric pressure} \left(\begin{matrix}\text{inspired } CO_2\\ \text{concentration}\end{matrix} + \frac{CO_2 \text{ output}}{\text{alveolar ventilation}}\right)$$

$$\text{e.g.: } \underset{\text{mm Hg}}{40} = \underset{\text{mm Hg}}{713} \left(0 + \frac{180}{3{,}200}\right) \quad \text{ml./min} \div \text{ml./min.}$$

And in the case of oxygen:

$$\text{alveolar } P_{O_2} = \text{dry barometric pressure} \left(\begin{matrix}\text{inspired } O_2\\ \text{concentration}\end{matrix} - \frac{O_2 \text{ uptake}}{\text{alveolar ventilation}}\right)$$

$$\text{e.g.: } \underset{\text{mm Hg}}{100} = \underset{\text{mm Hg}}{713} \left(\frac{21}{100} - \frac{225}{3{,}200}\right) \quad \text{ml./min.} \div \text{ml./min.}$$

The relationship between alveolar ventilation and alveolar gas tensions is non-linear and rather difficult to visualize. It is best displayed on a graph, and *Figure 51* shows the relationships based on conditions which are typical of anaesthesia. The diagram will repay careful study and the following points should be noted.

* This subject receives extended treatment for the case of oxygen in Chapter 12 (pages 333 et seq.).

(1) The relationship between alveolar gas tensions and alveolar ventilation is hyperbolic. When the ventilation is increased above the normal range, the

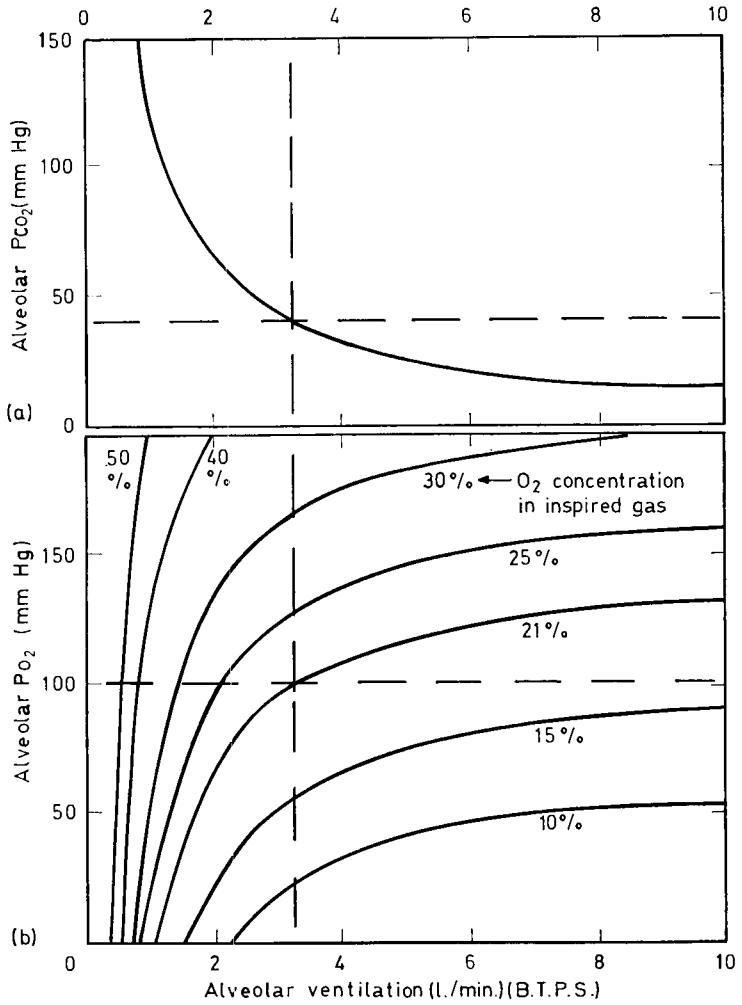


Figure 51. Alveolar gas tensions produced by different levels of alveolar ventilation. (a) The hyperbolic relationship between alveolar P_{CO_2} *and alveolar ventilation. (b) The relationship between alveolar* P_{O_2} *and alveolar ventilation for different levels of oxygen concentration in the inspired gas. The broken vertical line indicates an alveolar ventilation of 3·2 l./min. Dry barometric pressure, 760 − 47 = 713 mm Hg; carbon dioxide output, 150 ml./min. (S.T.P.D.) = 180 ml./min. (B.T.P.S.); oxygen uptake, 190 ml./min. (S.T.P.D.) = 225 ml./min. (B.T.P.S.). No allowance has been made for the difference between inspired and expired minute volumes*

alveolar gas tensions approach the inspired tensions asymptotically but dramatic changes do not occur on the flat part of the curves. Thus hyperventilation does not raise the alveolar P_{O_2} markedly, unless the alveolar ventilation was

previously reduced. On the other hand, reductions of alveolar ventilation may cause severe deterioration in alveolar gas tensions. Alveolar P_{O_2} falls steeply after reduction of ventilation below a critical level. The critical level is reduced by oxygen enrichment of the inspired gas, but the transitional zone then becomes narrower—often alarmingly so. For example, when the subject in *Figure 51* breathed 30 per cent oxygen, an alveolar ventilation of 1·2 l./min. would result in an alveolar P_{O_2} of 80 mm Hg, a level which is not dangerous in an otherwise healthy patient. If the alveolar ventilation were then reduced by only 400 ml./min., the alveolar P_{O_2} would fall to 14 mm Hg, a level which is not compatible with life.

(2) A change in the inspired P_{O_2} produces an equal change in the alveolar P_{O_2} if other factors remain the same (pages 336 et seq.). Consider an alveolar ventilation of 1·2 l./min. during air breathing. In the example shown in *Figure 51* this would result in an alveolar P_{O_2} of 16 mm Hg, which would not be compatible with life. If, however, the inspired air were enriched with oxygen to 30 per cent, that would amount to an increased P_{O_2} in the inspired gas of 64 mm Hg. If other factors remained the same, the alveolar P_{O_2} would also rise by 64 mm Hg to 80 mm Hg, a level which is not much below the normal range. As a general rule, it may be said that, if hypoxaemia due to hypoventilation is to be treated with oxygen-enrichment of inspired gas, then a modest level of enrichment will be sufficient. If more than 30 per cent oxygen is required, it follows that the hypoventilation should be treated by methods which increase the ventilation. There are some cases in which this is not possible and greater increases in the inspired oxygen concentration will then be required, but it must be appreciated that this will do nothing to reduce the concomitant elevation of P_{CO_2}. The addition of carbon dioxide to the inspired gas raises the alveolar P_{CO_2} in the same way as addition of oxygen raises the alveolar P_{O_2}.

(3) *Figure 51* shows clearly the dangers of decreasing the inspired oxygen concentration below 21 per cent, as was formerly common practice in dental anaesthesia and obstetric 'gas-air' analgesia. The maintenance of a high ventilation rate is essential during oxygen curtailment and the patient is exposed to grave risk if ventilation is reduced as, for example, by airway obstruction.

It must be stressed that the discussion of *Figure 51* relates to the alveolar P_{O_2} and not the arterial P_{O_2}. It will be seen in Chapters 9 and 12 that the arterial P_{O_2} may be much less than the alveolar P_{O_2}, and the difference constitutes a major cause of hypoxaemia associated with anaesthesia. This additional factor must be borne in mind in any consideration of the alveolar P_{O_2} which is required during anaesthesia. If oxygen saturation is considered instead of P_{O_2}, the non-linearity of the dissociation curve is added to the non-linearity of the rectangular hyperbolas in *Figure 51*. When ventilation is reduced, arterial saturation falls even more abruptly than the P_{O_2}.

It is also important to bear in mind the time course of changes in P_{CO_2} and P_{O_2} resulting from changes in ventilation (page 258). The values indicated in *Figure 51* relate to the steady state which is attained some time after a change in ventilation. Oxygen levels change quickly but, in the case of carbon dioxide, the changes are slow due to the large stores of carbon dioxide present in the body. The problem is considered in some detail in Chapters 11 and 12, but for the present it should be noted that, after a step change in ventilation, there is

an exponential approach towards the equilibrium values shown in *Figure 51*. (Exponential changes are discussed in Appendix D.) Changes in P_{O_2} are rapid and have a half-life of 30 seconds. Changes in P_{CO_2} are much slower, with a half-life of 4 minutes for a falling P_{CO_2} (Farhi and Rahn, 1955a; Nunn and Matthews, 1959). When P_{CO_2} is rising (following a reduction in ventilation) changes are even slower, with half-lives ranging from 4 to 15 minutes (Ivanov and Nunn, 1968).

CAUSES OF FAILURE OF VENTILATION

So far, most of this book has been devoted to factors influencing ventilation and most causes of ventilatory failure have already been described. This section is intended to classify the causes of ventilatory failure and present them as a unified scheme (*Figure 52*).

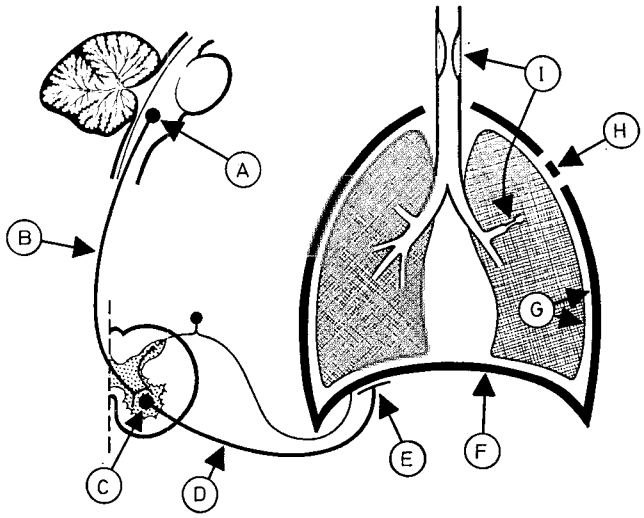


Figure 52. Summary of sites at which lesions, drug action or malfunction may result in ventilatory failure. (A) The 'respiratory centre'. (B) Upper motor neurone. (C) Anterior horn cell. (D) Lower motor neurone. (E) The neuromuscular junction. (F) The respiratory muscles. (G) Altered elasticity of lungs or chest wall. (H) Loss of structural integrity of chest wall and pleural cavity. (I) Increased airway resistance

The 'Respiratory Centre' (*see* Chapter 2)

The rhythmicity of respiration in man appears to have its origin in the neurones of the medulla (A in *Figure 52*). These neurones are very susceptible to oxygen lack, and central respiratory failure is an early effect of anoxia. Temporary apnoea often follows a severe anoxic episode, but fortunately spontaneous respiration usually returns after restoration of normal oxygenation. Hypoxia may be due to arterial desaturation, circulatory failure or raised intracranial pressure.

The respiratory neurones may also be depressed by very high levels of arterial P_{CO_2}, probably of the order of 300 mm Hg in the unanaesthetized subject, but at a lower P_{CO_2} in the presence of narcotic drugs (page 33). Reduction of P_{CO_2} below the apnoeic threshold level causes apnoea in the unconscious but usually not in the conscious patient (page 20). A wide variety of drugs will produce central apnoea; these include the opiates and all anaesthetic agents, provided the dosage is sufficiently high. Respiration may be reflexly arrested by a variety of noxious stimuli applied to the respiratory tract and other areas. However, the Breuer–Hering inflation reflex is weak in man and inflation to moderate pressures does not normally inhibit inspiration in anaesthetized man (page 38).

The commonest form of central apnoea encountered by the anaesthetist is failure of a patient to breathe at the end of an anaesthetic which has been conducted with paralysis and artificial hyperventilation. The condition is not serious although often troublesome and time wasting. It appears that the apnoea is due to the absence of general neuronal traffic when the P_{CO_2} is below the apnoeic threshold. Breathing can usually be restarted either by waking the patient or by elevation of P_{CO_2} above the threshold level (Ivanov and Nunn, 1969).

Finally, it should be noted that the respiratory neurones may be affected by trauma, infection or neoplasm.

Upper Motor Neurone

The upper motor neurones serving the respiratory muscles are liable to interruption in the neck. Those connecting with the phrenic nerves (cervical 3, 4 and 5) are seldom interrupted since the upper cervical cord is relatively well protected against trauma. However, the upper motor neurones connecting with the other inspiratory muscles are interrupted by the usual type of cervical dislocation (cervical 5–6). Upper motor neurones may be involved in various disease processes including tumour and demyelination, although seldom in syringomyelia.

Anterior Horn Cell

The anterior horn cells concerned with respiration may be affected by various disease processes, of which the most important is anterior poliomyelitis. All degrees of involvement occur including total paralysis of all respiratory muscles. The anterior horn cells are reversibly depressed by the drug mephenesin (Myanesin) which was formerly used as a relaxant in anaesthesia.

Lower Motor Neurone

The motor nerves of the respiratory muscles are prone to the normal traumatic risks and the phrenic nerves may be surgically interrupted. However, apnoea due to traumatic damage of the nerves supplying the respiratory muscles is improbable. Polyneuritis is the principal disease which may cause apnoea from disruption of conduction by these nerves. Interference with the gamma fibres (page 22) would cause severe dysfunction but there is no clear evidence of the occurrence of specific lesions of these fibres.

The Neuromuscular Junction

Nowadays, failure of conduction at the neuromuscular junction is probably the commonest cause of failure of ventilation. The most important disease processes acting at this site are myasthenia gravis and botulism. Drugs acting on this site include all the relaxants used in clinical anaesthesia, neostigmine and certain organo-phosphorus compounds. Procaine acts by preventing the synthesis of acetylcholine. Full discussion of these problems is not feasible in a textbook of respiratory physiology, and the reader is referred to the symposia on muscle relaxants published by *Anesthesiology* (Nov. 1959) and *British Journal of Anaesthesia* (March 1963).

The Respiratory Muscles

Disease of the respiratory muscles may cause respiratory failure, but discussion of the muscular dystrophies also lies outside the scope of this book. The efficacy of the inspiratory muscles may be impaired by deformity, injury and 'splinting' of the diaphragm by abdominal distension. A flattened diaphragm (as may be seen in tension pneumothorax) may contract forcefully but have little effect upon tidal ventilation.

Elasticity of Lungs and Chest Wall

Ventilatory failure may result from impairment of elasticity in organized empyema and disorders of the surface tension of alveolar lining fluid. Ventilatory reserve may be reduced from other causes in many of the diseases which affect elasticity, and these are considered in Chapter 3. Regional inequalities of ventilation may result from non-uniform loss of elasticity.

Loss of Structural Integrity of Chest Wall and Pleural Cavity

The introduction of air into the pleural cavity (closed pneumothorax) reduces the volume, the ventilation and probably the perfusion of the lung on that side. If the pressure of gas in the pleural cavity rises appreciably above atmospheric (tension pneumothorax), the ipsilateral lung is totally collapsed, the mediastinum is displaced and the contralateral lung partially collapsed; the convexity of the diaphragm is lost and ventilation may be critically impaired. The correction of this condition is a matter of urgency and the possibility of its occurrence must always be borne in mind. Deviation of trachea and apex beat, combined with hyper-resonance, usually make the diagnosis simple provided the possibility is considered. When the pleural cavity communicates with the atmosphere (open pneumothorax) there is a danger of the contralateral lung inhaling gas from the ipsilateral lung, which is not subjected to the normal reduction of intrathoracic pressure during inspiration. The degree of dysfunction depends on the size of the opening in the chest, but is also influenced by the degree of airway obstruction produced, for example, by approximation of the vocal cords. Pendulum movement of gas between the two lungs may be prevented by collapsing the exposed lung, a manœuvre familiar to surgeons who use local analgesia for thoracotomy.

Loss of rigidity of the rib cage may result in regional or general ventilatory failure. This may be therapeutic (thoracoplasty) or traumatic (crushed chest).

Various local devices may improve ventilation when failure results from

impairment of structural integrity of the chest wall but artificial ventilation, by intermittent positive pressure, is almost always effective and was the long-awaited solution to the problem posed by thoracic surgery. These problems have been discussed in greater detail by Mushin and the present author in *Thoracic Anaesthesia* (Mushin, 1963).

Airway Resistance

Chapter 4 has been devoted to the problems of airway resistance. It is much the most important cause of ventilatory failure, whether due to overt massive obstruction of the upper air passages or to diffuse, progressive disease of the small air passages.

Diagnosis of Cause of Ventilatory Failure

In cases of ventilatory failure, it is usually obvious whether respiratory efforts are being made or not. This distinction is of prime importance and divides the causes of failure into two groups of approximately equal importance.

Absent respiratory effort implies defective function in the central nervous system, peripheral motor nerves, neuromuscular junction or respiratory muscles (A–F in *Figure 52*). Ventilatory failure from dysfunction at any of these sites may present a broadly similar clinical picture. However, the history of events leading to ventilatory failure is usually sufficient to indicate the actual site and nature of the dysfunction. Nevertheless, after anaesthesia with induced neuromuscular block, it may be difficult to distinguish between ventilatory failure due to central causes and persistent neuromuscular block. Under these circumstances, it is useful to note the muscular contraction when a peripheral nerve (e.g. ulnar) is stimulated. Alternatively, the demonstration of action potentials in the phrenic nerve would also distinguish between the two conditions, although this is technically difficult. In practice, the distinction is often made by means of a variety of therapeutic tests which afford the anaesthetist an opportunity to display his acumen.

Forceful respiratory efforts in the presence of ventilatory failure mean reduced compliance, increased airway resistance or loss of structural integrity of the thoracic cage. Usually the latter is immediately apparent although it may be overlooked in cases of severe multiple injuries. The distinction between loss of compliance and increased resistance may be difficult. Attempts by the patient to ventilate with minimum work usually dictate an increased respiratory frequency with shallow breathing when compliance is reduced. Increased resistance, on the other hand, is usually associated with slow breathing. Expiratory resistance, particularly due to trapping (page 92), leads to an increased lung volume and often the patient deliberately checks expiratory air flow at the mouth to dilate his air passages (pursed-lip breathing). Inspiratory resistance shows characteristic indrawing of soft tissues around the bony thorax during inspiration (page 98). Auscultation is helpful and may define the presence and the phasing of obstruction. It should also help to distinguish between obstruction due to liquid material in the air passages and that due to narrowing of the air passages. Spasm of the air passages is most convincingly demonstrated by study of the response to bronchodilators, while absence of

response in a chronic case is often evidence of structural causes of obstruction (e.g. trapping). Oedema of the mucosa may be confused with spasm and both may respond to isoprenaline or adrenaline.

THE WORK OF BREATHING

During spontaneous respiration, the work of breathing is accomplished by the respiratory muscles of the patient. During artificial ventilation, the work of breathing is performed by the machine or person who has taken over responsibility for tidal exchange. In spite of the obvious difference in the source of energy, there are many similar features in the two types of breathing. In each case, the work is normally performed during inspiration; expiration is powered by the potential energy stored in the tissues which have been distorted from their resting position during inspiration. All the work is eventually used to overcome air flow resistance which results in its dissipation as heat. Approximately half the inspiratory work is so dissipated during inspiration, while the remainder is stored temporarily and then dissipated during expiration. Elasticity thus enables the work of *expiration* to be performed by the *inspiratory* muscles (*Figure 53*).

During both spontaneous and artificial respiration, there may be occasions when additional work is performed during expiration to hasten the expulsion of gas from the lungs. Typical examples are the use of expiratory muscles in coughing and the use of a subatmospheric pressure phase during I.P.P. ventilation of the lungs.

The actual rate of work performed by the respiratory muscles is quite remarkably small in the healthy resting subject. Under these circumstances the oxygen consumption of the respiratory muscles is only about 3 ml./min., or less than 2 per cent of the metabolic rate. Furthermore, of this tiny amount of energy, about 90 per cent is lost as heat within the respiratory muscles, so that only 10 per cent is available for moving gas. The efficiency is further reduced in many forms of respiratory disease, certain deformities, pregnancy and when the minute volume is increased (*Figure 54*). When approaching maximal ventilation, the efficiency falls to such a low level that additional oxygen made available by further increases of ventilation will be entirely consumed by the respiratory muscles (Otis, 1954). It is clear that under these circumstances a further increase in ventilation would result in net oxygen loss. This effectively limits the changes in the alveolar gas which can be brought about by *active*, though not *passive*, hyperventilation. This 'ceiling' of ventilation is only reached at very high levels of ventilation in the healthy patient. However, in diffuse obstructive respiratory disease, the 'ceiling' may be sufficiently low to impose a severe limit on exercise tolerance.

Units of Measurement

There is a good deal of confusion over the terminology and units of measurement of work.

Work is done when a force moves its point of application, and the amount of work is equal to the product of force and distance moved. The force may be applied to the plunger of a syringe raising the pressure of a gas contained therein. In this case, the work done is equal to the product of the mean pressure

and the change in volume, or alternatively to the product of the mean volume and the change in pressure. The units of work are identical whether the pro-

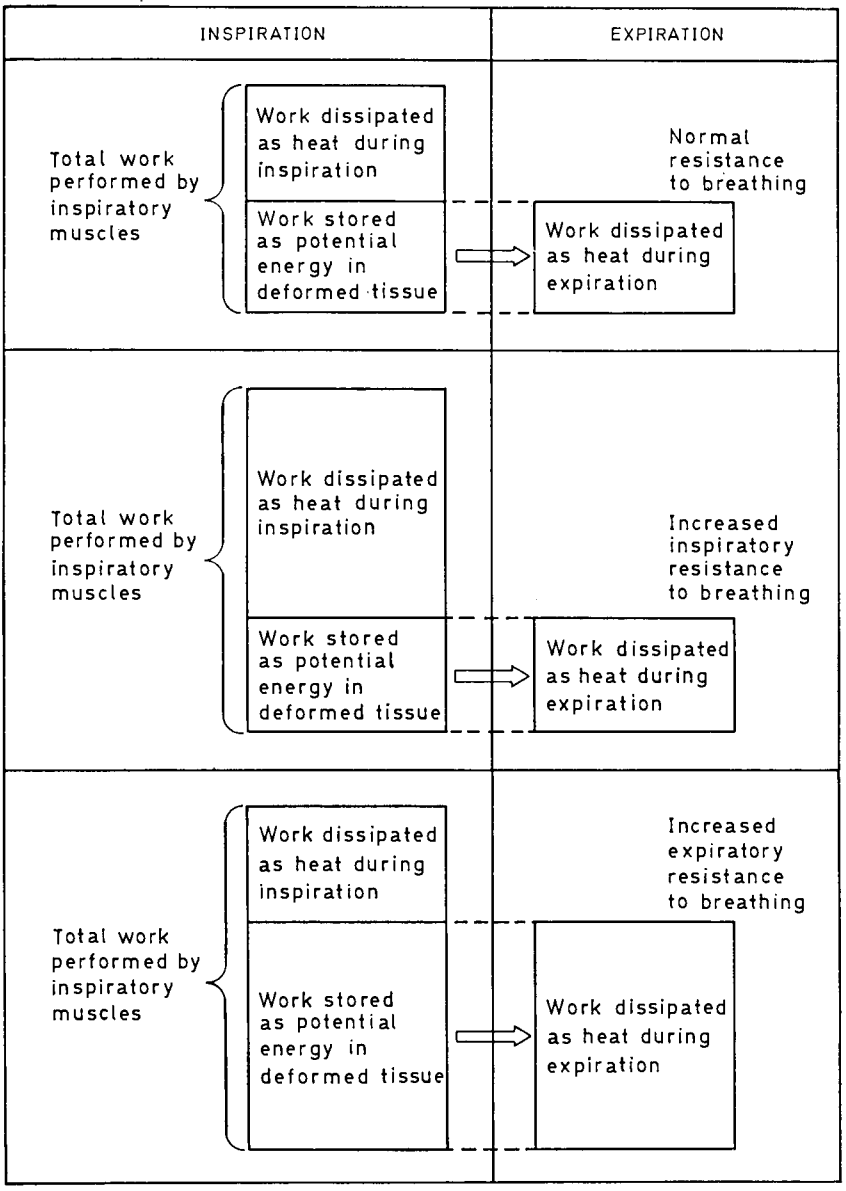


Figure 53. Source and dissipation of the work of breathing. The areas in each diagram correspond to the work of breathing. The total area on the left indicates the work done by the inspiratory muscles during inspiration

duct is *force* × *distance* or *pressure* × *volume*. The various units which may be used are listed in Appendix A.

Power is a measure of the rate at which work is being (or can be) performed. The 'work of breathing', when expressed as so many calories per minute is thus a misnomer, since we are referring to the rate at which work is being done. Power is the correct term and work is appropriate to a single event such as one breath.

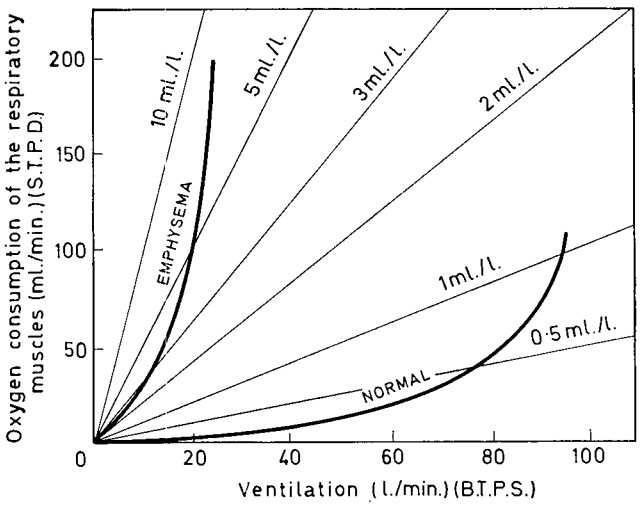


Figure 54. Oxygen consumption of the respiratory muscles plotted against minute volume of respiration. The isopleths indicate the oxygen cost of breathing in millilitres of oxygen consumed per litre of minute volume. The curve obtained from the normal subject shows the low oxygen cost of breathing up to a minute volume of 70 l./min. Thereafter the oxygen cost rises steeply. In the emphysematous patient, the oxygen cost of breathing is not only much higher at the resting minute volume, but it rises steeply as ventilation is increased. At a minute volume of 20 l./min., the respiratory muscles are consuming 200 ml. oxygen per minute, and a further increase of ventilation would consume more oxygen than it would make available to the rest of the body. (Reproduced after Campbell, Westlake and Cherniak (1957) by courtesy of the Editor of the Journal of Applied Physiology)

Dissipation of Work of Breathing

The work of breathing overcomes two different sources of resistance. The first is the elastic recoil of the tissues (Chapter 3). The second is the frictional resistance to gas flow afforded by the air passages and, to a much smaller extent, the frictional resistance of the movements of the tissues during ventilation (page 85). It is usual to ignore the very low resistance afforded by the inertia (or momentum) of static (or moving) gases and tissues.

Work Against Elastic Resistance

When a perfectly elastic body is deformed, none of the work is dissipated as heat and all is stored as potential energy. No body is perfectly elastic, but satisfactory conversion to potential energy is obtained in such devices as the clockwork motor.

In the case of respiration, it is easiest to consider inflation of the lungs by

positive pressure. *Figure 55a* shows a section of the pressure/volume diagram taken from *Figure 19*. As the lungs are inflated from the expiratory position to the inspiratory position, the alveolar pressure/volume line forms the hypotenuse of a triangle whose area will represent the work done against elastic resistance during inspiration. The area of a triangle (half the base times the height) will

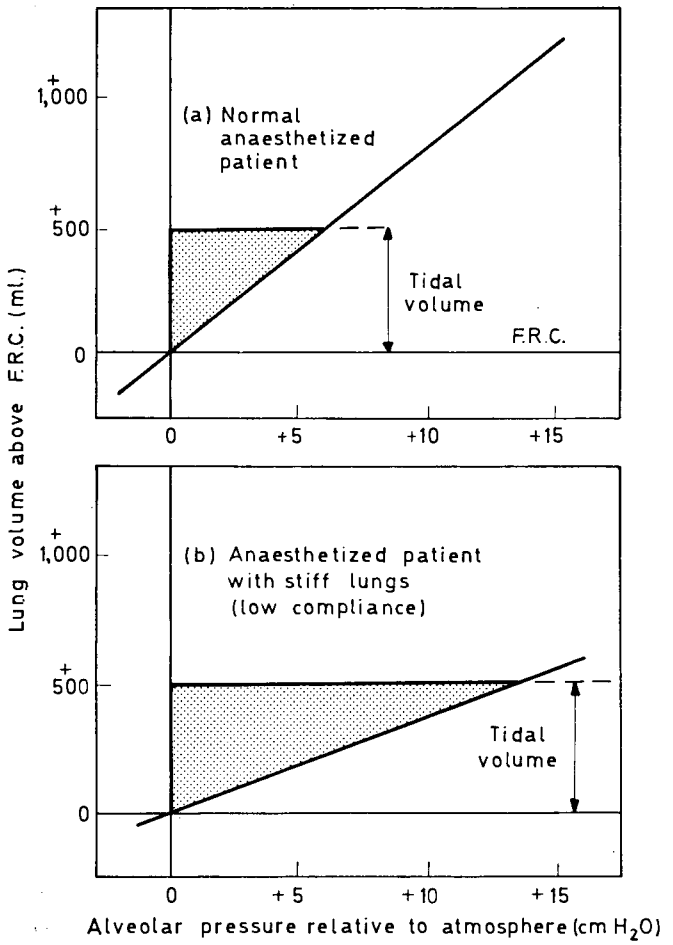


Figure 55. Work of breathing against elastic resistance. Pressure/volume plots of the lungs of anaesthetized patients (see *Figure 19*). *The length of the pressure/volume curve covered during inspiration forms the hypotenuse of a right-angled triangle whose area equals the work performed against elastic resistance. Note the area is greater when the pressure/volume curve is flatter* (*indicating stiffer or less compliant lungs*)

thus equal half the tidal volume times the pressure change (or the mean pressure times the volume change). This indicates the potential energy available for expiration. In *Figure 55b* the pressure/volume curve is flatter, indicating stiffer or less compliant lungs. For the same tidal volume, the area of the

triangle is increased. This represents a greater amount of work performed against elastic resistance and greater potential energy available for expiration.

Work Against Resistance to Gas Flow

Figure 55 describes conditions under which air flow resistance has been ignored by measuring alveolar pressure. In practice, of course, additional inflation pressure is required to overcome the resistance to gas flow afforded by the respiratory tract. At any instant, during inspiration, the mouth (or inflation) pressure will always be above the alveolar pressure, and simultaneous plots of volume and mouth pressure will describe a curve bowed to the right as in *Figure 56a. Figure 56b* represents a patient with normal compliance but with particularly high airway resistance. In each case the area between the curve OAC, and the alveolar pressure/volume line OYC represents the work expended in overcoming the frictional resistance to gas flow during inspiration. When the gas drawn into the lung is represented by the vertical distance OX (on the volume axis), the horizontal distance XY indicates the alveolar pressure (overcoming elastic resistance), YA indicates the mouth-to-alveolar pressure difference (overcoming flow resistance) while XA indicates the mouth pressure (overcoming both sources of resistance). The division of the inflation pressure into two components overcoming two sources of respiration is shown in *Figures 40, 43 and 44* which indicate the changes in lung volume, mouth and alveolar pressures when the lungs are inflated by an increase in mouth pressure. Methods are available for recording the changes shown in *Figures 56 and 58.* Such recordings are suitable for the direct calculation of the work of breathing from the various areas enclosed.

In the last few pages, we have considered the elastic recoil of the expiratory system as though it were a single entity, exerted by a single structure. This, of course, is not the case. It is true that the lungs exert an active elastic resistance opposing the inflation of the lungs, and store potential energy for powering expiration. However, it will be remembered that the equilibrium position of the chest wall is at a volume greater than the functional residual capacity. Therefore the elasticity of the chest wall is actually assisting the inflation of the lungs and it will similarly oppose expiration. The separation of the two sources of elastic resistance is far from simple and fortunately is of little clinical importance to the anaesthetist. Those who are interested in this problem are referred to Chapter 15 of the monograph by Campbell (1958).

There is an interesting dichotomy in studies of elastic recoil made by physiologists on the one hand, and anaesthetists on the other. Broadly speaking, the physiologist studies conscious subjects who are seldom, if ever, able to relax completely their respiratory muscles. Now it is impossible to measure the elasticity of a structure which has a variable amount of muscular tone and, therefore, the physiologist cannot easily study thoracic wall compliance or, indeed, total compliance which includes that of the thoracic wall. He therefore tends to concentrate on lung compliance studied with the aid of an oesophageal balloon for measurement of intrathoracic pressure. The anaesthetist, on the other hand, is frequently concerned with paralysis of the respiratory muscles and so avoids the difficulty of an indefinite thoracic compliance.

However, he does have difficulties in measuring the intrathoracic pressure in a supine subject (page 48) and, therefore, in separating lung and thoracic wall compliance. Consequently, he tends to concentrate his studies on total compliance which is, after all, of considerable practical importance in artificial ventilation.

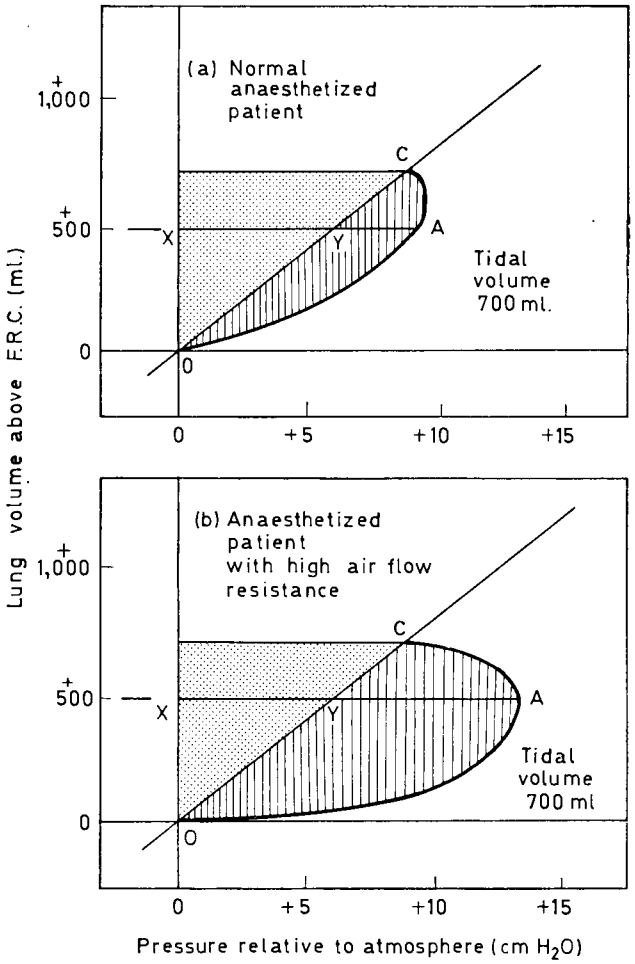


Figure 56. Work of breathing against air flow resistance. The sloping line (OYC) is the alveolar pressure/volume curve. The curve (OAC) is the mouth pressure/volume curve during inflation of the lungs. The area shaded with vertical stripes indicates the work of inspiration performed against air flow resistance. This work is increased in the patient with high resistance (b). At the point when 500 ml. gas has entered the patient, XY represents the pressure distending the lungs, while YA represents the pressure overcoming air flow resistance. XA is the inflation pressure at that moment. The stippled areas represent work done against elastic resistance (see *Figure 55*)

The Active Expiratory Phase

Passive expiration is normally adequate, not only for resting respiration, but

also for respiration under moderately difficult conditions. Thus minute volumes as high as 20 l./min. are normally obtained without the use of expiratory muscles, and we have seen in Chapter 4 that expiration against pressures up to about 12 cm H_2O is normally accomplished by augmentation of *inspiratory* effort without participation of expiratory muscles. This results in hyperinflation of the lung with increased elastic recoil available to overcome expiratory resistance. Nevertheless, for very high minute volumes and for expiration against very high pressures, the expiratory muscles are brought into play and their work must be included in the total work of breathing.

The Minimum Work of Breathing

For a constant minute volume, the work done against elastic resistance is increased when breathing is deep and slow. On the other hand, the work done against flow resistance is increased when breathing is rapid and shallow. If the two components are summated, and the total work plotted against the respiratory frequency, it will be found that there is an optimal respiratory frequency at which the total work of breathing is minimal (*Figure 57*). It is interesting to

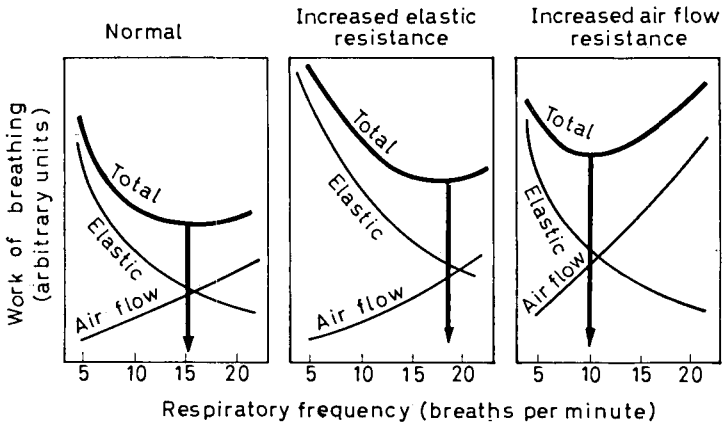


Figure 57. The diagrams show the work done against elastic and air flow resistance separately and summated to indicate the total work of breathing at different respiratory frequencies. The total work of breathing has a minimum value at about 15 breaths per minute under normal circumstances. For the same minute volume, minimum work is performed at higher frequencies with stiff (less compliant) lungs and at lower frequencies when the air flow resistance is increased

find that human subjects and animals tend to select a respiratory frequency which corresponds very closely to the frequency which may be calculated to require the minimum work (McIlroy and his colleagues, 1956). This applies to different species, different age groups in the same species and to patients with diseased lungs. When elastic resistance is high (pulmonary fibrosis, small animals, infants, etc.), the optimum frequency is high and rapid shallow breaths are favoured. When airway resistance is high, the optimum frequency is low and slow deep breaths are favoured. When supervising artificial ventilation, it would appear reasonable to form some estimate of the respiratory frequency likely to be associated with minimal work and to use a frequency of

that order for artificial ventilation. It is, however, also necessary to bear in mind that frequency affects the dynamic compliance (page 53) and also to consider the effect of different frequencies on distribution (Chapter 7).

Work of Breathing through Apparatus

It has already been pointed out that there are difficulties in expressing the resistance to breathing offered by a piece of breathing apparatus (pages 82 et seq.). For this reason, it may be preferable to measure the actual work done by the patient in breathing through the apparatus, and this figure may be readily compared with the patient's own work of breathing. It is clearly advantageous to measure the work of breathing through apparatus using the patient's respiratory waveform and with the gas mixture which the patient is

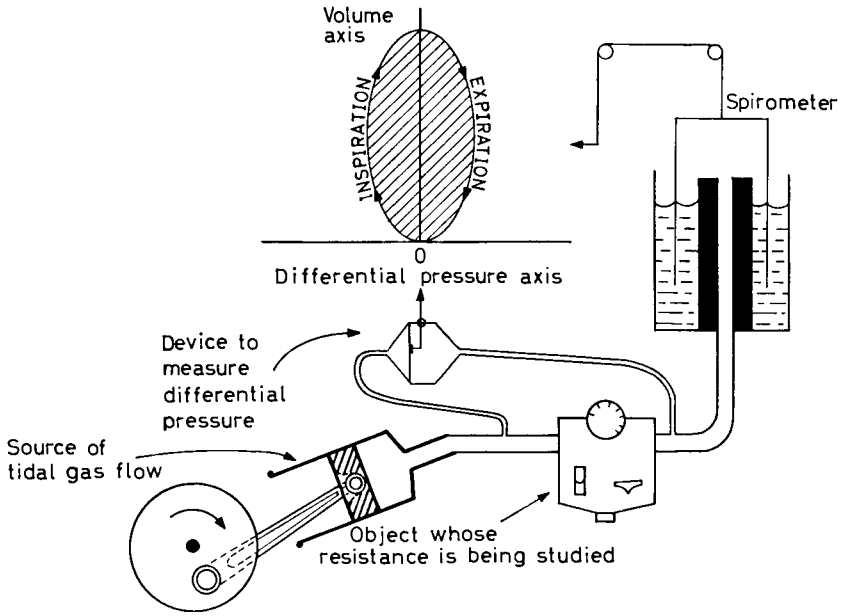


Figure 58. Experimental arrangement for studying the work of breathing through apparatus. Gas is made to pass to and fro through the apparatus, with the volume exchange recorded from a spirometer. A differential pressure manometer records the pressure drop across the apparatus. Various devices may be employed to arrange for volume to be plotted on one axis while pressure is simultaneously recorded on the other axis. A loop is then traced out, whose area is equal to the work of breathing through the apparatus. This apparatus is particularly suitable for studying the effect of different gas mixtures and different respiratory waveforms

actually breathing. The technique is not particularly difficult and may be used with little modification for measurement of work done in breathing against nasal resistance (Butler, 1960). A plot is prepared of gas volume passed against the pressure drop across the apparatus (*Figure 58*). With the two variables plotted simultaneously, this yields a loop of which the area represents the work done in breathing through the apparatus for a single breath. This method was used extensively by Cooper (1961) in the evaluation of the resistance afforded by breathing apparatus used in mines rescue work.

It is often sufficient to assess the work of breathing through apparatus more simply by multiplying the gas volume passed by the pressure drop across the apparatus at the 'effective mean flow rate' of gas. The latter quantity is not easy to define but may be taken as somewhat less than the peak gas flow rate (about 25 l./min. during anaesthesia with spontaneous respiration). The pressure drop at this flow rate may then be read off a graph of pressure drop plotted against flow rate (e.g. *Figure 25*), and multiplied by tidal volume to indicate work, during a single phase of the respiratory cycle. Multiplied by the respiratory frequency, this will indicate the work expended in one minute in overcoming apparatus resistance in one direction of flow. As an example, 10 litres moved against a pressure drop of 1 cm H_2O require the expenditure of approximately 10^7 ergs = 1 joule = 1 watt-second = 0·24 calories = 0·00024 Calories. If we assume an efficiency of 10 per cent, the respiratory muscles may be expected to develop $10 \times 0{\cdot}00024 = 0{\cdot}0024$ Calories. Approximately 1 litre of oxygen is consumed in the production of 5 Calories and therefore the task of moving 10 litres against a pressure drop of 1 cm H_2O requires the consumption of approximately 0·5 ml. oxygen, or one-sixth of the normal oxygen cost of breathing.

MEASUREMENT OF VENTILATION

In the measurement of ventilation we are concerned with gas flow rates and gas volumes, the former having the units of volume/time (L^3T^{-1}) and the latter the units of volume (L^3) (*see* Appendix A). There is some doubt as to whether the term 'minute volume' refers to a flow rate (litres/minute) or a volume (litres). Semantically the latter may be correct but it is clear that a flow rate is implied.

Tidal volume	×	respiratory frequency	=	minute volume
V_T	×	f	=	$\dot{V}$
L^3	×	T^{-1}	=	L^3T^{-1}

If volume is plotted against time (as on a spirometer trace) the slope of the line will indicate gas flow rate. When the flow rate is rapidly changing, the slope of a tangent to the curve will indicate the instantaneous flow rate (*Figure 59*). The slope of the tangent is the differential of volume with respect to time (dV/dt). Alternatively, when flow rate is plotted against time (as in pneumotachogram), the area under the curve between two points indicates the volume change between these points. The integral of the flow rate equals the volume change.

It is important to distinguish between two entirely different flow rates. The *minute volume* is defined as the tidal volume multiplied by the respiratory frequency. The *instantaneous flow rate* is the actual rate at which gas flows into or out of the respiratory system at any instant (dV/dt). Peak flow rates are the maximum flow rates occurring during breathing and are usually about four or five times greater than the minute volume (*Figure 31*). It is appropriate to consider peak flow rates when assessing the effects of resistance to breathing.

Sometimes it is necessary to distinguish between the inspiratory and expiratory minute volumes (or tidal volumes). Under normal circumstances, the inspiratory minute volume is about 50 ml. larger than the expiratory minute

volume, this being the amount by which the oxygen uptake exceeds the carbon dioxide output. However, during anaesthesia, exchange of nitrous oxide can result in very large differences between inspired and expired minute volume. As a rough approximation, the uptake of nitrous oxide (in ml./min.) equals:

$$\frac{1{,}000}{\sqrt{\text{duration of anaesthetic (minutes)}}}$$

(Severinghaus, 1954)

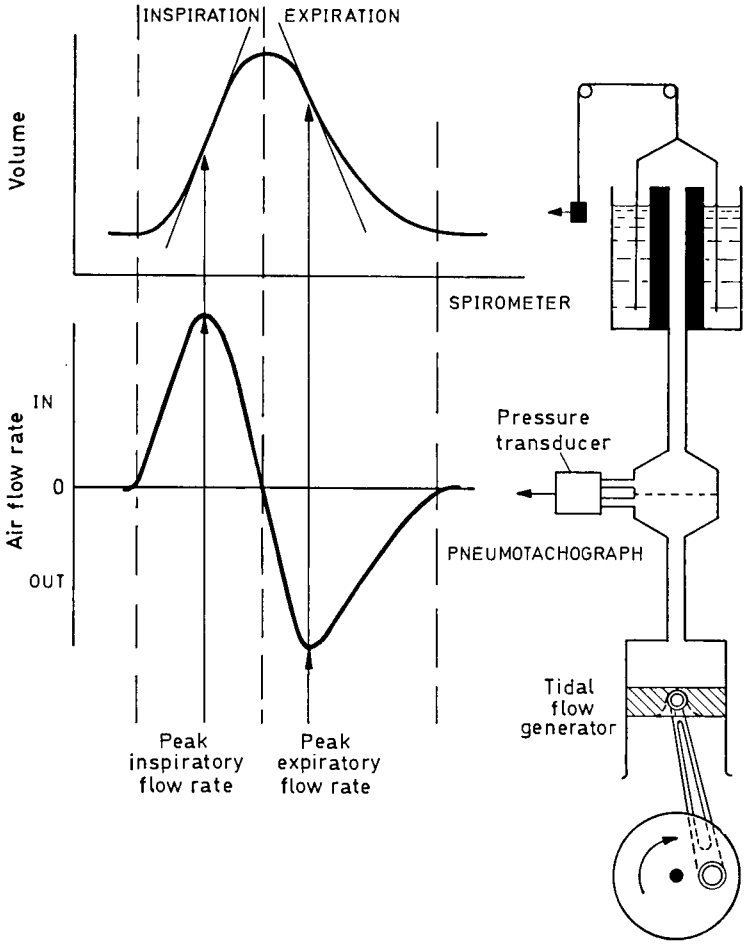


Figure 59. Relationship between volume and flow rate. The upper graph shows volume plotted against time; this type of tracing may be obtained with a spirometer. The lower graph shows instantaneous air flow rate plotted against time; this type of tracing may be obtained with a pneumotachograph. At any instant, the flow-rate trace indicates the slope of the volume trace, while the volume trace indicates the cumulative area under the flow-rate trace. Flow *is the differential of volume;* volume *is the integral of flow rate. Differentiation of the spirometer trace gives a 'pneumotachogram'. Integration of the pneumotachogram gives a 'spirometer trace'*

For example, after 16 minutes the uptake of nitrous oxide approximates to 1,000 divided by the square root of 16, which is 250 ml./min. Separate

measurement of inspired and expired minute volume presents considerable difficulty and the problems have been discussed by Nunn and Pouliot (1962) and by Smith (1964a).

The minute volume of ventilation may vary from as little as 3 l./min. in a deeply anaesthetized patient allowed to breathe spontaneously, to over 100 l./min. in an exercising subject and, for short periods of time, over 200 l./min. during the measurement of the maximum breathing capacity (M.B.C.). Techniques for measurement of pulmonary ventilation must satisfy the following requirements.

(1) The resistance to breathing must not be excessive at the ventilation rate which is to be measured.

(2) The apparatus must not impose a significant addition to the dead space through which the patient must breathe.*

(3) The response of the apparatus should be as flat as possible and must be appropriate to the ventilation rate which is being measured.

(4) The response must not be unduly influenced by the respiratory waveform or the nature of the respired gas.

Most clinical methods of measurement of ventilation afford negligible resistance at minute volumes up to 40 l./min. However, above this figure, and particularly during the measurement of M.B.C., a very low level of resistance is essential. Resistance to gas flow may be minimized by increasing the calibre of the tubes through which the patient breathes: inertia may be minimized by reduction of weight of moving parts, and resonant frequency may be kept high by suitable design.

In connection with accuracy, we shall make constant reference to the 'response' of an apparatus. This is defined as the indicated volume divided by the actual volume passed, and is often expressed as a percentage. The reciprocal of the response is the correction factor which must be applied. Response presents an important problem since, with most techniques, the response of the apparatus is not constant but tends to increase with increasing minute volume.

Measurement of Gas Flow Rate

Rotameters afford a most convenient method of measuring steady gas flow and are used widely for the measurement of fresh gas flow rate on anaesthetic apparatus. They can only be used for one specified gas since their calibration is influenced by the viscosity and specific gravity of the gas. (These properties are almost identical for nitrous oxide and carbon dioxide so that rotameters for these two gases are interchangeable.) Rotameters are available in a wide variety of ranges, for each of which the maximum flow rate is ten times the minimum.

The pneumotachograph is the most versatile method of measurement of gas flow rates, being particularly well suited to rapidly changing flow rates and the detection of transients, which are smoothed out in the record of any mechanical device such as a spirometer. The pneumotachograph is based on the measurement of the pressure gradient across a resistor through which the gas flow is laminar. In accordance with the Hagen–Poiseuille relationship (page 75), the

* This consideration is not relevant during the measurement of maximum breathing capacity (M.B.C.).

pressure gradient will be directly proportional to the flow rate. A variety of resistors are in use and many different types of pressure transducers are available, all of which convert displacement of a metal diaphragm into an electrical signal (*Figure 59*). The pressure gradient need not exceed a few millimetres of water and the resistance offered to the patient is therefore negligible. The volume constitutes only a small increase in apparatus dead space, and the patient may breathe to and fro through the pneumotachograph head.

When the highest levels of accuracy are required, pneumotachography presents very severe problems arising from the composition of the gases and their actual temperature as they pass through the laminar resistor. Both factors influence the viscosity of the gas on which the calibration depends (page 77). Smith (1964a) has considered these problems in detail and suggested means by which they may be overcome.

The slope of a spirometer trace (*Figure 59*) will give an over-all idea of flow rates but is not well suited to detecting transients of high flow rate. Irregularities of flow rate are faithfully recorded on a pneumotachogram, but they tend to be smoothed out in the differential of a spirometer trace due to the inertia of moving parts.

Wright's peak flowmeter is a useful method for the measurement of maximum peak expiratory flow which is a valuable index of expiratory airway resistance (page 110). In this instrument the expiratory gas stream displaces a baffle whose peak displacement is indicated on a dial. The apparatus is easily portable and suitable for the pre-operative assessment of patients in different wards scattered throughout the hospital (Bodman, 1963). Wright's peak flowmeter will give a higher reading than may be derived from the slope of a spirometer trace but not as high as the value indicated on a pneumotachogram, comparable figures for a healthy male being as follows:

maximum peak expiratory flow rate

by slope of spirogram	250 l./min.
by Wright's peak flowmeter	500 l./min.
by pneumotachography	800 l./min.

Measurement of Ventilatory Volumes

Spirometry

The water-sealed spirometer is the most accurate method of measurement of minute volume and is the method against which the accuracy of other techniques is assessed. Unfortunately spirometers are cumbersome, difficult to transport and cannot easily be incorporated in gas circuits without entailing rebreathing. At low respiratory frequencies, their calibration (linear displacement per litre) is constant and is the reciprocal of the cross-sectional area. As the frequency increases, spirometers over-read until they reach their resonant frequency at which the whole system oscillates and the reading is grossly in error. Above the resonant frequency, damping occurs until finally the spirometer ceases to respond at all. The presence of soluble gases does not cause the error which might be expected and it is difficult to detect any loss of nitrous oxide into the water of a spirometer bath (Nunn, 1958b).

Tissot spirometers usually have a capacity of over 100 litres and are not used for measurement of tidal exchange. They are employed either as reservoirs for inspired gas or else for collection of expired gas. Minute volume is usually read direct from the total movement of the bell occurring over a period of several minutes.

M.B.C. spirometers are designed for use with high frequencies and large minute volumes. The essential features are wide-bore connections, a lightweight bell, a squat broad bell, thin cord instead of chain, two small pulley wheels instead of one large one and a water-bath designed for a high resonant frequency (Bernstein and Mendel, 1951; Bernstein, D'Silva and Mendel, 1952).

Bronchospirometers have a small diameter to magnify the small unilateral tidal volume. Similar dimensions are suitable for recording low levels of ventilation during anaesthesia, and the specification in *Table 17* is satisfactory up to frequencies of 35 breaths per minute, with an error of less than 2 per cent when used in conjunction with anaesthetic gas circuits (Nunn, 1956).

Table 17

Specifications for a wet spirometer suitable for recording the ventilation of anaesthetized patients breathing spontaneously

Capacity of bell	2 l.
Diameter of bell (internal)	9·2 cm.
Length of bell	30 cm.
Weight of bell	89·5 g.
Thickness of bell	0·314 mm.
Material of bell	Anodized aluminium
Diameter of core (external)	7·9 cm.
Distance from core to sides of tank	6·8 cm.
Weight of counterweight (including pen)	75·5 g.
Suspension	Thin cord
Pulleys	Two in number, 1·5 in. diameter, aluminium, mounted on ball races.
Sensitivity	1 cm. per 67 ml. (A.T.P.S.)

The resonant frequency of the system is 96 breaths per minute (B.P.M.). The response is less than 105 per cent of static response up to 50 B.P.M. Its use in association with the continuous-flow spirometer causes some damping up to frequencies of 35 B.P.M., resulting in an error of less than ± 2 per cent within this range of respiratory frequency. The sensitivity is sufficient for recording the depressed ventilation of deep anaesthesia.

The box-bag spirometer is a system which permits spirometric measurements of minute volume without rebreathing (Donald and Christie, 1949). The system has been adapted to the circumstances of anaesthesia by Nunn and Pouliot (1962), and may be converted for use during artificial ventilation (Nunn, Bergman and Coleman, 1965). It probably affords the most accurate method for the separate measurement of inspired and expired minute volumes (*Figure 60*).

The continuous-flow spirometer (Nunn, 1956) is a derivative of the box-bag spirometer which permits continuous spirometric measurement of minute volume during anaesthesia using any of the gas circuits in clinical use (*Figure 61*).

Wedge spirometers are entirely dry and resemble bellows with two plates hinged together. The frequency response is good and they tend to be more portable and convenient than water-sealed spirometers.

Display for spirometers is traditionally by ink registration on a rotating kymograph. However, the pulley over which the cord passes may be made to rotate the wiper of a potentiometer from which an electrical read-out can easily be obtained. A differentiating circuit can then be used to indicate gas flow rate.

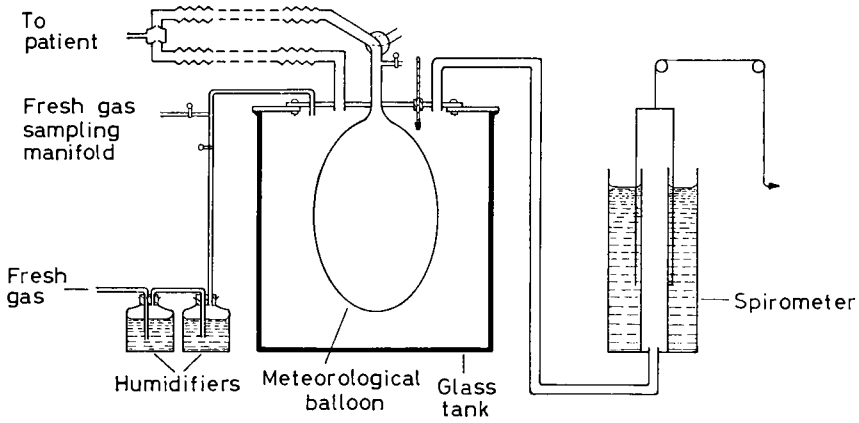


Figure 60. In the box–bag spirometer system, the patient inhales from the box and exhales into the bag. The tidal volume and the difference between the inspiratory and expiratory respiratory volumes are read directly from the spirometer. Inspiratory and expiratory gas may be sampled and analysis permits measurement of exchange of all gaseous components. The system may be reversed (i.e. inspiration from the bag) for studying the response to different inhaled gas mixtures. (Reproduced from Nunn and Pouliot (1962) by courtesy of the Editor of the British Journal of Anaesthesia)

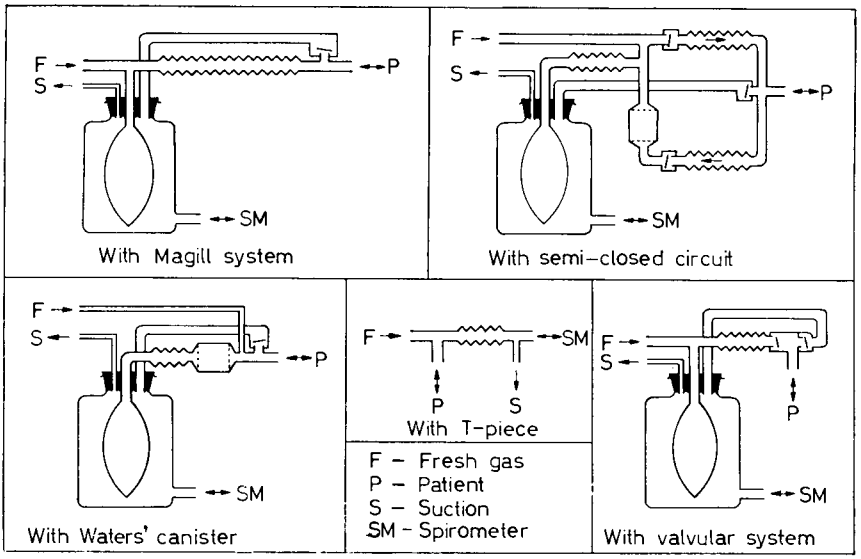


Figure 61. The continuous-flow spirometer enables spirometric records to be made when patients are breathing spontaneously with any anaesthetic gas circuit. Gas is aspirated from the tube marked 'S' until the spirometer trace is level, the amount aspirated being approximately equal to the fresh gas flow rate. When the trace is level, the tidal exchange is indicated with an accuracy of ± 2 per cent. (From Nunn (1956) by courtesy of the Editor of British Journal of Anaesthesia)

Gas Meters

Apart from a spirometer, the most accurate method of measuring gas volumes is by the use of a wet gas meter. This device records the volume of gas which flows past a type of paddle wheel in which a water-seal is used to contain the gas within each successive compartment. The apparatus is fairly expensive and requires careful handling since displacement of the water level influences the calibration. It is most suitable for continuous low flow rates of gas and it is therefore customary to collect expired air in a Douglas bag before passing the contents through a wet gas meter. Gas volumes to be measured must be at pressures close to atmospheric.

Dry gas meters are more robust and cheaper than wet meters, but less accurate. The mechanism is analogous to a two-cylinder double-acting steam engine. The stream of gas is diverted by a system of valves to act alternately on either side of a pair of leather bellows which are linked to a shaft out of phase by 90 degrees. The system has undergone many decades of refinement and is used widely for the metering of coal gas. Potentially it is extremely repeatable and it may therefore be calibrated to indicate gas flow with a very high level of accuracy, but unfortunately errors can arise from failure of the valves to seat correctly. Contact with the seating is maintained chiefly by gravity and these meters must, therefore, be kept upright.

They read correctly at a flow rate of about 20 l./min., under-reading below this and over-reading above it. However, after recent calibration the error should not amount to more than a few per cent. Dry gas meters will respond with reasonable accuracy to unidirectional tidal flow and are commonly incorporated in the expiratory gas circuit. It should be remembered, however, that the pathway of gas through the meter constitutes the whole bulk of the meter (about 20 litres). Therefore, patients must never be connected directly to breathe to and fro through dry gas meters. Furthermore, with certain gas circuits during intermittent positive pressure, several hundred millilitres of gas may be compressed into a dry gas meter during the inspiratory phase. It is therefore essential to arrange the valves of the circuit in such a way that this Boyle's law effect does not give an erroneous measurement of the tidal volume. A non-rebreathing system is usually satisfactory but circle systems may be used with valves between the patient and the meter (Nunn, 1958a).

The Parkinson and Cowan dry gas meter gives accurate readings for volumes which are multiples of 2·5 litres (the volume required for one cycle of the mechanism). Volumes which are not exact multiples of 2·5 litres may be in error by as much as 250 ml. and therefore it is advisable to measure minute volumes over two or three minutes if a reasonable level of accuracy is required. Dry gas meters are not satisfactory for the measurement of a single tidal volume. Errors associated with the use of dry gas meters have been discussed by Cooper (1959).

The Wright Respirometer (Figure 62)

This device is a miniature air turbine with moving parts of very low inertia (Wright, 1955). The revolutions are recorded by means of a gear train and dial of the type used in wrist watches. The instrument indicates directly the number of litres which have passed between two successive readings. The respirometer

responds to gas flow in one direction only and may therefore be used with tidal flow. The internal volume is only 22 ml. and the patients may breathe to and fro through the apparatus with negligible increase in resistance and dead space.

In common with all inferential gas meters the response is dependent on the flow rate, since slip occurs to a greater degree as the flow rate is decreased. The instruments are adjusted to give correct readings at 20 l./min. continuous flow, or 7 l./min. reciprocating flow. Above this figure the response increases to become steady at about 10 per cent high for large minute volumes. At lower flow rates the instrument reads low, being about 10 per cent low at a continuous flow of about 10 l./min. or a reciprocating flow of about 3 l./min. (sinusoidal flow). However, the performance at low minute volumes is markedly improved

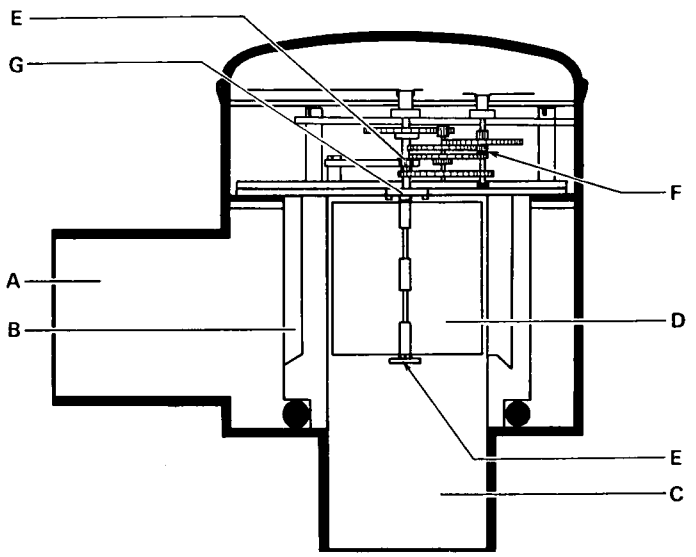


Figure 62. Longitudinal section through the Wright respirometer. (A) Inlet mount. (B) Tangential slots in cylindrical stator ring. (C) Outlet mount. (D) Two-bladed rotor. (E) Jewelled bearings. (F) Gear train. (G) Mercury seal. (Reproduced by permission of British Oxygen Co. Ltd.)

when the respiratory waveform departs from sinusoidal (as it usually does during anaesthesia) and when nitrous oxide is inhaled. The performance of the apparatus has been considered in some detail by Nunn and Ezi-Ashi (1962), who reached the conclusion that the accuracy was in excess of clinical requirements. In the event of hypoventilation, the instrument will read low and therefore exaggerate the departure from normality. Its use is thus fundamentally safe. The respirometer may be modified to give a direct and continuous registration of minute volume (Webb, 1965).

The Ventigrator

The ventigrator is a double-ended symmetrical venturi tube with a central pressure tap and two interconnected end taps. Gas flow in either direction

causes a fall in pressure at the centre tap relative to the pressure at the interconnected end taps. When the patient breathes to and fro through the apparatus, a pressure difference is developed during both inspiration and expiration: the mean pressure difference, integrated with respect to time, is a function of the minute volume. Unfortunately, this ingenious device suffers two serious disadvantages. Firstly, the pressure developed is so small that a sensitive and fragile device is required to measure it. Secondly, the pressure is proportional to the square of the minute volume. This means that at low minute volumes, the deflection of the meter is small and difficult to read. On the other hand, at larger minute volumes the reading rapidly passes off-scale. The performance of the apparatus was studied by Nunn and Ezi-Ashi (1962).

Miscellaneous Dry Gas Meters

There are on the market a variety of meters (manufactured by Dräger, Monaghan, Bennett, etc.) which are intermediate in size between dry gas meters incorporating bellows and the Wright inferential respirometer. Some of these have been reviewed by Byles (1960).

The Integrated Pneumotachogram

It has already been pointed out that the integrated pneumotachogram will give an indication of respiratory volume exchange which approaches the accuracy of the spirometer, provided that certain precautions are taken to ensure that calibration is not invalidated by electrical drift or by changes in gas temperature and composition. Once these difficulties have been overcome, the pneumotachograph imposes very little derangement of anaesthetic gas circuits and has even been used successfully in the difficult circumstances of out-patient dental anaesthesia (Smith, 1964b).

Use of Rotameters with a Non-rebreathing System

During artificial ventilation certain mechanical ventilators are supplied with a continuous flow of fresh gas which is broken down into tidal volumes, the Manley ventilator being a typical example. Under these circumstances, the patient's minute volume is indicated by the fresh gas flow rate (as shown on the rotameters), provided there are no leaks in the system. This forms a most useful, reliable and reasonably accurate method of determining the minute volume of the patient.

The same principle may be used during spontaneous respiration with a fresh gas reservoir and a valvular non-rebreathing gas circuit, or during artificial ventilation with a device which draws a fixed minute volume from a reservoir. Provided that the reservoir does not become either depleted or overfilled, the flow rate of fresh gas into the reservoir must equal the patient's respiratory minute volume. The particular value of this method of measuring ventilatory exchange is that no additional apparatus is required and, apart from the question of leakage, the accuracy is only limited by that of the rotameters which is normally far in excess of the accuracy required for measurement of minute volume for clinical purposes.

CHAPTER 7

RESPIRATORY DEAD SPACE AND DISTRIBUTION OF THE INSPIRED GAS

The previous chapters have been concerned with the factors which influence the pulmonary ventilation considered as the total quantity of gas which passes into and out of the lungs. So far there has been no detailed consideration of the proportion of the total volume flow which actually takes part in gas exchange.

It was realized in the last century that an appreciable part of each inspiration did not penetrate to those regions of the lungs in which gas exchange occurred and was therefore exhaled unchanged. This fraction of the tidal volume has long been known as the dead space, while the effective part of the minute volume of respiration is known as the alveolar ventilation. The relationship is as follows:

$$\begin{matrix}\text{alveolar} \\ \text{ventilation}\end{matrix} = \begin{matrix}\text{respiratory} \\ \text{frequency}\end{matrix} \left(\begin{matrix}\text{tidal} \\ \text{volume}\end{matrix} - \begin{matrix}\text{dead} \\ \text{space}\end{matrix} \right)$$

It is often useful to think of two ratios. The first is:

$$\frac{\text{dead space}}{\text{tidal volume}}$$ (often abbreviated to V_D/V_T and expressed as a percentage)

The second useful ratio is:

$$\frac{\text{alveolar ventilation}}{\text{minute volume}}$$

The first fraction is the wasted part of the breath, while the second is the utilized portion of the minute volume. The sum of the two fractions is unity and one may easily be calculated from the other.

Figure 63 shows in diagrammatic form the various components of a single expirate. The first part to be exhaled will be from the *apparatus dead space* if the subject is employing any form of breathing apparatus, as is usually the case during anaesthesia. The next component will be from the *anatomical dead space*, which corresponds to the volume of conducting air passages. Thereafter gas is exhaled from the alveolar level and the diagram shows two representative alveoli. One is perfused and, from this, *'ideal' alveolar gas* is exhaled. The other alveolus is unperfused and so does not permit gas exchange. From this alveolus is exhaled gas approximating in composition to inspired gas. This gas is known as *alveolar dead space gas* and is an important constituent of the expired gas of anaesthetized patients, although of little significance in normal conscious subjects. It will be seen in *Figure 63* that the final part of the expirate consists of a mixture of 'ideal' alveolar gas and alveolar dead space gas. A sample of this gas is called an *end-tidal*, or preferably an *end-expiratory* sample. Sometimes,

however, it is referred to as a sample of *alveolar gas*. There are thus problems of definition which have not yet been resolved.

Alveolar gas, as defined by Haldane and Priestley (1905) is gas sampled at the end of a forced expiration. Its composition approximates to that of end-expiratory gas since, in a healthy subject, composition changes little between the ends of normal and forced expirations. This interpretation was universal until recently, when it became realized that end-expiratory gas may be actually a mixture of gas from perfused and unperfused alveoli (*Figure 63*). Since only the

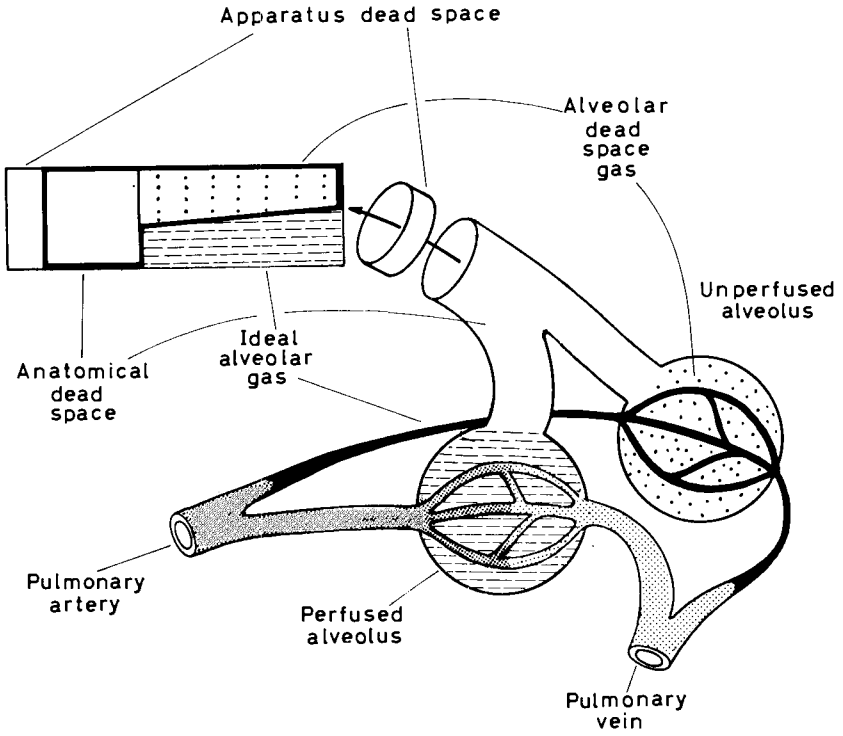


Figure 63. Components of the expired gas of an anaesthetized patient. The rectangle is an idealized representation of a single expirate. The physiological dead space equals the sum of the anatomical and alveolar dead spaces and is outlined in the heavy black line. The alveolar dead space does not equal the volume of the unperfused spaces at alveolar level but only that part of their contents which is exhaled. This varies with the tidal volume

former takes part in gas exchange, it was felt that it should be distinguished and the term 'ideal' alveolar gas was introduced (Riley and his colleagues, 1946). Usage has led to dropping of the qualifying term 'ideal' and, for many workers, 'alveolar' is taken to mean 'ideal alveolar'.

The distinction between 'ideal' alveolar and end-expiratory gas is by no means of theoretical interest alone, but is of considerable importance in almost all patients with whom an anaesthetist may be concerned. To prevent confusion, when describing gas samples in this book, the unqualified term 'alveolar' is

avoided so far as is possible. When it does appear, it is used in a simplified statement in which alveolar dead space is ignored and an expirate is considered as consisting simply of (anatomical) dead space gas and alveolar gas. For symbols, the small capital A relates to 'ideal' alveolar gas (e.g. $P_{A_{CO_2}}$ = 'ideal' alveolar P_{CO_2}) while end-expiratory gas is distinguished by a small capital E, suffixed with a prime (e.g. $P_{E'_{CO_2}}$ = end-expiratory P_{CO_2}).

Figure 63 is, of course, purely diagrammatic and it should not be imagined that all alveoli fall into two watertight compartments—perfused and unperfused. There exists an infinite gradation between alveoli with zero blood flow, through those with average blood flow, to those with excessive blood flow. However, it is sometimes helpful from the quantitative standpoint to consider alveoli *as though* they fell into the categories shown in the diagram. This convention is implicit in the definition of the physiological dead space (*see* page 191).

ANATOMICAL DEAD SPACE*

The gills of fishes are perfused by a stream of water which enters by the mouth and leaves by the gill slits. All of the water is available for gaseous exchange. Birds and mammals, however, employ tidal ventilation which suffers from the disadvantage that a considerable part of the inspired gas comes to rest in the conducting air passages and is thus not available for gaseous exchange.

This imperfection was understood in the nineteenth century when the volume of the anatomical dead space was calculated from post-mortem casts of the respiratory tract (Zuntz, 1882; Loewy 1894). The value so obtained was used in the calculation of the composition of the alveolar gas according to the Bohr equation (1891). This was before the concept of alveolar dead space had arisen and at that time alveolar gas simply referred to that part of the expirate which followed the anatomical dead space gas.

The Bohr equation may be simply derived as follows. During expiration all the CO_2 eliminated is contained in the alveolar gas. Therefore:

$$\begin{array}{c}\text{quantity of } CO_2 \text{ eliminated in the} \\ \text{alveolar gas}\end{array} = \begin{array}{c}\text{quantity of } CO_2 \text{ eliminated in the} \\ \text{mixed expired gas}\end{array}$$

that is to say:

$$\begin{array}{c}\text{alveolar } CO_2 \text{ concentration} \\ \textit{multiplied by} \text{ alveolar ventilation}\end{array} = \begin{array}{c}\text{mixed-expired } CO_2 \text{ concentration} \\ \textit{multiplied by} \text{ minute volume}\end{array}$$

or, for a single breath:

$$\text{alv. } CO_2 \text{ conc.} \times (\text{tidal volume} - \text{dead space}) = \text{mixed-expired } CO_2 \text{ conc.} \times \text{tidal volume}$$

Now there is no serious difficulty in measuring the tidal volume and the mixed-expired CO_2 concentration. Therefore the alveolar CO_2 concentration may be derived if the dead space be known or, alternatively, the dead space may be derived if the alveolar CO_2 concentration be known. In the nineteenth

* Definitions relate to measurement techniques and are postponed to the end of the section (page 184).

century, it was not realized that alveolar gas had a relatively constant composition during the latter part of expiration and could be sampled as end-expiratory gas. Therefore, at that time it was customary to use the Bohr equation for calculation of the alveolar CO_2 concentration, substituting an assumed value for the dead space. After Haldane's historic discovery of the constancy of the alveolar gas, the position was reversed and the dead space became the more difficult quantity to measure. Therefore, after 1905, the alveolar CO_2 concentration was measured directly and the Bohr equation used to calculate the dead space.

At this point we must return to the semantic problems surrounding the use of the word alveolar. In the two paragraphs above, the word alveolar refers to that portion of the expirate which follows the anatomical dead space gas, and its composition would be similar to end-expiratory gas. Using the Bohr equation to measure the anatomical dead space, the appropriate value for the 'alveolar CO_2 concentration' is the end-expiratory CO_2 concentration. If the 'ideal' alveolar CO_2 concentration is used, then the value for the dead space yielded by the calculation will be that of the physiological dead space according to the definition in *Figure 63.*

Value for 'alveolar' CO_2 concentration substituted in Bohr equation	*Corresponding value obtained for dead space*
End-expiratory CO_2 concentration	Anatomical dead space
'Ideal' alveolar CO_2 concentration	Physiological dead space

This distinction between ideal alveolar and end-expiratory gas is fundamental for understanding dead space and is the clue to the controversy which existed for many years between Haldane and Krogh (reviewed by Bannister, Cunningham and Douglas, 1954). In the resting normal conscious healthy subject, the alveolar dead space is very small indeed. Therefore the anatomical and physiological dead spaces are, for practical purposes, identical and there is only a very small difference between the CO_2 concentration of the end-expiratory and the ideal alveolar gas. However, during anaesthesia, in the presence of respiratory disease, after haemorrhage and during exercise the difference becomes appreciable. The clinician, and the anaesthetist in particular are greatly concerned with these states and, therefore, it is appropriate that they should distinguish carefully between the anatomical and physiological dead space, and between the end-expiratory and ideal alveolar gas.

Measurement of the Anatomical Dead Space

The anatomical dead space may be measured in the cadaver by filling the respiratory tract with molten lead, plaster of Paris, wax, Marco resin or simply water. During life, the anatomical dead space is measured as an undergraduate physiological experiment by solution of the Bohr equation using the CO_2 concentration of the end-expiratory gas. The equation given above simplifies into the following familiar form:

$$\text{anatomical dead space} = \text{tidal volume} \left(\frac{\text{end-expiratory } CO_2 \text{ conc.} - \text{mixed expired } CO_2 \text{ conc.}}{\text{end-expiratory } CO_2 \text{ conc.} - \text{inspired } CO_2 \text{ conc.}} \right)$$

In fact, it is not essential to use CO_2 concentrations and it is perfectly valid to employ oxygen or any tracer gas which may be added for that purpose.

If the CO_2 concentration at the lips is measured continuously with a rapid gas analyser, and then plotted against the volume actually expired, the resulting graph in a normal subject has the form shown in *Figure 64*. The 'alveolar

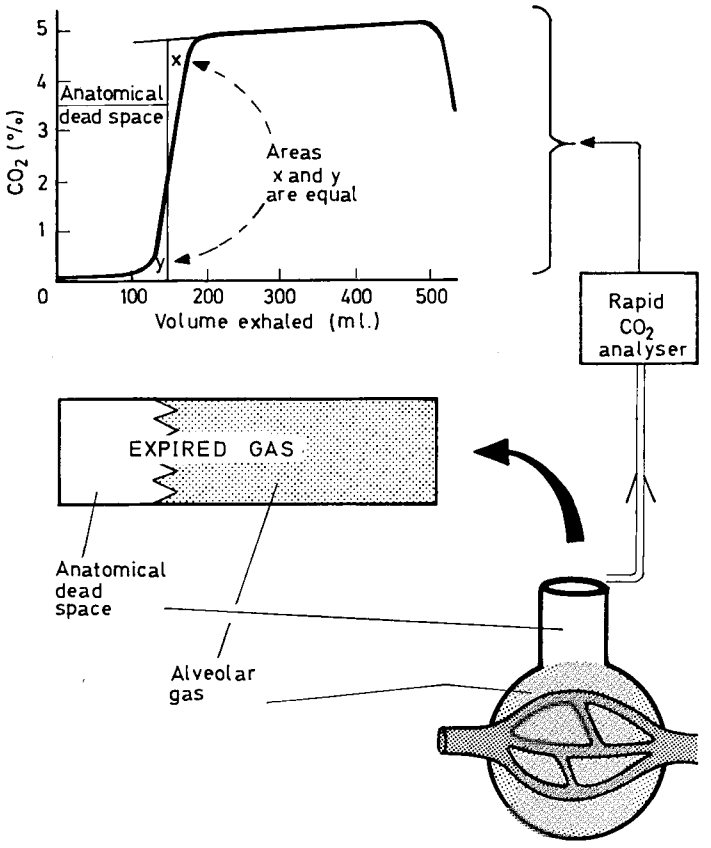


Figure 64. Measurement of the anatomical dead space using carbon dioxide as the tracer gas. If the gas passing the patient's lips is continuously analysed for carbon dioxide concentration, there is a sudden rise to the alveolar plateau level, after the expiration of gas from the anatomical dead space (conducting air passages). If the instantaneous CO_2 concentration is plotted against the volume exhaled (allowing for delay in the CO_2 analyser), a graph similar to that shown above is obtained. A vertical line is constructed so that the two areas x and y are equal. This line will indicate the volume of the anatomical dead space

plateau' of CO_2 concentration is not flat but slopes gently. The significance of this is discussed on page 205. It is possible to solve the Bohr equation from values read off the graph but it is simpler to employ the graphical solution shown on the diagram. This approach has greatly simplified measurements of anatomical dead space and has now become the standard method. The technique was introduced by Fowler (1948) using a rapid nitrogen analyser to

follow a single expiration after the inspiration of 100 per cent oxygen. In his original description of the method Fowler referred to the quantity measured as the physiological dead space, but it is now generally known as anatomical dead space. After 1950, infra-red carbon dioxide analysers came into use and DuBois and his colleagues (1952) described the use of a rapid carbon dioxide analyser for measuring the anatomical dead space. It was later shown that identical values for dead space were given by measurement of the expiratory concentration of oxygen, carbon dioxide, nitrogen or helium (Bartels and his colleagues, 1954). Choice of the indicator gas now depends largely on the availability of apparatus for measuring the concentration of one of these gases with a sufficiently rapid response (95 per cent response in less than 150 milliseconds).

Factors Influencing the Anatomical Dead Space

The volume of the anatomical dead space is influenced by many factors, some of which are of great practical importance to the survival of the patient during anaesthesia.

Size of the subject must clearly influence the dimensions of the conducting air passages, and Radford (1955) has drawn attention to the fact that the volume of the air passages (in millilitres) approximates to the weight of the subject (in pounds*).

Posture influences the anatomical dead space, and Fowler (1950a) quotes the following mean values:

sitting	147 ml.
semi-reclining	124 ml.
supine	101 ml.

Position of the neck and jaw has a pronounced effect on the anatomical dead space, and studies by Nunn, Campbell and Peckett (1959) have indicated the following mean values in three conscious subjects (not intubated):

neck extended, jaw protruded	143 ml.
normal position	119 ml.
neck flexed, chin depressed	73 ml.

It is noteworthy that the first position is that which is sought by anaesthetists to procure the least possible airway resistance. Unfortunately, it also results in the maximum dead space.

Age is usually associated with an increase in anatomical dead space but this may well be associated with an increased incidence of chronic bronchitis which usually results in an enlarged calibre of the major air passages (Fowler, 1950b).

Lung volume at the end of inspiration affects the anatomical dead space since the volume of the air passages is a function of the lung volume. The effect is not very large, being of the order of 20 ml. additional anatomical dead space for each litre increase in lung volume (Shepard and his colleagues, 1957).

Tracheal intubation or tracheostomy will bypass the extrathoracic anatomical dead space. This was found to be 72 ml. in six cadavers, while the intrathoracic

* 1 lb. = 0·45 kg.

anatomical dead space was found to be 66 ml. in three intubated patients (Nunn, Campbell and Peckett, 1959). Intrathoracic anatomical dead space of 12 intubated anaesthetized patients had a mean value of 63 ml. (Nunn and Hill (1960). Between mask-breathing and intubated anaesthetized patients, a difference in total functional dead space of 82 ml. has been found by Kain, Panday and Nunn (1969). An undefined part of the difference would have been due to the additional apparatus dead space in the former state. Tracheal intubation or tracheostomy will bypass approximately half of the total anatomical dead space, although this advantage will clearly be lost if a corresponding volume of apparatus dead space is added to the circuit. The improvement conferred by tracheostomy in cases of ventilatory failure is probably due to three factors: (1) reduction in dead space; (2) increased facility for clearing bronchial secretions; and (3) reduction of airway resistance in the pharynx. A fourth advantage accrues from the ease with which intermittent positive pressure ventilation may be instituted when there is a tracheostomy.

Pneumonectomy will result in a reduction of anatomical dead space if the excised lung was functional (Fowler and Blakemore, 1951).

Hypoventilation results in a marked reduction of the anatomical dead space as measured by Fowler's method. This effect limits the fall of alveolar ventilation resulting from small tidal volumes. It is important in the case of anaesthetized patients who are left to breathe for themselves when there is either heavy central depression of respiration or partial neuromuscular blockade of the respiratory muscles. It is not generally realized that tidal volumes as small as 100 ml. are frequently permitted by anaesthetists and the patients are usually none the worse for this gross physiological trespass.

There are probably two factors which reduce the anatomical dead space during hypoventilation. Firstly, there is a tendency towards streamline or laminar flow of gas through the air passages. Inspired gas advances with a cone front and the tip of the cone penetrates the alveoli before all the gas in the conducting passages has been washed out (*Figure 22*). This, in effect, reduces what we may call the 'functional anatomical dead space' below its value morphologically defined. The reduction of functional anatomical dead space at low tidal volumes was predicted by Rohrer in 1915 and, in the same year, Henderson, Chillingworth and Whitney demonstrated the axial flow of tobacco smoke through glass tubing. The second factor reducing dead space during hypoventilation is the mixing effect of the heart beat which tends to mix all gas lying below the carina. This effect is negligible at normal rates of ventilation, but becomes more marked during hypoventilation and during breath holding. Thus in one hypoventilating patient, Nunn and Hill (1960) found alveolar gas at the carina at the commencement of expiration. A similar effect occurs during breath holding when alveolar gas mixes with dead space gas as far up as the glottis.

In conscious subjects some inspired gas may be detected in the alveoli with tidal volumes as small as 60 ml. (Briscoe, Forster and Comroe, 1954). In anaesthetized patients with tidal volumes less than 350 ml., Nunn and Hill (1960) found the 'functional' anatomical dead space to be about one-fifth of the tidal volume, a number of patients having values less than 25 ml. at tidal volumes below 250 ml.

Drugs acting on the bronchiolar musculature will affect the anatomical dead space, and an increase has been noted after atropine by Higgins and Means (1915), Severinghaus and Stupfel (1955) and Nunn and Bergman (1964). Nunn and Bergman found a mean increase of 18 ml. in six normal subjects, while Severinghaus and Stupfel reported an increase of 45 ml. The latter also reported significant increases with the ganglion-blocking agents hexamethonium and trimetaphan. Histamine caused a small decrease in anatomical dead space.

Hypothermia has been reported to increase the anatomical dead space in dogs (Severinghaus and Stupfel, 1955), but observations by the author (1961a) suggest that there is little significant change in man.

Definition of Anatomical Dead Space

It will now be clear that there are two possible definitions of anatomical dead space.

(1) *Morphological definition:* volume of the conducting air passages which are not lined with respiratory epithelium, as measured by casts of the air passages or by geometrical measurements.

(2) *Functional definition:* that part of the inspired tidal volume which is expired unchanged at the beginning of expiration, as measured by simultaneous records of expired gas volume and gas composition (synonymous with *series dead space*).

The morphological definition is now seldom used, and the anatomical dead space commonly refers to its functional volume as measured by the method of Fowler (1948).

ALVEOLAR DEAD SPACE

Alveolar dead space may be defined as that part of the inspired gas which passes through the anatomical dead space to mix with gas at the alveolar level, but which does not take part in gas exchange. The cause of the failure of gas exchange is lack of effective perfusion of the spaces to which the gas is distributed at the alveolar level. Parallel dead space (Folkow and Pappenheimer, 1955) is synonymous with alveolar dead space. *Figure 65* shows, in diagrammatic form, the possible causes of alveolar dead space.

Factors Influencing Alveolar Dead Space

Hydrostatic failure of alveolar perfusion.—The top alveolus in *Figure 65* lies above the level reached by the pressure head of the pulmonary arterial blood. This cause of alveolar non-perfusion probably applies to the supraclavicular parts of the lungs of the normal subject in the upright position. Studies with radioactive gases have clearly shown that the perfusion of the lungs decreases in a linear fashion from the bases to the apices, reaching very low values at the level of the second rib (West, 1962). Such differences are reduced when the subject lies down, probably because the hydrostatic pressure of the column of blood in the pulmonary arterial tree is then reduced by about a half (West, 1963).

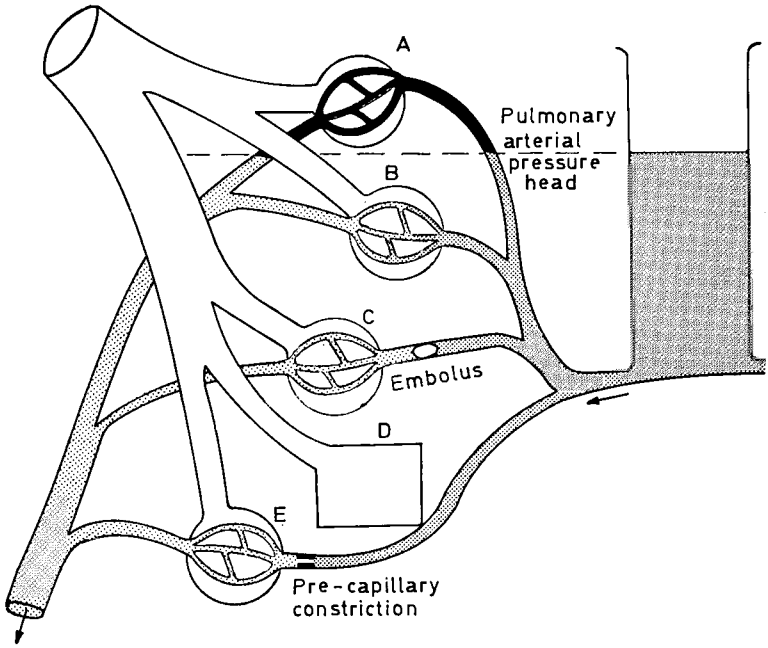


Figure 65. Diagrammatic representation of different forms of alveolar dead space. (A) The uppermost alveolus lies above the pressure head of the pulmonary arterial blood, a normal occurrence in the upright position but more marked in pulmonary hypotension. (B) Normally perfused alveolus. (C) Failure of perfusion due to an embolus lodged in the afferent pulmonary vessel. The embolus may be thrombus, fat, gas or foreign body. (D) An unperfused but communicating air space in parallel with the alveoli. (E) It is not clear to what extent pulmonary vasoconstriction can deprive alveoli of their circulation sufficiently to increase the alveolar dead space

Table 18

Values for dead space in conscious subjects

	Upright position	*Supine position*	*Authors*
Anatomical dead space	147 ml. 128 ml.* 150 ml.	101 ml. 120 ml.* 107 ml.	Fowler (1950a) Riley and his colleagues (1959) Larson and Severinghaus (1962)
Physiological dead space	219 ml. 191 ml. 144·5 ml.† 174·4 ml.‡	136 ml. 151 ml. 94·0 ml.† 123·6 ml.‡	Riley and his colleagues (1959) Larson and Severinghaus (1962) Raine and Bishop (1963)

* Results obtained on one subject.
† Subjects under 40 years of age.
‡ Subjects over 40 years of age.

The effect of posture on perfusion of alveoli is also apparent from values for alveolar dead space which may be derived from studies of physiological and anatomical dead space in different positions. It will be remembered that:

alveolar dead space = physiological dead space − anatomical dead space

Table 18 shows the differences in anatomical and physiological dead space

between the upright and supine positions. In general, larger differences occur in the physiological dead space, suggesting that the alveolar dead space is increased in the upright position, although the results of Larson and Severinghaus (1962) do not support this view.

In the lateral position it appears that approximately two-thirds of the pulmonary blood flow is distributed to the dependent side. During spontaneous respiration the greater part of the ventilation is also distributed to the lower lung and there is probably little change in alveolar dead space. If, however, the patient is ventilated artificially in the lateral position, it is likely that ventilation is distributed in favour of the upper lung, particularly in the presence of an open pneumothorax (Nunn, 1961a). Under these conditions, it may be expected that much of the ventilation of the upper lung will constitute alveolar dead space. This interesting problem is discussed in greater detail later in this chapter (page 197).

Pulmonary hypotension.—Non-perfusion of alveoli will be markedly increased in pulmonary hypotension which occurs in many forms of low-output circulatory failure. The effect is particularly marked in severe haemorrhage which is associated with a great increase in physiological dead space, due to failure of perfusion of a considerable proportion of the ventilated alveoli (Gerst, Rattenborg and Holaday, 1959; Freeman and Nunn, 1963). It seems likely that similar changes occur after coronary occlusion and perhaps after the administration of atropine, which increases alveolar dead space (Nunn and Bergman, 1964) and is known to reduce the pulmonary arterial pressure (Daly, Ross and Behnke, 1963).

Gross increases in the alveolar dead space are almost certainly the principal cause of the increases in physiological dead space reported during anaesthesia with deliberate hypotension (Eckenhoff and his colleagues, 1963). The same study found dead space was also influenced by head-up tilt and raised airway pressures, both of which factors would enhance the adverse effects of reduction of cardiac output (and presumably pulmonary arterial pressure) due to the hypotensive agents. These authors reported a number of patients with physiological dead space in excess of 75 per cent of the tidal volume; severe alveolar hypoventilation could easily occur under these circumstances if the anaesthetist was not aware of the effect.

Pulmonary embolus.—The middle alveolus in *Figure 65* shows obstruction of its afferent vessel due to embolus. Demonstration of an increased physiological (or preferably alveolar) dead space is an elegant confirmation of obstruction in the pulmonary arterial tree. Severinghaus and Stupfel (1957) found an increase in alveolar dead space after the intravenous administration of air to dogs. Stein and his colleagues (1961) have obtained clear evidence of an increase in alveolar dead space in dogs after the migration of peripheral thrombi into the pulmonary circulation. Greenbaum and his colleagues (1965) have shown large increases in physiological dead space in two patients with fat emboli from fractured long bones.

Ventilation of non-vascular air space.—The next form of alveolar dead space shown in *Figure 65* is the ventilation of an air sac with no vasculature. This occurs in obstructive lung disease following widespread destruction of alveolar septa and

the contained vessels. This is the principal cause of the very marked increase in physiological dead space reported in patients with chronic lung disease (Donald and his colleagues, 1952).

Obstruction of pre-capillary pulmonary vessels.—The final form of alveolar dead space in *Figure 65* is due to pre-capillary obstruction of the pulmonary blood vessels. The pulmonary circulation shows very little evidence of active control of distribution of the circulation as is seen in the systemic circulation. The studies of West (1963) support the view that the pulmonary circulation is a low-pressure perfusion through tubes of relatively constant calibre. Distribution is thus largely passive and gravity dependent. However, there is some evidence of an active homeostatic distribution away from areas of low oxygen tension. This effect appears to be feeble and is discussed at some length in the next chapter (page 216), which is also concerned with the response of the pulmonary circulation to drugs.

Obstruction of the pulmonary circulation by external forces.—The anaesthetist is frequently confronted with kinking, clamping or blocking of a pulmonary artery during thoracic surgery. This may be expected to result in an increase in dead space depending on the ventilation of the section of lung supplied by the obstructed vessel.

Alveolar Dead Space during Anaesthesia

Although the alveolar dead space is quite small in the normal conscious subject, it seems to be invariably enlarged during general anaesthesia with either spontaneous respiration or artificial ventilation (Nunn and Hill, 1960); similar changes were reported in dogs by Severinghaus and Stupfel in 1957. In anaesthetized man the alveolar dead space averages 70 ml. but is markedly influenced by the magnitude of the tidal volume (*Figure 66*).

The cause of the increase in the alveolar dead space during anaesthesia has so far not been satisfactorily explained. One possibility would be a preferential distribution of inspired gas away from the areas perfused by the pulmonary blood flow. Alternatively, there might be a preferential distribution of pulmonary blood flow away from the best ventilated alveoli. Finally, the increase might be due to an over-all worsening of the degree of maldistribution which is seen in the normal conscious subject but which is scarcely great enough to result in a measurable alveolar dead space. Whatever the changes in the anaesthetized state, they are apparently sufficient to offset the advantages accruing from the supine position which is usual during anaesthesia. It was mentioned above that, in the normal conscious subject, the assumption of the supine position results in a considerable improvement in the relative distribution of inspired gas and pulmonary blood flow.

There are so many factors which influence the size of the alveolar dead space during anaesthesia that very careful experimental design is necessary to determine the effect of any one factor. Usually only the physiological dead space is measured, but it is often possible to be reasonably certain that changes are in the alveolar rather than the anatomical component. For example, it was mentioned in Chapter 5 (page 130) that physiological dead space is greater when the duration of inspiration is reduced. This effect is shown in *Figure 66b*, which also illustrates the further increase when a subatmospheric pressure is

used during expiration. It is thought that short inspirations are distributed preferentially to badly perfused alveoli, while a more leisurely rate of inspiration allows time for distribution to better perfused alveoli which, it is postulated, have a longer time constant of inflation.

The effects of duration and depth of anaesthesia may also be considered under the heading of alveolar dead space because any effect is likely to be in the

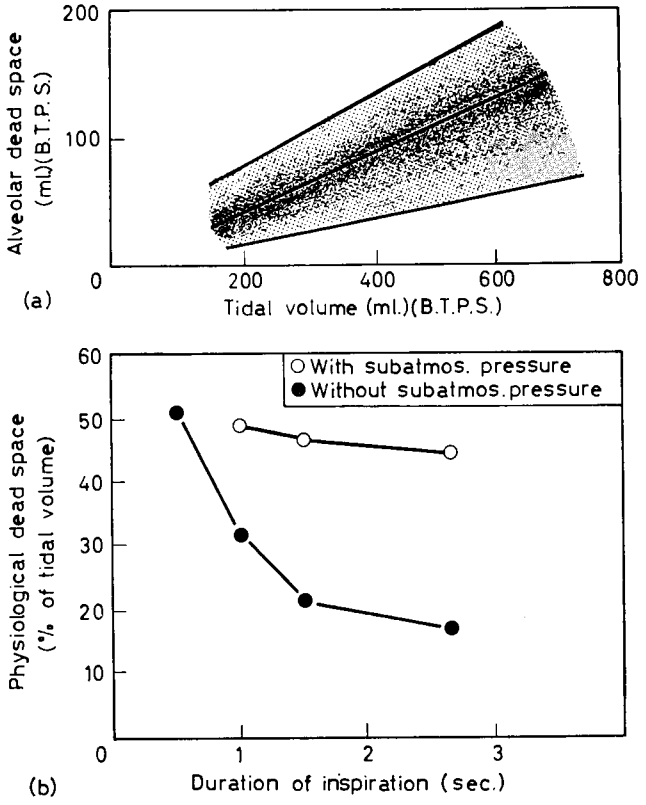


Figure 66. Factors influencing alveolar dead space during anaesthesia. (a) The alveolar dead space as a function of tidal volume in healthy anaesthetized intubated patients. There appears to be no significant difference in this respect between artificial and spontaneous respiration. (b) The effect of the duration of inspiration on the total physiological dead space—the effect being probably on the alvelar component. The use of a subatmospheric pressure phase during expiration increases the dead space but variations in the waveform have little effect apart from any influence on duration (after Watson, 1962b)

alveolar component. There is no unanimity of opinion on the influence of duration. An early report by Thornton (1960) suggested that there might be a progressive rise of physiological dead space during the course of an anaesthetic, and this was later demonstrated by Askrog and his colleagues (1964). However, this effect has not been confirmed by Nunn, Bergman and Coleman (1965), Kain, Panday and Nunn (1969) or Cooper (personal communication). The

reason for the disagreement is not clear but may have been due to progressive changes in some additional factor which was not operative in the studies which found no change. The effect of depth of anaesthesia is not yet established but preliminary observations by Kain, Panday and Nunn (1969) suggest that a relationship may exist, possibly by reduction of pulmonary arterial pressure.

The alveolar component of the physiological dead space will be increased during anaesthesia by any factor which reduces pulmonary flow or pressure. A convincing increase was demonstrated by Eckenhoff and his colleagues (1963) following hypotension induced by ganglion block. It is probably the alveolar component which is principally involved in the positive correlation of physiological dead space with age, which may be observed during anaesthesia (Nunn, Bergman and Coleman, 1965) as in the conscious state (Raine and Bishop, 1963). A review of a number of studies by Cooper (1967) led to the conclusion that, as a rough approximation:

$$V_D/V_T \text{ per cent} = 33 + \frac{\text{age}}{3}$$

(Value of V_D was increased artificially by 70 ml. to compensate for the volume of the upper respiratory tract bypassed by the endotracheal tube.)

Measurement of the Alveolar Dead Space

The alveolar dead space is measured as the difference between the physiological and anatomical dead spaces determined separately but at the same time. Often only the physiological dead space is measured. There are few circumstances in which the anatomical dead space is grossly increased and it is usually possible to attribute a large increase in physiological dead space to an increase in the alveolar component.

The arterial/end-expiratory P_{CO_2} *difference* is a convenient and relatively simple method of assessing the magnitude of the alveolar dead space. In *Figure 63*, expired gas is shown as consisting of four components. The first two, apparatus and anatomical dead spaces, are exhaled in series before the next two which are exhaled in parallel beside one another. Thus the final portion of an expirate consists of a mixture of 'ideal' alveolar gas and alveolar dead space gas. If the patient has an appreciable alveolar dead space, it follows that:

(1) it is impossible to sample or analyse 'ideal' alveolar gas;

(2) the P_{CO_2} of end-expiratory gas will be less than that of 'ideal' alveolar gas, since it is diluted with alveolar dead space gas which is practically free of CO_2.

If, for example, 'ideal' alveolar gas has a P_{CO_2} of 40 mm Hg and the end-expiratory P_{CO_2} is found to be 20 mm Hg, it follows that the end-expiratory gas consists of equal parts of 'ideal' alveolar gas and alveolar dead space gas. Thus if the tidal volume is 500 ml. and the anatomical dead space 100 ml., the components of the tidal volume would be as follows:

anatomical dead space	100 ml.
alveolar dead space	200 ml.
'ideal' alveolar gas	200 ml.

The physiological dead space would be 100 + 200 = 300 ml. and the V_D/V_T ratio 60 per cent.

In practice, the method has two complications. Firstly, the alveolar dead

space gas is not entirely CO_2-free since end-expiratory gas is re-inhaled into the alveolar dead space at the start of inspiration. Secondly, it has been pointed out that 'ideal' alveolar gas cannot be sampled directly if it is contaminated with alveolar dead space gas. The solution to this difficulty has been to substitute arterial P_{CO_2} for 'ideal' alveolar P_{CO_2}. The rationale of this has been explained in detail by Riley and his colleagues (1946), and is widely accepted. It is based on two premises.

(1) There is never a measurable gradient of P_{CO_2} between alveolar gas and blood leaving the pulmonary capillaries.

(2) Since the mixed venous/arterial P_{CO_2} difference is small (normally 6 mm Hg), no reasonable degree of venous admixture (shunt) is likely to produce a serious rise in arterial P_{CO_2} above the level in the end-pulmonary capillary blood.

The second premise is only approximately true, since a 33 per cent shunt would raise the arterial P_{CO_2} by about 3 mm Hg if the mixed venous/arterial P_{CO_2} difference were 6 mm Hg. Nevertheless, the use of arterial blood for this purpose has proved immensely valuable, and measurement of the arterial/end-expiratory P_{CO_2} difference is probably the most convenient method of estimating the alveolar dead space.

In practice, arterial blood is sampled during the measurement of the end-expiratory P_{CO_2}. The arterial P_{CO_2} is then measured and compared with the end-expiratory value. End-expiratory P_{CO_2} may be measured directly with a rapid analyser sampling from the mouth (infra-red or mass spectrometer) or alternatively, end-expiratory gas may be collected for analysis by a variety of techniques (Rahn and his colleagues, 1946a; Nunn and Pincock, 1957). A significant positive correlation has been found during anaesthesia between the arterial/end-expiratory P_{CO_2} difference and the alveolar dead space (Nunn and Hill, 1960).

Direct experimentation has confirmed the validity of this approach. Theye and Fowler (1959) and Julian and his colleagues (1960) have performed partial obstruction of the pulmonary arterial bed and shown clearly the resultant increase of arterial/end-expiratory P_{CO_2} difference. However, there appears to be a homeostatic mechanism which deflects ventilation away from unperfused areas of the pulmonary field so that the alveolar dead space resulting from pulmonary arterial obstruction tends to be maximal at first and then decreases (Severinghaus and his colleagues, 1961). This change appears to be mediated by an increase in airway resistance of the affected parts, resulting in preferential ventilation of the remaining perfused lung.

The magnitude of the arterial/end-expiratory P_{CO_2} difference is of practical importance if end-expiratory P_{CO_2} is used as an indirect measure of the arterial P_{CO_2}. In the presence of severe respiratory disease with abnormalities of distribution (e.g. emphysema) the difference is so large and variable that measurements of end-expiratory P_{CO_2} are of little value. During anaesthesia the difference appears to be relatively constant in healthy subjects. Ramwell (1958) and Nunn and Hill (1960) were in close agreement on the following points.

(1) During anaesthesia, in normal healthy subjects, the arterial/end-expiratory P_{CO_2} difference has a mean value of 5 mm Hg with a range of 0–10 mm Hg.

(2) The magnitude is uninfluenced by the actual level of the P_{CO_2}.

(3) The magnitude appears to be similar for spontaneous and artificial ventilation.

Higher levels for arterial/end-expiratory P_{CO_2} difference have been found during thoracic surgery and there was greater variability, values probably being influenced by the degree of expansion of the exposed lung (Nunn, 1961a).

PHYSIOLOGICAL DEAD SPACE

The physiological dead space is defined as that part of the tidal volume which does not participate in gaseous exchange. Nowadays it is universally defined by the Bohr mixing equation with substitution of arterial P_{CO_2} for alveolar P_{CO_2}:

$$\text{physiological dead space} = \text{tidal volume} \left(\frac{\text{arterial } P_{CO_2} - \text{mixed-expired } P_{CO_2}}{\text{arterial } P_{CO_2} - \text{inspired } P_{CO_2}}\right)$$

It follows from this equation that the physiological dead space approximates closely to the functionally important measurement of the ineffective part of the ventilation. Alveolar ventilation is therefore measured as:

$$\text{respiratory frequency} \times \left(\text{tidal volume} - \text{physiological dead space}\right)$$

or alternatively as:

$$\left(1 - \frac{\text{physiological dead space}}{\text{tidal volume}}\right) \times \text{respiratory minute volume}$$

Thus if the physiological dead space is 30 per cent of the tidal volume, (V_D/V_T = 30 per cent), the alveolar ventilation will be 70 per cent of the respiratory minute volume. The use of the V_D/V_T ratio is strongly recommended since the ratio tends to remain fairly constant while the actual value for the physiological dead space may vary widely with changing tidal volumes.

This approach is radically different from the assumption of a constant 'dead space' which is subtracted from the tidal volume, the difference then being multiplied by the respiratory frequency to indicate the alveolar ventilation. This approach is fundamentally unsound under almost all the clinical circumstances encountered by the anaesthetist: the errors which follow the assumption of a constant 'dead space' may be very large indeed, as can be seen in the example in *Table 19* which is taken from a woman of 47 years undergoing hysterectomy.

Table 19

Tidal volume	*Physiological dead space*	V_D/V_T *ratio*
170 ml. (spontaneous respiration)	63 ml.	37%
614 ml. (artificial ventilation)	234 ml.	38%

The proportionality between dead space and tidal volume was first demonstrated by Enghoff in 1931. In a later publication (1938) he suggested that the dead space be measured by substitution of the arterial P_{CO_2} in Bohr's equation, thus introducing the modern concept of the physiological dead space. He used the term *Volumen inefficax* to stress its functional nature, in contrast to the original term for the dead space—*schädlichen Raum*—which rested on a morphological definition and was akin to the current concept of the anatomical dead space. Enghoff used the term *Inefficax Quotient* to describe V_D/V_T ratio and was able to demonstrate that the ratio remained relatively constant for one individual during hyperventilation and exercise.

In practice, the concept of a relatively constant V_D/V_T ratio simplifies calculations of alveolar ventilation from minute volume, and one easily becomes accustomed to thinking of the alveolar ventilation as a constant fraction of the minute volume.

Factors Influencing the Physiological Dead Space

Since the physiological dead space equals the sum of the anatomical and alveolar dead space, the factors influencing the physiological dead space have already been considered under the appropriate headings (pages 182–189).

Physiological Dead Space during Anaesthesia

The previous pages have given abundant evidence for the increase in physiological dead space during anaesthesia, and many of the factors which appear to influence the dead space have been considered.

For practical purposes there is overwhelming evidence that physiological dead space should be considered as a fraction of the tidal volume (V_D/V_T ratio) rather than as a fixed volume. For a healthy, intubated, young adult the V_D/V_T ratio has been found in many studies to have a mean value within the range of 30–33 per cent during uncomplicated anaesthesia with spontaneous or artificial ventilation. However, inclusion of normal apparatus dead space raises this figure to about 46 per cent in intubated patients and about 64 per cent in patients breathing from a mask (Kain, Panday and Nunn, 1969). These values relate to what may be called the total functional dead space which equals the physiological dead space *plus* the apparatus dead space functionally measured. Cooper (1967) added 70 ml. of apparatus dead space to his patients as a compensation for the volume of the upper airway bypassed by the endotracheal tube. He obtained a mean value of V_D/V_T ratio of approximately 50 per cent which is compatible with the measurements quoted above. Thus, when using values of V_D/V_T ratio from the literature for calculation of the effective part of the tidal volume, it is important to be quite clear whether the author made allowance for apparatus dead space (q.v.). It is no less important in any calculation to take into account the effect of respiratory health, age, haemodynamic state and unusual respiratory frequencies.

Effects of an Increased Physiological Dead Space

Regardless of whether an increase in physiological dead space is due to the anatomical or alveolar components, alveolar ventilation is reduced, unless there is a compensatory increase in minute volume.

Reduction of alveolar ventilation due to an increase in physiological dead space produces changes in the 'ideal' alveolar tensions which are identical to those produced by an equivalent reduction in respiratory minute volume. Alveolar P_{CO_2} will rise and alveolar P_{O_2} fall, the two bearing a relationship to one another which is influenced only by the composition of the inspired gas and, to a small extent, the respiratory exchange ratio. The changes may be derived from *Figure 51*, but are shown more clearly on an oxygen–carbon dioxide diagram as in *Figure 67*. Values for the changes in alveolar gas tension may be conveniently determined from the universal alveolar air equation (page 153).

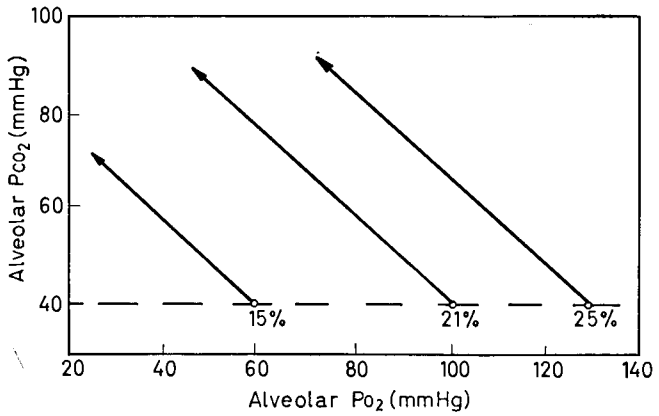


Figure 67. Pathways of changes in alveolar gas tensions during alveolar hypoventilation. The information may be derived from Figure 51. Alveolar hypoventilation may result either from reduction of minute volume or from increase in any component of the dead space. The resultant effect upon both P_{O_2} *and* P_{CO_2} *is similar, although the alveolar* P_{O_2} *is also influenced directly by the inspired oxygen concentration, which is indicated at the foot of the three lines in the diagram*

It is almost always possible to counteract the effects of an increase in physiological dead space by a corresponding increase in the respiratory minute volume. If, for example, the minute volume is 10 l./min. and the V_D/V_T ratio 30 per cent, the alveolar ventilation will be 7 l./min. If the patient were then subjected to pulmonary embolism resulting in an increase of the V_D/V_T ratio to 50 per cent, the minute volume would need to be increased to 14 l./min. to maintain an alveolar ventilation of 7 l./min. Should the V_D/V_T increase to 80 per cent, the minute volume would need to be increased to 35 l./min. to maintain the alveolar ventilation, and so on. In principle, all that is necessary is to adjust the minute volume until the arterial P_{CO_2} attains the required level. It is, however, impossible to judge what is an adequate ventilation by examination of the expired air if there is a substantial increase in the alveolar dead space.

Measurement of Physiological Dead Space

In the past, the measurement of physiological dead space has been undertaken mainly in the interests of research. It is, however, quite a simple matter

and is of considerable value in the management of patients who are ventilated artificially for long periods. Its value lies in the fact that it is the link between respiratory minute volume and alveolar ventilation. It is thus a major factor in defining the total minute volume which is needed to produce a required arterial P_{CO_2} in a particular patient.

Arterial blood and expired air are collected simultaneously over a period of two or three minutes (*Figure 68*). The collection of the expired air is difficult when the patient is conscious since the use of the gas-collecting apparatus tends to cause hyperventilation, often further accentuated by the arterial

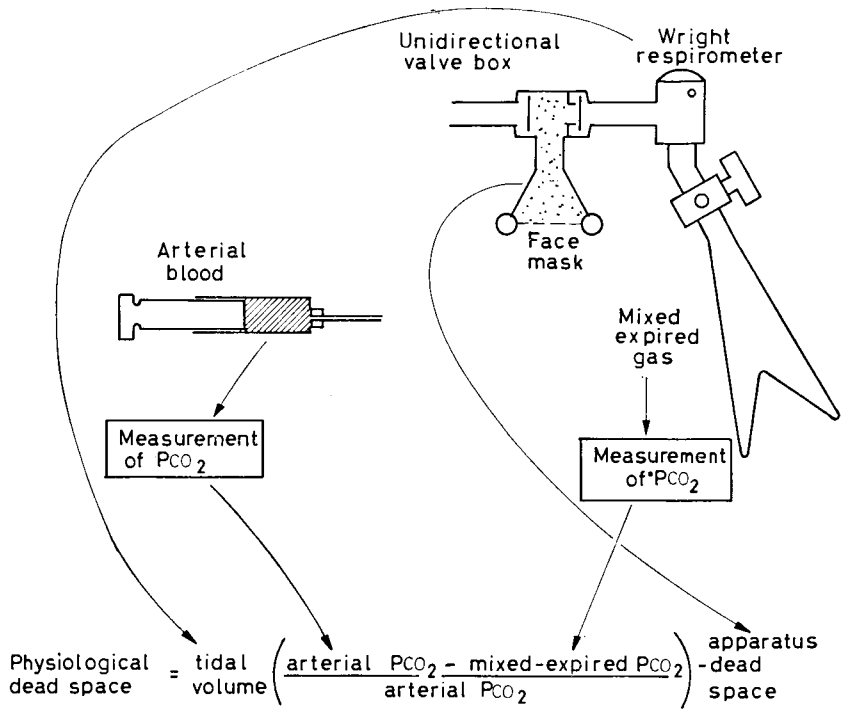


Figure 68. Clinical measurement of physiological dead space. Arterial blood and mixed-expired gas are collected simultaneously over a period of 2–3 minutes. Values for P_{CO_2} *are then substituted in the Bohr equation. Tidal volume is conveniently determined with a Wright respirometer and the apparatus dead space by water displacement*

puncture. After collection, blood and gas are removed to the laboratory and the P_{CO_2} of each determined. Suitable methods are discussed on page 322.

Provided that the inspired gas is free from carbon dioxide, physiological dead space is indicated by the following form of the Bohr equation:

$$\text{physiological dead space} = \text{tidal volume} \left(\frac{\text{arterial } P_{CO_2} - \text{mixed-expired gas } P_{CO_2}}{\text{arterial } P_{CO_2}}\right) - \text{apparatus dead space}$$

Apparatus dead space includes such items as the face mask and unidirectional valve box. It is usually measured by water displacement and is often found to be

surprisingly large. Tidal volume may be determined by a variety of techniques; the Wright respirometer is the most convenient and may easily be incorporated in the gas-collection apparatus (*Figure 68*).

The result is best expressed as the ratio of the physiological dead space to the tidal volume and will be found to be reasonably constant in the same patient under the same circumstances, provided that there is no change in the pulmonary circulation (such as pulmonary embolism). It should, however, be stressed that the physiological dead space is a functional concept defined by its method of measurement. It does not follow that the expired air is actually divided into the watertight compartments shown in *Figure 63.* Scatter of ventilation/perfusion ratios (page 234) undoubtedly contributes to the measured physiological dead space from which it cannot be distinguished by the methods of measurement described in this section.

APPARATUS DEAD SPACE AND REBREATHING

Thus far, we have considered apparatus dead space as though it were always a simple extension of the patient's anatomical dead space and could be treated as such during measurement. This approach is perfectly valid provided that we are only considering endotracheal tubes, mouthpieces and such equipment. A face mask, however, presents a more difficult problem since it is possible that the whole of the gas space under the mask may not be washed out by the tidal volume. Under these conditions we are again confronted by the difference between the morphological and the functional definitions that were noted in relation to anatomical dead space. Usually, only the morphological definition is considered and apparatus dead space is commonly measured by filling with water. Measurement of the functional apparatus dead space may, however, be made by means of the technique of Fowler (1948) (page 181). In this case, the gas sampling point must lie at the junction between the apparatus dead space and the anatomical dead space; with carbon dioxide being used as the tracer gas, the measurement is made during inspiration. In effect, one measures the volume which must be inhaled through the apparatus dead space before uncontaminated inspired air is reached. Functional apparatus dead space may also be determined by measuring physiological dead space with and without added apparatus dead space.

Concepts of apparatus dead space and rebreathing have been explored in some detail by Nunn and Newman (1964). These authors found the problem far more complicated than might appear at first sight. The principal points which they made are as follows.

(1) A variety of gas circuits are in common use by anaesthetists and these circuits impose many different patterns of rebreathing.

(2) The gas rebreathed may be end-expiratory gas (as with a simple face mask), mixed expired gas (as in circuit C described by Mapleson, 1954), or any combination of these gases.

(3) Contamination of inspired gas may occur early in inspiration, for example, with the use of simple mouthpieces. However, in other circuits (such as Ayre's T-piece) contamination may occur late in inspiration. This gas may come to rest in the patient's anatomical dead space and therefore take no part in gas exchange although it has been inhaled into the patient's respiratory tract.

(4) If gas exhaled from the patient's anatomical dead space is stored and then re-inhaled (as may occur with the Magill gas circuit), this will not influence gas exchange although, considered in terms of gas volumes, rebreathing has occurred.

(5) The effective 'mean inspired gas composition' has two alternative meanings. The first refers to the mean composition of the gas which enters the patient's respiratory tract. The second is restricted to the gas which enters functioning alveoli and so influences gas exchange.

(6) 'Mean inspired gas composition' is difficult to measure in the presence of rebreathing. It cannot be derived from a plot of instantaneous gas composition against time, since the required value is the concentration integrated with respect to volume and not to time.

(7) An inspiratory gas sampler which will indicate the effective mean inspired gas composition in the presence of changes in inspired gas composition must sample not necessarily at a steady rate, but at a rate which is proportional to the instantaneous inspiratory gas flow rate. Such a device is practicable and has been developed by Bookallil and Smith (1964).

Effects of Apparatus Dead Space

It must be borne in mind that apparatus dead space hampers not only the elimination of carbon dioxide, but also the uptake of oxygen, the uptake of inhalational anaesthetic agents and also their subsequent elimination. Usually these effects are harmful to the patient's interest (unless it is intended to raise the P_{CO_2} to a desirable level by rebreathing).

Generally, the introduction of apparatus dead space or rebreathing affects all these exchanges equally. However, dissociation is possible. A notorious example is the incorrect use of a Waters' canister with fresh gas introduced into the side of the canister distal from the patient, beside the relief valve. Provided the soda-lime is fresh, the apparatus dead space for CO_2 consists only of the connections between the patient and the canister. However, for oxygen the apparatus dead space must include in addition the intergranular space of the canister since the patient must breathe through the canister for his expired gas to be recharged with oxygen. The situation is then complex and it is necessary to consider the patient as having two alveolar ventilations: one for carbon dioxide and a second, much smaller one, for oxygen!

Anaesthetists show astonishing ingenuity in 'improving' gas circuits. While these often appear harmless, it sometimes proves that the effects are surprisingly complex and it may become almost impossible to determine the composition of the gas which the patient is inhaling. Control of the gaseous environment is essential for good anaesthesia, and the anaesthetist should know precisely what the patient is breathing at all times. For this reason the author prefers to use gas circuits which avoid rebreathing, appreciating that the control of the gaseous environment is gained at some additional cost in gases and volatile anaesthetic agents. This price appears reasonable.

DISTRIBUTION OF THE INSPIRED GAS

The distribution of the inspired gas may be considered in a number of contexts. In the first place, it may be considered purely as spatial distribution in relation

to anatomical structures. Secondly, it may be considered in relation to the distribution of pulmonary blood, differentiating between the ventilation of unperfused alveoli at one extreme and the failure of ventilation of perfused alveoli at the other extreme. Finally, the distribution of inspired gas may be considered in terms of the rate at which different alveoli fill and empty.

It frequently happens that these distinctions are not clearly made, and confusion may result from a failure to appreciate the precise meaning of the phrase 'distribution of inspired gas' in a particular situation.

Spatial and Anatomical Distribution of Inspired Gas

At the time of writing, there is a paucity of information about the spatial distribution of inspired gas and the factors which may influence it. This is largely due to the practical difficulties of measuring the ventilation of different parts of the lungs. The following approaches have been used.

(1) Inspection and auscultation of the chest will indicate gross changes in the distribution of the inspired gas such as follow collapse of the greater part of one lung.

(2) Chest radiography and screening provide some qualitative information about the relative ventilation of different parts of the lung fields.

(3) Bronchospirometry is used to differentiate the ventilation of the two lungs and, to a certain extent, of different lobes.

(4) Pneumography provides an indication of the change in circumference of the thorax at different levels. From such measurements it is possible to make some estimate of volume changes.

(5) Radioactive tracer gases may be used to study the ventilation of areas of lung over which appropriate counters are placed.

(6) Gas expired from different lobes may be sampled at bronchoscopy and analysis will indicate relative ventilation.

Distribution between the two lungs is influenced by posture and by the manner of ventilation. In the normal conscious seated subject, studies with divided airways show that the right lung enjoys a ventilation slightly greater than that of the left side, and this is no doubt associated with the fact that the volume of the right lung is a little greater than that of the left lung (*Figure 69*). The supine position is associated with a reduction in the F.R.C. but the relative ventilation of the two lungs is not changed.

In the lateral position the studies of Svanberg (1957) have shown that the lower lung is always better ventilated regardless of the side on which the subject is lying although there remains a tendency towards greater ventilation of the right side. It appears surprising at first that the lower lung should be better ventilated than the upper since the volume of the lower lung is less, and it is especially liable to atelectasis (Faulconer, Gaines and Grove, 1946). However, the diminished volume of the dependent lung is associated with the lower diaphragm lying higher in the chest and so being more sharply curved. It will, therefore, be able to contract more effectively during inspiration (*Figure 46*). We shall see later that this preferential ventilation of the lower lung accords with increased perfusion of the lower lung so that the ventilation/perfusion

ratios of the two lungs are not greatly altered on assuming the lateral position (page 233).

This relationship is, unfortunately, disturbed during artificial ventilation, when the high diaphragm of the lower side no longer confers any advantage in ventilation. On the contrary, the weight of the mediastinum rests on the lower

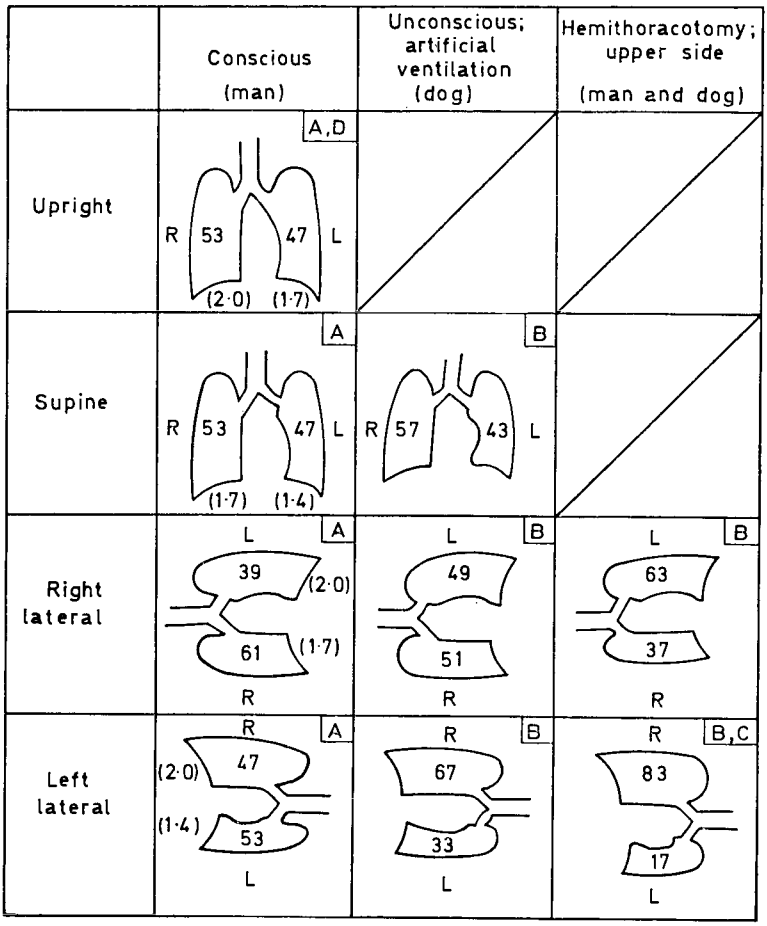


Figure 69. This diagram illustrates the relative distribution of inspired gas between the two lungs under various circumstances which have been investigated. The figure written within the lungs indicates the percentage of the total ventilation received by that lung. Figures in parentheses show the lung volume (litres). In the upright conscious man, the figures are the mean of the values given by the two authorities. (A) Man (Svanberg, 1957). (B) Dog (Rehder, Theye and Fowler, 1961). (C) Man (Nunn, 1961a). (D) Man (Comroe and his colleagues, 1962)

lung and limits its ability to expand during I.P.P. ventilation. The studies of Potgieter (1959) showed a considerable reduction in the total compliance of the lower lung plus chest wall, when the patient was turned into the lateral nephrectomy position. On the assumption that the ventilation of the two lungs

was in proportion to the static pressure/volume relationships, observed by Potgieter, the ventilation of the lower lung would be of the order of 40 per cent of total ventilation. These figures accord well with data from dogs (Rehder, Theye and Fowler, 1961), although dogs in the supine position show a marked preferential ventilation of the right lung, and this complicates the interpretation of the data in the lateral position (*Figure 69*). The tendency towards overventilation of the upper lung was found to be accentuated when the upper thorax was opened and the exposed lung allowed to expand freely. A single observation by Nunn (1961a) during thoracotomy confirmed the gross maldistribution of ventilation that may occur under these circumstances (*Figure 69*).

Lobar ventilation may be studied with the catheter of Mattson and Carlens (1955). This device permits study of the right upper lobe, which was found to enjoy about 40 per cent of the ventilation of the right lung in the supine position and fractionally less in the upright position.

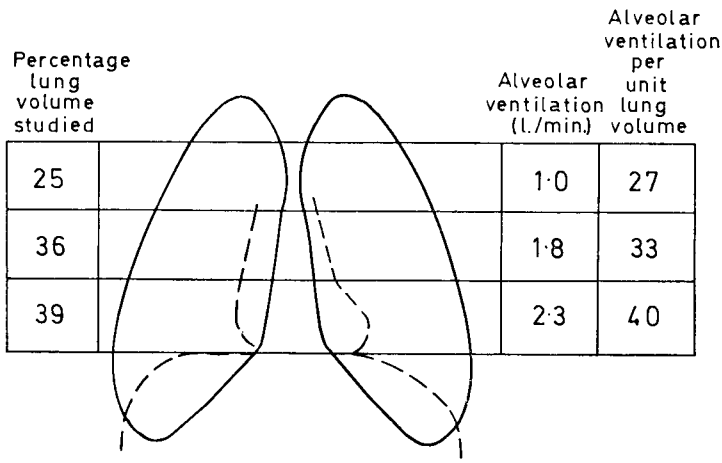


Figure 70. Relative ventilation of different areas of the lungs (upright position). On the left is shown the percentage distribution of the total lung volume studied. On the right are shown the alveolar ventilation of each slice together with its ventilation per unit lung volume in the slice. Note that there is a moderate increase in the ventilation per unit lung volume from the apices downwards. Compare this diagram with Figure 82, which shows the perfusion of these slices of lung by the pulmonary blood flow. (Recalculated and redrawn from West (1962))

Horizontal slices of lung have been studied by West (1962) using a radioactive isotope of oxygen. He found the slices to have different degrees of ventilation with a progressive increase in ventilation (per unit lung volume) the nearer the slices lay to the diaphragm (*Figure 70*). These variations are of minor importance in comparison to the gross differences in perfusion which were found and which will be discussed in greater detail in Chapter 9 (page 233).

Changes in the external geometry of the chest have received little attention. Agostoni (1965) has suggested that volume changes might be related, not only to alterations in rib cage and abdominal circumference, but also to the ratio of the

circumference to the dorsoventral diameter. Clearly the elevation of the rib cage could also be measured. Movements of the diaphragm have long been studied by radiography, but it must be remembered that the diaphragm is subject to passive movement and radiological evidence of movement cannot necessarily be interpreted as evidence of contraction.

The effects of anaesthesia on the spatial distribution of inspired gas have received little attention. An exception is the observation of Snow (1947) that expansion of the rib cage decreased in the deeper planes of general anaesthesia. Miller (1938) was perhaps the first to display pneumograph tracings to support this contention. Many people believe that the spatial distribution of inspired gas is different during artificial ventilation. It would seem that it could only be fortuitous if distribution were the same during both spontaneous and artificial respiration, since the mechanism of breathing is quite different in the two instances.

Distribution of Inspired Gas in relation to Pulmonary Blood Flow

We have seen that inspired gas distributed to regions which have no pulmonary capillary blood flow cannot contribute to gaseous exchange and that this fraction of the tidal volume constitutes the alveolar dead space. This was fully appreciated by John Hunter who, in the eighteenth century, wrote:

> 'In animals where there is no circulation there can be no lungs: for lungs are an apparatus for the air and blood to meet, and can only accord with motion of blood in vessels . . . As the lungs are to expose the blood to the air, they are so constructed as to answer this purpose exactly with the blood brought to them, and so disposed in them as to go hand in hand.'

Alternatively, where regions of the lungs are perfused but deprived of ventilation, the blood perfusing these regions mixes with the blood draining normal alveoli and constitutes venous admixture or shunt. This phenomenon is discussed at length in Chapter 9 after discussion of the causation and incidence of maldistribution of the pulmonary blood flow. The distribution of inspired gas in relation to pulmonary blood flow is the most important aspect of the distribution of inspired gas.

Distribution of Inspired Gas in relation to the Rate of Alveolar Filling

We have already seen in Chapter 5 (page 117) that the rate of inflation of the lung is a function of compliance and airway resistance. The product of the compliance and resistance equals the time constant which is:

(1) the time required for inflation to 63 per cent of the final volume attained if inflation is prolonged indefinitely;

OR

(2) the time which would be required for inflation of the lungs if the initial gas flow rate were maintained throughout inflation (*see Figure 126*).

These considerations apply equally to small areas of the lungs, and in *Figure 14* were shown fast and slow alveoli, the former with a short time constant and the latter with a long time constant.

We may now consider ventilation of the lungs when different parts have different time constants. The diagrams (*Figure 71*) may look as though we are considering different lungs and the reasoning would certainly apply to cases where the time constants of the lungs were different. We are, however, equally concerned with the general situation in which different *functional units* of lung have different time constants, without specifying the size or the anatomical location of these units.

The considerations are fundamentally similar for spontaneous respiration or for artificial ventilation with a constant or sine-wave flow generator (*Figures 43 and 44*). We shall, however, present the problem by considering the special case of passive inflation of the lungs by development of a constant mouth pressure. This seems to simplify the presentation, although Otis and his colleagues (1956) have chosen to present the subject as illustrated by ventilation of the lungs in response to development of a sinusoidal mouth pressure. Their presentation may be more lucid to those who are familiar with the theory of alternating current.

Let us consider two functional units of equal compliance and resistance (*Figure 71a*). If the mouth pressure is suddenly increased to a constant level, there will be an increase in volume of each lung unit equal to the mouth pressure multiplied by the compliance of the unit. The time course of inflation will follow the wash-in type of exponential function and the time constant will be equal to the product of compliance and resistance of each unit. The time courses will thus be identical, and if the inspiratory phase is terminated at any instant, the pressure in each will be identical since the alveolar pressures will equal volume change divided by compliance of each unit.

Next let us consider two functional units, one of which has half the compliance but twice the resistance of the other (*Figure 71b*). The time constants of the two will thus be equal. If a constant inflation pressure is maintained, the one with the lower compliance will increase in volume by half the volume change of the other. Nevertheless, the pressure build-up within each unit will be identical. Thus, as in the previous example, the relative distribution of gas between the two functional units will be independent of the rate or duration of inflation. If the inspiratory phase is terminated at any point, the pressure in each unit being identical, no redistribution will occur between the different units.

In the next example (*Figure 71c*), the compliances of the two units are identical but the resistance of one is twice that of the other. Therefore, its time constant is double that of its fellow and it will fill more slowly, although the volume increase in both units will be the same if inflation is prolonged indefinitely. Relative distribution between the units is thus dependent upon the rate and duration of inflation. If inspiration is checked by closure of the upper airway after two seconds (for example), the pressure will be higher in the unit with the lower resistance. Gas will then be redistributed from one unit to the other as shown by the arrow in *Figure 71c*.

Figure 71d shows a pair of units with identical resistances but the compliance of one being half that of the other. Its time constant is thus half that of its

fellow and it enjoys a more rapid time course of inflation. However, since its compliance is half that of the other, the ultimate volume increase will only be

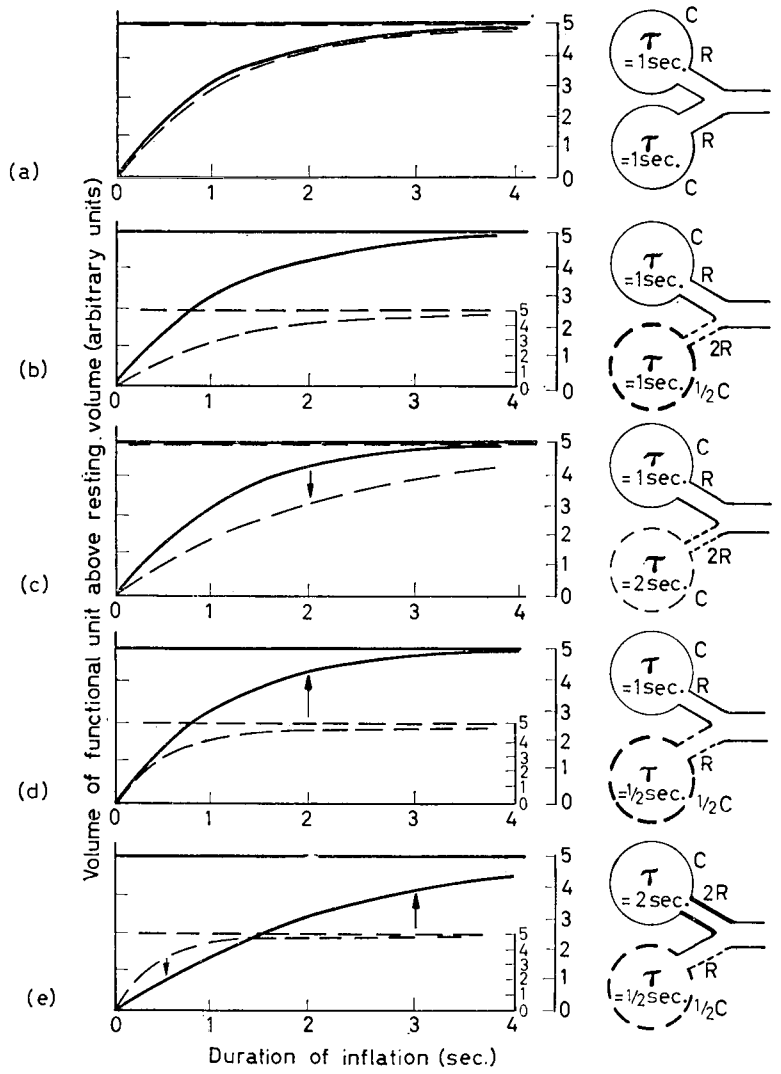


Figure 71. The effect of mechanical characteristics on the time course of inflation of different functional units of the lung when exposed to a sustained constant inflation pressure. The Y co-ordinate is volume change, but a scale showing intra-alveolar pressure is shown on the right. The continuous curve relates to the upper unit and the broken curve to the lower unit, in each case. Separate pressure scales are necessary when the compliances are different. See text for explanation of the changes

half that of the other unit when the inflation is prolonged indefinitely. It will again be seen that the relative distribution of gas between the two units is not constant throughout inflation, and is therefore dependent upon the rate and

duration of inflation. Pressure rises more rapidly in the unit with the lower compliance, and if inspiration is checked by closure of the upper airway at two seconds (for example) gas will be redistributed from one unit to the other as shown by the arrow in *Figure 71d.*

An interesting and complex situation occurs when one unit has an increased resistance and another a reduced compliance (*Figure 71e*). It will be remembered that this combination was chosen to introduce the concept of fast and slow alveoli in *Figure 14.* In the present example the time constant of one unit is four times that of the other, while the ultimate volume changes are determined by the compliance as in the previous example. When the inflation pressure is sustained, the unit with the lower resistance shows the greater volume change at first, but rapidly approaches its equilibrium volume. Thereafter the other unit undergoes the major volume changes, the inflation of the two units clearly being out of phase with one another. Throughout inspiration, the pressure build-up in the unit with the shorter time constant is always greater and, if inspiration is checked by closure of the upper airway, gas will be redistributed from one unit to the other as shown by the arrows in *Figure 71e.*

If the inflation pressure is sustained indefinitely, the volume change enjoyed by different units of the lungs will depend solely upon their compliance. *If their time constants are equal,* the build-up of pressure in the different units will be identical at all times during inflation and therefore:

(1) Distribution of inspired gas will be independent of the rate, duration or frequency of inspiration.

(2) Dynamic compliance (so far as it is influenced by considerations discussed in relation to *Figure 14*) will not be affected by changes in frequency.

(3) If inspiration is checked by closure of the upper airway, there will be no redistribution of gas within the lungs.

If, however, *the time constants of different units are different,* from whatever cause, it follows that:

(1) Distribution of inspired gas will be dependent on the rate, duration and frequency of inspiration.

(2) Dynamic compliance will be decreased as respiratory frequency is increased.

(3) If inspiration is checked by closure of the upper airway, gas will be redistributed within the lungs.

In the normal subject, the variation between the time constants of different parts of the lungs is apparently very small, and the characteristics listed above cannot easily be detected (Fowler, 1952; Otis and his colleagues, 1956). However, many forms of respiratory disease, including asthma and emphysema, result in an increase in the scatter of time constants for different functional units and the characteristics of this type of maldistribution are easily detected.

Effect of Maldistribution of Inspired Air on Gas Mixing

This subject is important for two reasons. Firstly, it constitutes the usual method of detecting certain types of maldistribution. Secondly, it has an adverse effect on most forms of inhalation therapy including inhalation anaesthesia.

Various therapeutic manœuvres require the replacement of the nitrogen in the alveolar gas with a different gas. Examples are the administration of 100 per cent oxygen in severe shunting, replacement of nitrogen with helium to diminish the resistance to breathing, and finally the replacement of nitrogen with nitrous oxide which is very widely practised in general anaesthesia. In each case the nitrogen is washed out and another gas (oxygen, helium or nitrous oxide) is washed in to replace it. Replacement takes place, not only in the alveolar gas, but in all the tissues of the body and this is relatively more important in the case of the more soluble gases (oxygen being a special case since it is consumed within the body and so can never come into equilibrium between the different tissues). The exchange of gases within the different body compartments is a complex story but we can profitably discuss exchange within the lungs at this stage.

If we ignore, for the time being, the exchange of a gas within the tissue compartments, the wash-in and wash-out of gases in the lungs may be considered as an exponential function (Appendix D). Thus if a patient inhales 100 per cent oxygen, the alveolar nitrogen concentration falls according to a wash-out exponential function (*Figure 125*). If, on the other hand, he inhales a mixture of constant helium concentration, the alveolar helium concentration rises according to a wash-in exponential function (*Figure 126*) towards a plateau concentration equal to that in the inspired gas (the gaseous environment). In each case the time constant* of change of alveolar gas is the same and equals:

$$\frac{\text{functional volume of the lungs}}{\text{alveolar ventilation}}$$

If, for example, the lung volume is 3 litres and the alveolar ventilation is 6 litres/minute, the time constant will be 30 seconds.

This makes an important assumption—that every alveolus is ventilated in proportion to its volume. If this is not the case, we must consider not a single time constant, but a whole family of time constants for different functional units of the lungs. Some will therefore exchange rapidly and some slowly. The over-all picture is that of delayed equilibrium, and after a finite interval (say seven minutes) it is found that the alveolar gas concentrations have not changed as rapidly as would otherwise be expected. It may, furthermore, be shown that the wash-out curve is not that of a simple exponential, but shows two or more components, the areas with short time constants being dominant early and the areas with long time constants being dominant later. Several examples may be cited.

If a patient breathes 100 per cent oxygen, the alveolar nitrogen will normally be reduced to less than 2·5 per cent after seven minutes. This fall may be delayed by maldistribution. The fall of nitrogen concentration is the basis of the 'nitrogen wash-out test' but the rate of rise of oxygen concentration is often of direct interest to the anaesthetist and others who are concerned with patients with deranged lung function.

We have already considered the helium wash-in method of measurement of functional residual capacity (page 5). Clearly the rate at which equilibrium

* This time constant should not be confused with the time constant of lung emptying which equals the product of compliance and resistance.

is attained between spirometer and lungs is also a measure of the equality of distribution. Thus the measurement of functional residual capacity can conveniently be combined with a test of distribution.

At a more practical level, all anaesthetists are familiar with the delay in both induction of and recovery from inhalational anaesthesia in patients with advanced lung disease resulting in maldistribution. In cases of emphysema it is as difficult to ensure a rapid induction with inhalational agents as it is to ensure a rapid recovery from inhalational anaesthesia. It is, however, important to remember that delay in exchanging alveolar gas may also be due to hypoventilation, increased dead space or to an increased functional residual capacity. Therefore, delayed change of alveolar gas, after changing the inspired gas, is *not necessarily* indicative of impaired distribution of inspired gas. Nevertheless, it is strongly suggestive if the other quantities are known to be within the normal range.

Bergman (1963b) has compared the nitrogen wash-out curves in a group of patients first while conscious, later when anaesthetized but breathing spontaneously and finally when anaesthetized, paralysed and ventilated artificially. Alveolar ventilation was approximately the same in each case. He analysed the curves to indicate the fraction of total lung volume and the alveolar dilution factor for three components—rapid, intermediate and slow. No changes were found in any of these quantities in the three states which were studied. This is suggestive that either anaesthesia does not result in a change in the spatial distribution of gas, or perhaps that there is a change in spatial distribution which does not influence the pattern or rate of nitrogen wash-out. This remains to be seen, but Bergman has shown unequivocally that the wash-in and wash-out of lung gases should proceed at the same rate during anaesthesia as in the conscious subject.

Effect of Maldistribution on the Alveolar 'Plateau'

If the different functional units of the lung empty synchronously during expiration, the composition of the expired air will be approximately constant after the anatomical dead space gas has been expelled.* This, however, does not occur in maldistribution due to lung disease such as emphysema. In this case, it is usually found that those parts of the lungs which have a defective ventilation for their volume are 'slow', with either high compliance, high resistance or both. Thus they have a prolonged time constant for change of alveolar gas as well as prolonged time constant for emptying and filling. This is hardly surprising since normal respiratory frequencies do not permit uniform distribution in patients with emphysema and, therefore, ventilation is preferentially distributed in favour of the fast alveoli. Since the slow alveoli may well have the larger volume, it will be seen that the two types of maldistribution are linked. Some functional units are slow to fill and empty, and these are hypoventilated for their volume; therefore they are slow to respond to a change in the inspired gas composition. This forms the basis of an important test of maldistribution which, unlike the multi-breath nitrogen wash-out test (described above), will only detect maldistribution if there is sequential emptying of functional units of lung such as we have described above. The test is shown diagrammatically in *Figure 72*. The subject, who has been breathing

* During expiration the P_{CO_2} rises slightly while the P_{O_2} falls since the subject is effectively breath holding once expiration commences.

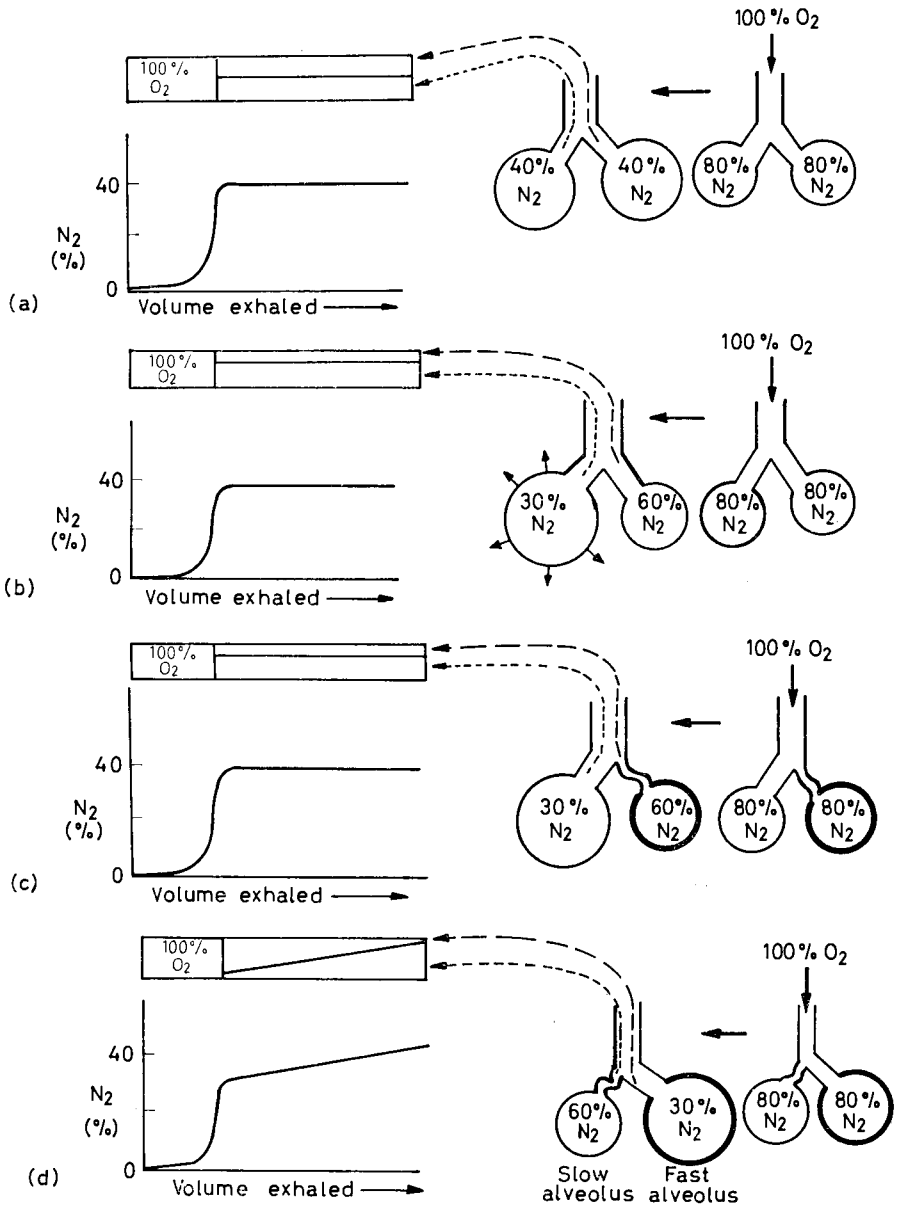


Figure 72. The single-breath nitrogen wash-out test in different types of maldistribution. Reading the diagram from right to left, the subject inhales a deep breath of 100 per cent oxygen and then exhales into a nitrogen meter. (a) Normal subject with uniform distribution. (b) Maldistribution due to non-uniform pull of inspiratory muscles. (c) Maldistribution due to non-uniform mechanical factors in lung units but all having the same time constant. (d) Maldistribution due to non-uniform mechanical factors in lung units resulting in different time constants. Only this type of maldistribution alters the slope of the curve of the expired nitrogen

air, takes a single deep breath of 100 per cent oxygen sufficient to raise the alveolar oxygen concentration to about 50 per cent. The patient then exhales deeply and the nitrogen concentration is measured at the patient's lips. (It would be just as satisfactory to monitor the oxygen concentration, but it happens that it is much easier to measure nitrogen concentrations by an instrument with a sufficiently rapid response.) We may now consider what is found under four different circumstances (*Figure 72a–d*).

(1) *Figure 72a* shows two identical functional units. Following the inspiration of a single breath of oxygen, the nitrogen concentration in each unit is reduced to the same value and the exhaled nitrogen concentration must therefore remain constant throughout the latter part of expiration.

(2) *Figure 72b* shows functional units of identical mechanical properties but which are subjected to unequal forces during inspiration. As a result, the nitrogen concentration is reduced by a greater amount in the better ventilated unit. If expiration is passive, the expirate will consist of the same proportion from each unit throughout expiration. Therefore the exhaled nitrogen concentration will be constant throughout the latter part of expiration, at a value intermediate between that of the two units.

(3) *Figure 72c* shows two units of different mechanical properties but which nevertheless have the same time constant. (The unit on the right may be considered as having double the resistance and half the compliance of the unit on the left.) In these circumstances, ventilation will be preferentially distributed to the unit with the higher compliance and lower resistance (*see Figure 71b*). However, if expiration is passive, the expirate will again consist of the same proportion from each unit throughout expiration. Therefore the exhaled nitrogen concentration will remain constant throughout the latter part of expiration as in the previous example.

(4) *Figure 72d* has two units with different time constants resulting from different mechanical properties. These are of the type which were used in *Figure 14* to illustrate fast and slow alveoli. During inspiration of finite length, the faster unit will be preferentially ventilated, and its nitrogen concentration will therefore be lower. During expiration, the faster unit empties more rapidly at first while gas from the slower unit forms a proportionately greater part of the end-expiratory gas. Thus the proportion of gas from the two units changes during expiration and the nitrogen concentration rises progressively.

In examples (2) and (3), there is definite maldistribution of inspired gas, but this is not revealed by the single-breath nitrogen test. Only when the time constants of the units differ will the maldistribution be revealed by the test (as in example (4)). This point is frequently glossed over by those who are chiefly concerned with maldistribution caused by lung disease. This is because maldistribution due to the commoner forms of lung disease is usually associated with different time constants and *sequential emptying*. Therefore, under these circumstances the single-breath nitrogen test is a valid method of detection of maldistribution of inspired gas. Anaesthetists, however, may well be confronted with maldistribution which is not associated with changes in time constants, and which could not be demonstrated by the single-breath nitrogen test. Maldistribution of this type might result from the use of the lateral position, intercostal paralysis or from artificial ventilation.

Before leaving the single-breath nitrogen test, two small points may be noted. Firstly, even with perfect distribution the exhaled nitrogen concentration rises slightly during the latter part of the exhalation. This is because oxygen is being consumed in greater volume than carbon dioxide is being produced. Therefore, the alveolar nitrogen concentration always rises slightly as expiration proceeds. (Normal alveolar gas contains 80–81 per cent nitrogen.) The upper limit of normal is a rise of 1·5 per cent (more in older subjects) between the exhalation of 750 ml. and 1,250 ml. after the inhalation of a large breath of oxygen. The second point is that fast alveoli must inhale more than their share of gas lying in the anatomical dead space. Thus the slow alveoli do have a marginal advantage in that their delayed filling results in the uptake of relatively more uncontaminated fresh gas.

MEASUREMENT OF DEAD SPACE AND DISTRIBUTION OF INSPIRED GAS

Most chapters of this book end with a brief account of the principles of the methods of measurement which are relevant to the matters discussed. This chapter has departed from the usual practice since the methods of measurement not only aid the understanding of dead space but actually constitute the definition of certain quantities. It therefore seemed best to mention the methods of measurement as they arose in the text. For convenience, their location is indicated below.

CHAPTER 8

THE PULMONARY CIRCULATION

The flow of blood through the pulmonary circulation is approximately equal to the flow through the whole of the systemic circulation. It therefore varies from about 6 l./min. under resting conditions to as much as 25 l./min. in severe exercise (Åstrand and his colleagues, 1964). Although the flow rates are similar in the two systems, the pressures are greatly different, pulmonary arterial pressures being approximately one-sixth of systemic. The pulmonary vascular resistance is thus much less than that of the systemic circulation and consequently the pulmonary circulation has little ability to vary the distribution of blood flow within the lung fields. This is in marked contrast to the systemic circulation which is able to vary the distribution of blood flow within very wide limits in response to the changing requirements of the individual. We shall see that the pulmonary circulation, lacking the power of selective distribution, is very markedly affected by gravity with a preponderance of circulation in the dependent parts of the lung fields.

The distribution of the pulmonary blood flow has important consequences on gaseous exchange. We have seen in the last chapter that failure of perfusion of parts of the lung prevents exchange occurring with the gas which ventilates those parts, and it is convenient to consider the ventilation of unperfused regions as dead space ventilation. Localized failure of ventilation means that blood perfusing such parts cannot participate in gas exchange and thus constitutes venous admixture similar in effect to a right-to-left shunt. The two abnormalities are fundamentally similar but the resemblance is masked by the fact that blood flow is continuous while gas flow is tidal. It is helpful to represent both flows as continuous and to consider the lungs as a black box* with a gas inflow and outflow and a blood inflow and outflow (*Figure 73*). The object of this black box is to achieve equilibrium of oxygen and carbon dioxide tensions between the two outflow streams. However, the plumbing of neither side is perfect and in each case the effluent is contaminated with a part of the corresponding inflow. The precise mechanism by which this takes place is often difficult to determine, but it may be possible to obtain valuable guidance on the management of patients by considering the lung as though it functions in the manner shown in *Figure 73.*

PULMONARY BLOOD VOLUME

As a first approximation the right heart pumps blood into the pulmonary circulation, while the left heart pumps away the blood which returns from the

* According to current usage, a 'black box' is a process or device, whose internal workings are not understood by the operator, but whose function is important and may be studied in detail without appreciation of the internal mechanism.

lungs. Therefore, provided that the output of the two sides is the same, the pulmonary blood volume will remain constant. However, very small differences in the outputs of the two sides will result in large changes in pulmonary blood volume if they are maintained for more than a few beats. Harris and Heath (1962) have pointed out that if the stroke output of the left ventricle were persistently to exceed that of the right ventricle by 0·1 ml., the lungs would become exsanguinated within two hours. The mechanism which prevents this happening is not understood, but Starling's law of the heart is probably concerned.

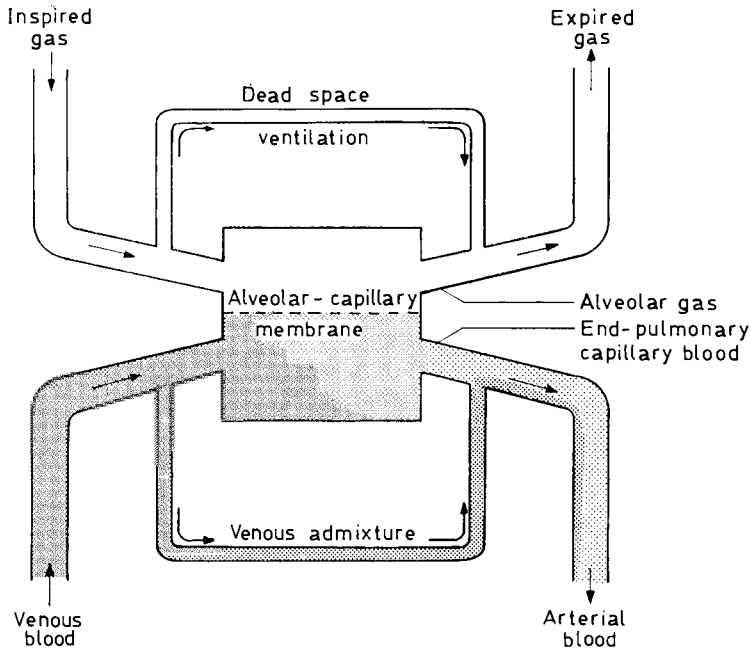


Figure 73. In this functional representation of gas exchange in the lungs, the flow of gas and blood is considered as a continuous process with movement from left to right. Under most circumstances, equilibrium is obtained between alveolar gas and end-pulmonary capillary blood, the gas tensions in the two phases being almost identical. However, alveolar gas is mixed with dead space gas to give expired gas. Meanwhile, end-pulmonary capillary blood is mixed with shunted venous blood to give arterial blood. Thus both expired gas and arterial blood have gas tensions which differ from those in alveolar gas and end-pulmonary capillary blood

When we leave our first approximation and attempt to get nearer to the truth, we see that the relationship between the inflow and outflow of the pulmonary circulation is really rather complicated. *Figure 74* is a summary of some of the relevant anatomical features. The lungs receive a significant quantity of blood from the bronchial arteries which usually arise from the arch of the aorta. Blood from the bronchial circulation returns to the heart in two ways. From a plexus around the hilum, blood from the pleurohilar part of the bronchial circulation returns to the systemic veins via the azygos veins, and this fraction may thus be regarded as normal systemic flow neither arising

from nor returning to the pulmonary circulation. However, another fraction of the bronchial circulation, distributed more peripherally in the lung, passes through post-capillary anastomoses to join the pulmonary veins, constituting an admixture of venous blood with the arterialized blood from the alveolar capillary networks (Marchand, Gilroy and Wilson, 1950).

The paragraph above relates to the normal subject. The situation may be further complicated when blood flows through pre-capillary anastomoses from the bronchial arteries to the pulmonary arteries. The communications have been called 'sperr arteries' meaning muscular vessels which act as sluice gates.

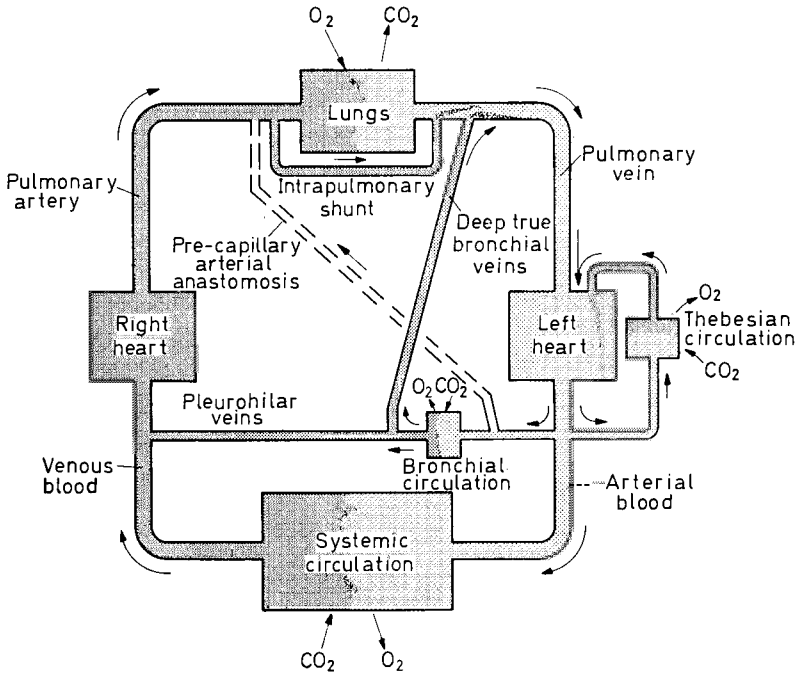


Figure 74. Schema of bronchopulmonary anastomoses and other forms of venous admixture in the normal subject. Part of the bronchial circulation returns venous blood to the systemic venous system (pleurohilar veins) while another part returns venous blood to the pulmonary veins and so constitutes venous admixture. Other forms of venous admixture are the Thebesian circulation of the left heart and flow through atelectatic parts of the lungs. The existence of pre-capillary bronchopulmonary anastomoses in the normal subject is controversial. It will be clear from this diagram why the output of the left heart must be slightly greater than that of the right heart

These anastomoses are thought to be present in the normal subject (Verloop, 1948; von Hayek, 1960), but they are of definite functional importance in cases of pulmonary oligaemia. This has been demonstrated after experimental ligation of a branch of the pulmonary artery in dogs (Cockett and Vass, 1951), but congenital pulmonary atresia is the most important natural cause of the condition. It should be noted that arterial bronchopulmonary anastomoses achieve the same purpose as a Blalock–Taussig operation.

The catalogue of abnormal communications between the pulmonary and

systemic circulations can be continued almost indefinitely, and the reader is referred to the treatise of Aviado (1965). It is not unusual for aberrent pulmonary veins to drain into the right atrium. Furthermore, flow may be reversed through normally occurring channels. Thus, in pulmonary venous hypertension due to mitral stenosis, pulmonary venous blood may traverse the bronchial venous system to gain access to the azygos system.

Factors Influencing Pulmonary Blood Volume

The quantity of blood within the pulmonary circulation is 10–20 per cent of total blood volume, between 500 and 1,000 ml. The volume fluctuates during the cardiac cycle since inflow exceeds outflow during systole. It is also likely that the cyclical pressure changes caused by respiration will influence pulmonary blood volume which has been found to decrease during a Valsalva manœuvre, and during positive pressure breathing (Fenn and his colleagues, 1947). Conversely, it is said that pulmonary blood volume is increased during negative pressure breathing (Slome, 1965).

Posture.—A great many authors, cited by Harris and Heath (1962), are agreed that pulmonary blood volume is directly influenced by posture. When a subject changes from the supine to the erect position the pulmonary blood volume falls by 27 per cent, a change which is of the same order as the decrease in cardiac output under the same circumstances. It is thought that both changes are due to pooling of blood in dependent parts of the systemic circulation.

Drugs.—Since the systemic circulation has much greater vasomotor activity than the pulmonary circulation, it is to be expected that an over-all increase in the tone of capacity vessels will squeeze blood from the systemic into the pulmonary circulation. This may result from the administration of vasoconstrictor drugs, from release of endogenous catecholamines or by passive compression of the body in a G-suit. Conversely, it seems likely that pulmonary blood volume would be diminished when systemic tone is diminished, as for example by sympathetic ganglion blockade. Large decreases in pulmonary blood volume have been reported during spinal anaesthesia, but increases sometimes occurred when the patient was in the Trendelenburg position (Johnson, 1951). In general it may be said that vaso-active drugs produce a complementary relationship between pulmonary and systemic blood volumes.

Pulmonary venous hypertension (due, for example, to mitral stenosis) would be expected to result in an increased pulmonary blood volume. There has, however, been difficulty in the experimental demonstration of any significant change.

Anaesthesia.—There have been few studies of the effect of general anaestheia on pulmonary blood volume. Johnson (1951) found no significant changes when patients received premedication of morphine and scopolamine. Light ether anaesthesia (stage III, plane 2) was associated with a small increase of pulmonary blood volume (+40 ml.) which was not statistically significant. Deep anaesthesia (stage III, plane 3) was associated with a significant fall of pulmonary blood volume (−160 ml.). Barbiturate anaesthesia reduced the pulmonary blood volume in all patients by a mean value of 340 ml., but only half this change was found when curare was used in addition to the barbiturate.

All measurements were carried out prior to the commencement of surgery when there had been no significant changes in total blood volume.

The Extent of the 'Pulmonary Blood Volume'

The measurement of pulmonary blood volume is difficult, and lacks the precision which is obtainable in the measurement of many other circulatory variables.* Harris and Heath (1962) have reviewed the available methods which must lie outside the scope of the present volume. Here it is sufficient to say that they are indirect and most actually measure the 'central blood volume', an indefinite quantity which, apart from the pulmonary vascular system, includes the chambers of the heart and also certain parts of the systemic vascular system depending upon the placement of the catheters used in the measurement technique. Pulmonary capillary volume may be calculated from measurements of diffusing capacity (page 279) and this technique yields values of the order of 80 ml.

In view of the difficulties in measurement, it is perhaps fortunate that pulmonary blood volume is of limited interest from the clinical standpoint, and can often be estimated with sufficient accuracy from the density of the vascular markings seen in a chest radiograph. Considerably greater importance attaches to pulmonary vascular pressures and flow, which are considered in the next two sections of this chapter.

PULMONARY VASCULAR PRESSURES

Pulmonary arterial pressure is only about one-sixth of systemic arterial pressure, although the capillary and venous pressures are not greatly different for the two circulations (*Figure 75*). There is thus only a small pressure drop along the

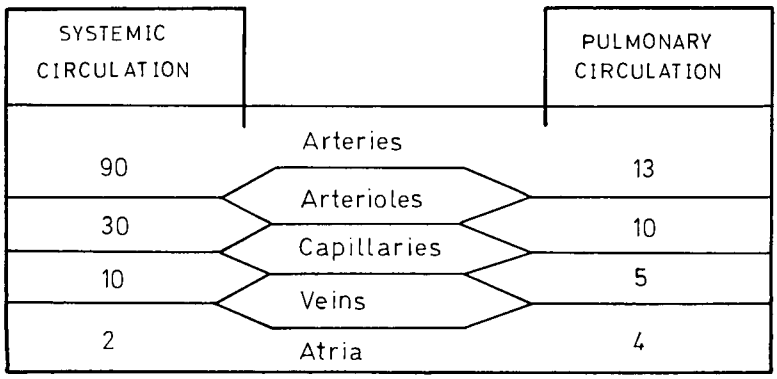


Figure 75. Comparison of pressure gradients along the systemic and pulmonary circulations. (Mean pressures relative to atmosphere, mm Hg)

pulmonary arterioles and consequently little possibility for active regulation of the distribution of the pulmonary circulation. There is also little damping of the arterial pressure wave and the pulmonary capillary blood flow is markedly pulsatile.

* Measurement techniques are outlined in the section starting on page 225.

Consideration of pulmonary vascular pressures carries a special difficulty in the selection of the reference pressure. Systemic pressures are customarily measured with reference to ambient atmospheric pressure. Thus a systolic pressure of 120 mm Hg implies a pressure of 120 mm Hg above atmospheric (i.e. an absolute pressure of 120 + 760 = 880 mm Hg). This approach is not always satisfactory when considering the pulmonary circulation because it gives us insufficiently precise information about the important pressure gradient between the inside of pulmonary capillaries and the extravascular space. Neither does it tell us anything about the pressure gradients which cause the

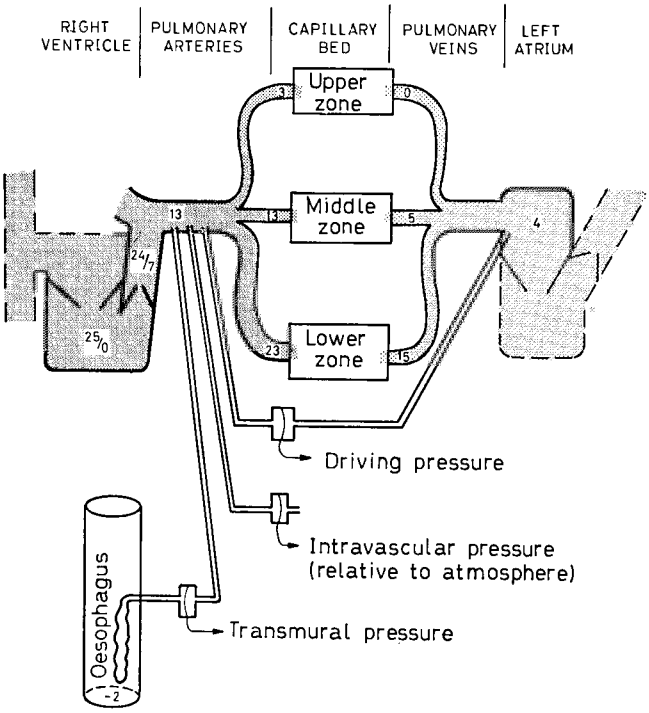


Figure 76. Normal values for pressures in the pulmonary circulation (mm Hg). Systolic and diastolic pressures are shown for the right ventricle and pulmonary trunk. Note the effect of gravity on pressures at different levels in the lung fields. Three differential manometers are shown connected to indicate driving pressure, intravascular pressure and transmural pressure

blood to flow onwards against the pulmonary vascular resistance into the left atrium. We therefore require to distinguish between pressures within the pulmonary circulation expressed in the three different forms listed below. Measurement techniques may be adapted to indicate these pressures directly (*Figure 76*).

Intravascular pressure is the pressure at any point in the circulation relative to atmosphere. This is the customary way of expressing pressures in the systemic circulation.

Transmural pressure is the difference in pressure between the inside of a vessel and the tissue surrounding the vessel. In the case of the larger pulmonary vessels, the outside pressure is the intrathoracic pressure (commonly measured as the oesophageal pressure as in *Figure 76*). In the case of the capillaries, the outside pressure is closer to alveolar pressure, but its precise value is difficult to determine since the relevant space is the interstitial space between the alveolar membrane and the capillary membrane (*Figure 3b*). The pressure in this space is probably intermediate between alveolar and intrathoracic.

The transmural pressure gradient would drive fluid out of the circulation were it not prevented by the osmotic pressure of the plasma proteins, normally about 25 mm Hg. Should this pressure be exceeded by the transmural pressure, pulmonary oedema results and may grossly interfere with gas exchange.

Driving pressure is the difference in pressure between one point in the circulation and another point downstream. The driving pressure of the pulmonary circulation as a whole is the pressure difference between pulmonary artery and left atrium. This is the pressure which overcomes the flow resistance and should be used for determination of vascular resistance.

These differences are far from being solely academic. The capillary transmural pressure gradients may be markedly influenced by the intra-alveolar pressure which may be raised by positive pressure respiration and reduced by the use of a subatmospheric pressure phase during expiration. The former is thus beneficial and the latter detrimental in threatened pulmonary oedema. However, the intracapillary pressure is directly influenced by changes in alveolar pressure (page 225) and account must therefore be taken of the induced change in intravascular pressure.

The difference between pulmonary arterial intravascular pressure (relative to atmosphere) and the pulmonary driving pressure is of importance in distinguishing between different causes of pulmonary hypertension. If the primary lesion is a raised left atrial pressure, the pulmonary arterial intravascular pressure will be raised but the driving pressure will not be increased unless there is a secondary rise in pulmonary vascular resistance. Left atrial pressure is measured by three possible techniques.

(1) Wedge pressures are obtained by advancing the cardiac catheter into the pulmonary artery until it impacts.
(2) The left atrium may be punctured by a needle at bronchoscopy.
(3) The atrial septum may be pierced from a catheter in the right atrium.

Typical normal values within the pulmonary circulation are shown in *Figure 76*. The effect of gravity on the pulmonary vascular pressures may be seen, and it will be clear why pulmonary oedema is most likely to occur in the lower zones of the lungs where the intravascular pressures and the transmural pressure gradients are highest.

Factors Influencing Pulmonary Vascular Pressures

Posture.—It is difficult to study the effect of change of posture on pulmonary blood pressure, since the actual levels of pressure are so low that they are markedly influenced by movement of the reference level. However, it seems

likely that the upright position is associated with a lower pulmonary arterial pressure in patients with pulmonary hypertension (Donald and his colleagues, 1953). Wedge pressures are also reduced. Intrathoracic pressure is also lower in the upright position, so it is unlikely that capillary transmural pressure is greatly affected.

Exercise results in an increased pulmonary blood flow and, with moderate exercise, the pulmonary arterial pressure is raised in the supine but not the upright position (Dexter and his colleagues, 1951). Even in the supine position, the pressure tends to return to the resting level if the exercise is continued (Sancetta and Rakita, 1957).

Intra-alveolar pressure changes up to about 8 mm Hg normally cause an equal change in pulmonary arterial pressure (Lenfant and Howell, 1960). There is a rise in pressure during a Valsalva manœuvre and cyclical changes occur during spontaneous respiration with pressures higher during expiration and lower during inspiration. Information is required on the magnitude of the effect of lung inflation on pulmonary intracapillary pressure. Since small rises in alveolar pressure cause an equal rise in pulmonary arterial intravascular pressure, there should be no reduction in capillary transmural pressure gradient unless the capillary pressure fails to rise as much as the arterial pressure. With larger changes in alveolar pressure it is known that the rise in pulmonary arterial pressure is less than the rise in alveolar pressure and the disparity may be greater in patients with circulatory disorders. Favourable results in the treatment of pulmonary oedema by intermittent positive pressure suggest that this is so (Greene, Dameron and Bush, 1952).

Hypoxia.—Breathing of low concentrations of oxygen is associated with a rise in pulmonary arterial pressure which is related to the resultant arterial saturation (Fritts and his colleagues, 1960). A saturation of 77 per cent results in a rise of pressure of the order of 5 mm Hg. Driving pressure is increased proportionately more than the pulmonary blood flow, and therefore the pulmonary vascular resistance is increased. However, the increased resistance cannot be precisely related to the oxygen saturation of the blood which perfuses the lung.

It is thought that the hypoxic stimulus must arise in the alveoli or the pulmonary capillaries, since the response is identical during forward and retrograde perfusion of the lungs (Duke, 1954). Nevertheless, the mechanism of this response remains obscure. Any generalized or humoral mechanism is discounted by the production of a unilateral increase in pulmonary vascular resistance when a gas mixture deficient in oxygen is breathed by one lung only (*see* below). Most workers are agreed that sympathetic denervation or sympathetic blockade by drugs are equally ineffective in preventing the rise of pulmonary arterial pressure due to hypoxia, and West, Dollery and Naimark (1964) obtained a typical response in an isolated dog lung preparation. Whatever the mechanism of this response, it is clear that it has potential teleological significance as a means of diverting the pulmonary blood flow away from regions in which the oxygen tension is low. The subject is discussed at great length by Aviado (1965).

Hyperoxia has little effect upon pulmonary arterial pressure in the normal subject, but many authors have reported a fall in patients with chronic pulmonary disease. This is not always accompanied by a proportionate fall of pulmonary blood flow and, in such cases, oxygen reduces the pulmonary vascular resistance.

Hypercapnia.—Fall of pH due to hypercapnia or metabolic acidosis causes a sharp rise in pulmonary arterial pressure and pulmonary vascular resistance (Barer, Howard and McCurrie, 1967).

Drugs.—Acetylcholine has been used extensively in studies of the pulmonary circulation. When introduced into the pulmonary artery, the rate of hydrolysis is so rapid that the drug is destroyed before it can act upon the systemic circulation. Acetylcholine results in a relaxation of vasomotor tone, causing the pulmonary arterial pressure to fall by an amount which depends on the tone present before the administration of the drug. The response to acetylcholine may thus be used as an indicator of the degree of vasomotor tone that exists in the pulmonary circulation. Small falls of pressure occur in the normal subject but much greater falls occur in hypoxic subjects and those with pulmonary hypertension resulting from congenital heart disease, emphysema or mitral stenosis (Harris and Heath, 1962). A number of references cited by these authors concur in the view that atropine does not affect pulmonary arterial pressure and is without vasomotor action of the pulmonary circulation. However, Daly, Ross and Behnke (1963) reported a fall in pressure following 2 mg. of atropine (intravenously), and Nunn and Bergman (1964) suggested that this might be a cause of the increase in alveolar dead space which they found to follow the administration of atropine. Sympathomimetic drugs which act primarily upon the alpha receptors result in an increase in pulmonary arterial pressure, while those drugs which act primarily upon the beta receptors cause a fall of pressure, particularly when this is elevated. Ganglion-blocking agents generally cause a fall in pressure and this has also been noted in the case of aminophylline. The effects of drugs have been extensively reviewed by Harris and Heath (1962) and Aviado (1965) to whom reference should be made.

Anaesthesia.—Our knowledge of the effects of anaesthesia on pulmonary vascular pressures is still very incomplete. The principal studies are summarized in *Figure 77*, which shows changes in pulmonary arterial pressure (*Y* axis) plotted against changes in pulmonary blood flow (*X* axis). In general the pulmonary blood flow (cardiac output) was either unchanged or somewhat reduced. The pulmonary arterial pressure was markedly increased during ether anaesthesia (spontaneous respiration and artificial ventilation) while, with cyclopropane, the pressure was only increased during spontaneous respiration when the P_{CO_2} was elevated to 55 mm Hg.

During anaesthesia with barbiturate and curare there was a moderate elevation of pulmonary arterial pressure, during spontaneous respiration, but it was noted that there was a 'greatly decreased respiratory volume' in several of these patients and hypoxia was often present (Johnson, 1951).

The reader should not be tempted to infer the pulmonary vascular resistance from all of the studies illustrated in *Figure 77*. It seems very unlikely that the

elevated pulmonary arterial pressure could be due to increased blood flow, but most of the studies fail to distinguish between a true increase in the pulmonary vascular resistance and a raised left atrial pressure.

Disease.—Many forms of pulmonary disease are associated with a rise in pulmonary vascular pressures and these conditions are of considerable practical concern to the anaesthetist. Mitral stenosis and incompetence are the principal conditions leading to an elevation of pressure in the left atrium. It will be clear that the maintenance of the pulmonary driving pressure requires a corresponding increase of the pulmonary arterial pressure, but this must be associated with a rise of pulmonary capillary pressure as well. In many cases of mitral stenosis, there is a secondary increase in pulmonary vascular resistance which

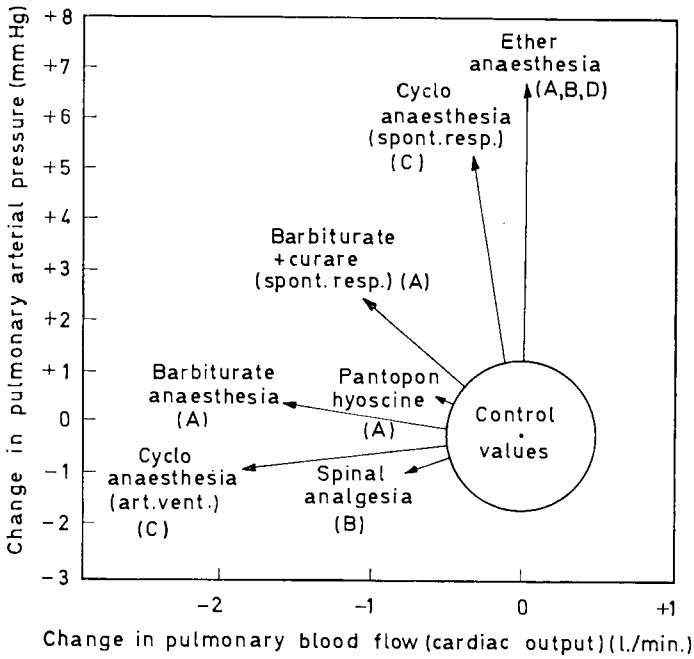


Figure 77. A summary of changes in the pulmonary circulation which have been reported during anaesthesia. No significant changes have been reported during halothane anaesthesia (Wyant and his colleagues, 1958), or with curare and artificial ventilation (Wyant, Chang and Merriman, 1962). (A) Johnson (1951). (B) Wyant, Donaldson and Merriman (1961). (C) Etsten, Reynolds and Li (1955). (D) Wyant, Chang and Merriman (1962)

results in further elevation of the pulmonary arterial pressure. The cause of this change is unknown. The work of the right ventricle is increased and, in severe cases, increased vascular resistance limits the benefit accruing from mitral valvotomy since the mitral valve is no longer the only site of increased resistance to the circulation. Pulmonary vascular resistance rises in many forms of chronic lung disease and also in cases of pulmonary embolus. In a small number of patients the change appears to be primary and analogous to systemic hypertension.

Pulmonary hypertension may result from an increased pulmonary blood flow. However, following pneumonectomy, the remaining lung, if healthy, appears to be able to take the entire resting pulmonary blood flow without rise in pulmonary arterial pressure. The most important pathological cause of increased flow is left-to-right shunting through a patent ductus arteriosus, atrial or ventricular septal defects. Under these circumstances the pulmonary circulation is greater than the systemic circulation and may be sufficient to result in pulmonary hypertension, even with normal vascular resistance. However, secondary changes commonly result in an increase in vascular resistance, causing a further rise in pulmonary arterial pressure.

Pulmonary hypotension results from pulmonary atresia and, as we have seen, this induces an increased flow through pre-capillary anastomoses from the bronchial circulation, collateral flow sometimes being as great as one litre per minute.

PULMONARY BLOOD FLOW

Total pulmonary blood flow is approximately equal to cardiac output and is a topic which belongs to the field of circulation rather than respiration. We shall not therefore consider total pulmonary blood flow in any more detail than is necessary for an understanding of the changes in pulmonary vascular pressure and resistance. As anaesthetists, however, we are greatly concerned with the distribution of pulmonary blood flow, and the next chapter will be devoted to this important subject.

Methods for the measurement of pulmonary blood flow are outlined at the end of this chapter, but at this stage it should be pointed out that the older methods of measurement of cardiac output (Fick and dye) measure the pulmonary capillary blood flow, together with the venous admixture (*Figure 73*). On the other hand, the body plethysmograph measures only the pulmonary blood flow. In this method, the alveoli are filled with nitrous oxide at a concentration of about 15 per cent, and the amount of nitrous oxide taken up by the blood is measured by whole body plethysmography. If the mean alveolar P_{N_2O} and the solubility of nitrous oxide in blood are known, it is possible to calculate the pulmonary blood flow on the assumption that the alveolar P_{N_2O} equals the arterial P_{N_2O} and the mixed venous P_{N_2O} is zero. The method may be used to measure the instantaneous capillary blood flow, which is found to be pulsatile.

PULMONARY VASCULAR RESISTANCE

Vascular resistance is an expression of the relationship between driving pressure and flow, as in the case of resistance to gas flow (*Figure 21*). There are, however, important differences. It will be remembered that when gases flow through rigid tubes the flow is either laminar, turbulent, or a mixture of the two. In the first case pressure increases in direct proportion to flow rate and the resistance remains constant (Poiseuille's law). In the second case pressure increases according to the square of the flow rate, and the resistance increases with flow. When the type of flow is mixed, the pressure rises in proportion to the flow rate raised to a power between one and two, typical examples being shown in *Figure 27*.

The circumstances differ in the case of blood since the tubes through which

the blood flows are not rigid, but tend to expand as flow is increased, particularly in the pulmonary circulation. Consequently the resistance tends to fall as flow increases and the plot of pressure against flow rate may be neither linear nor curved-with-the-concavity-upwards, but curved-with-the-concavity-downwards. As an added complication, blood is a non-Newtonian fluid (due to the presence of the corpuscles) and its viscosity varies with the shear rate and therefore its linear velocity through tubes. The situation is thus two degrees more complicated than in the case of gas flow, although the practical importance of these points should not be exaggerated. In fact, regardless of these considerations, there is a widespread convention that vascular resistance should be expressed as though the vessels were rigid and Poiseuille's law was obeyed. Resistance is usually expressed in the form directly analogous to electrical resistance which is used for laminar gas flow (*Figure 21*):

$$\text{resistance} = \frac{\text{driving pressure}}{\text{flow rate}}$$

In the case of the pulmonary circulation, the driving pressure is the difference in pressure between pulmonary artery and left atrium. Sometimes the pressure in the left atrium is measured directly by atrial puncture, but more often the 'wedge pressure' taken at cardiac catheterization is considered to be representative of pulmonary venous pressure. Flow rate is usually taken as cardiac output.

Vascular resistance may be expressed in terms of any convenient units of pressure and flow rate such as mm Hg for driving pressure and l./min. for blood flow. If absolute units are preferred, driving pressure may be expressed in dynes per square centimetre (dyn/sq. cm.), the conversion factor being 1,333 (*see* Appendix B) and blood flow rate in cc./sec. Resistance is then expressed in units of dyn sec. cm^{-5},* the normal value for the pulmonary circulation being of the order of 100. The measurement of pulmonary vascular resistance is important not only in the diagnosis of the primary cause of pulmonary hypertension, but also for the detection of increased pulmonary vascular resistance which often develops in patients in whom the primary cause of pulmonary hypertension is raised left atrial pressure.

Pulmonary Vascular Resistance during Anaesthesia

Figure 77 shows changes in the intravascular pulmonary arterial pressure plotted against cardiac output reported under various forms of anaesthesia. The reader was cautioned against inferring any changes in pulmonary vascular resistance from these data since in only one study was the pulmonary venous pressure measured. Most of the authors have nevertheless proceeded to calculate 'pulmonary vascular resistance' on the assumption (or in the hope) that left atrial pressure approximated to zero and that the pulmonary arterial intravascular pressure was the same as the pulmonary driving pressure. If the left atrial pressure were raised, then the erroneously calculated 'pulmonary vascular resistance' would in fact equal the sum of the true vascular resistance and an ill-defined quantity related to the elevation of the left atrial pressure.

* Vascular resistance is frequently expressed in units of dyn/sec./cm^{-5}. This is incorrect (*see* Appendix A).

Further elucidation requires measurement of left atrial pressures and most investigators have been unwilling to subject anaesthetized patients to this procedure. There is, however, one important study which has reported wedge pressures in addition to pulmonary arterial pressures as shown in *Table 20.*

Table 20

	Control	*Ether anaesthesia*		*Post-control*	*Units*
		Spontaneous respiration	*Artificial ventilation*		
Pulmonary arterial pressure	15·3	24·6	23·7	22·9	mm Hg
Wedge pressure	8·2	11·2	17·2	12·7	mm Hg
Driving pressure	7·1	13·4	6·5	10·2	mm Hg
True pulmonary vascular resistance	102	160	96	109	dyn sec. cm^{-5}

After Wyant, Donaldson and Merriman (1961).

We may note the following points from the study.

(1) Left atrial pressures were elevated throughout the study, possibly due to use of breathing apparatus which elevated the alveolar pressure, and thence the intrathoracic pressure.

(2) Left atrial pressure was markedly elevated during artificial ventilation and accounted for most of the pulmonary hypertension.

(3) There was a true increase in pulmonary vascular resistance during ether anaesthesia with spontaneous respiration.

(4) There was no increase in true pulmonary vascular resistance during ether anaesthesia with artificial ventilation.

It is not at all surprising that the left atrial pressures should be elevated during anaesthesia and this is inevitable during artificial ventilation by I.P.P., unless a subatmospheric pressure is used during expiration. The increase in true pulmonary vascular resistance during ether is probably due to the ether itself. It is, however, curious and unexpected that this unequivocal effect should be abolished by artificial ventilation.

Localization of the Pulmonary Vascular Resistance

It will be recalled that by far the greatest part of the systemic resistance is within the arterioles, along which the pressure falls from a mean value of about 90 mm Hg down to about 30 mm Hg (*Figure 75*). This pressure drop largely obliterates the pulse pressure wave, and the capillary flow is not pulsatile to any great extent. In the pulmonary circulation, the pressure drop along the arterioles is very much smaller than in the systemic circulation, being probably only of the order of 3 mm Hg. A further pressure drop of about 5 mm Hg occurs along the length of the pulmonary capillaries (*Figure 75*). Thus the pulmonary capillary bed constitutes about 60 per cent of the total vascular resistance of the pulmonary circulation, in contrast to the systemic capillary bed which constitutes only 25 per cent of the total vascular resistance of the systemic circulation.

It seems likely that the nature of vascular resistance is different in the arteriolar and capillary sections of the pulmonary circulation. Such vasomotor activity as exists in the pulmonary circulation is probably confined to the arteriolar section. Both parts are, however, passively influenced by the degree of distension of the alveoli and indeed of the vessels themselves.

Effect of Inflation of the Lung

The mechanism of the effect of inflation of the lung on the pulmonary vessels is extremely complex, but the quantitative effect on pulmonary vascular resistance has recently been clarified. Much confusion and dispute has arisen

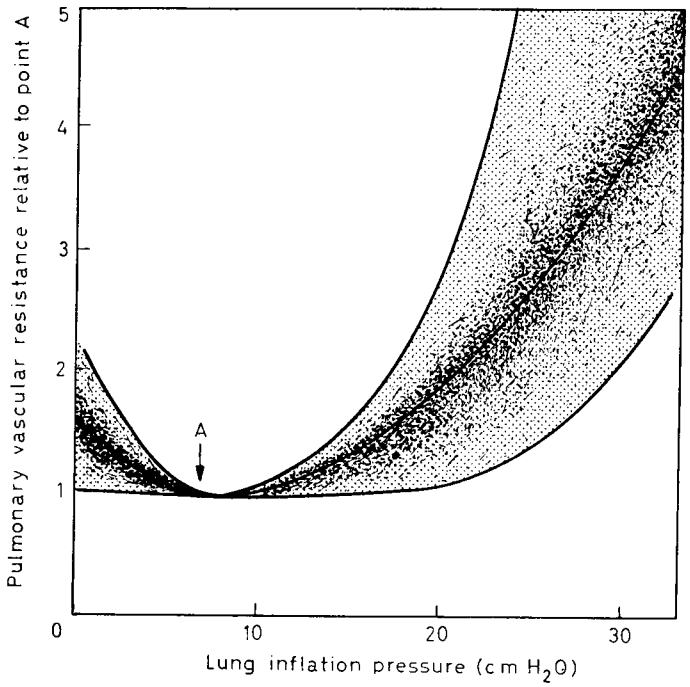


Figure 78. The mean and range of the response of pulmonary vascular resistance to changes in lung inflation pressure, relative to the resistance at the point A corresponding to the F.R.C. The diagram is composite and incorporates results reported by Burton and Patel (1958) for open-chested rabbits, Banister and Torrance (1960) for isolated cats' lungs, and Whittenberger and his colleagues (1960) for open-chested dogs

in the past and it appears that this has, to a large extent, been due to failure to appreciate that pulmonary vascular resistance must be derived from driving pressure and not from pulmonary arterial or transmural pressure. This is very important since inflation of the lungs normally influences the pressure in the oesophagus, pulmonary artery and left atrium.

When pulmonary vascular resistance is correctly calculated from the driving pressure, there is reasonable agreement that, in the open-chested or isolated preparation, the pulmonary vascular resistance is minimal at an inflation pressure of the order of 5–10 cm H_2O (*Figure 78*). Change in inflation

pressure may have very little effect upon resistance but the usual response is for the resistance to increase markedly with a rise of pressure and, to a less extent, with a fall of pressure. The response to complete collapse (zero inflation pressure) is variable, the mean change being of the order of a 50 per cent increase, probably due to kinking of vessels. There is certainly no massive increase in resistance as a result of acute collapse, and there are therefore no grounds to support the comforting myth that circulation immediately ceases through an *acutely* collapsed lung or section of a lung. Indeed, this fallacy has been directly exploded by Bjork (1953) and by Aviado (1960). In *longstanding* collapse, the circulation is reduced but this is due to structural changes in the vessels.

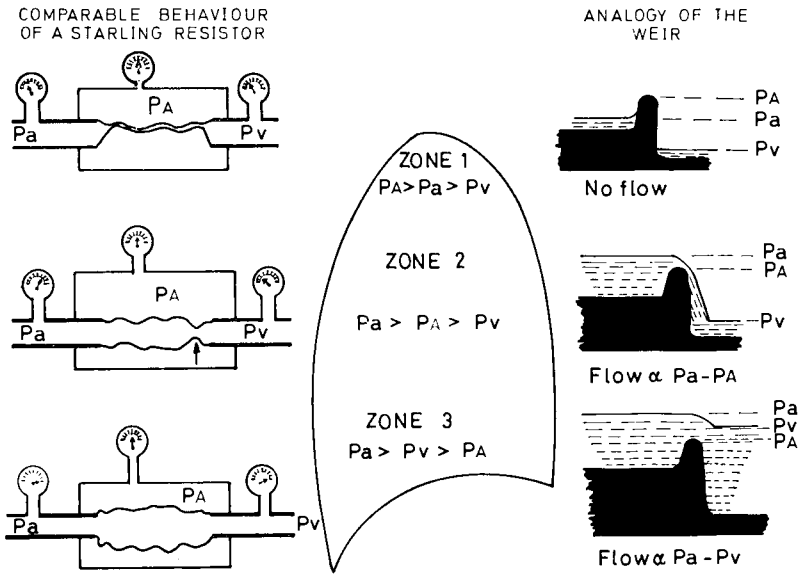


Figure 79. The effect of gravity upon pulmonary vascular resistance is shown by comparison with a Starling resistor (left) and with a weir (right). Pa, *pressure in pulmonary artery;* PA, *pressure in alveoli;* Pv, *pressure in pulmonary vein (all pressures relative to atmosphere). See text for full discussion*

Although it is possible to determine the gross effect of inflation of the lungs upon pulmonary vascular resistance, it is less easy to discover the mechanism of this effect. It seems likely that inflation of the lungs increases the calibre and the volume of the larger blood vessels. This is achieved by the tethering effect of surrounding lung tissue which is sufficient to develop substantial subatmospheric pressures in the large vessels during expansion of the isolated non-perfused lung (Howell and his colleagues, 1961). However, opposite changes occur in the smaller vessels which are collapsed as the lung is expanded by inflation.

The interplay of alveolar pressure, flow rate and vascular resistance is best considered by dividing the lung field into three zones (West, Dollery and Naimark, 1964; West and Dollery, 1965). In the upper zone (zone 1 of *Figure 79*), the pressure within the arterial end of the collapsible vessels is less than the

alveolar pressure, and therefore insufficient to open the vessels which remain collapsed. The behaviour of these vessels is similar to that of a Starling resistor, which is a thin-walled rubber tube placed in a reservoir whose pressure can be varied (*Figure 79*). Provided the pressure outside the tube exceeds the pressure inside, there can be no flow regardless of the venous pressure, which is thus irrelevant: this is the condition in the upper parts of the lungs of the human subject in the upright position. The situation is analogous to a weir in which the upstream water level is below the top of the weir.

In the mid-zone (zone 2 of *Figure 79*), the pressure at the arterial end of the collapsible vessels exceeds the alveolar pressure and, under these conditions, a collapsible vessel, behaving like a Starling resistor, permits flow in such a way that the flow rate depends upon the arterial-to-alveolar pressure difference. (Resistance in the Starling resistor is concentrated at the point marked with the arrow in *Figure 79*.) The larger the difference, the more widely the collapsible vessels will open and the lower will be the vascular resistance. Note that the venous pressure is still not a factor which affects flow or vascular resistance. This condition is still analogous to the weir with the upstream depth (head of pressure) corresponding to the arterial pressure, and the height of the weir corresponding to alveolar pressure. Clearly the flow of water over the weir depends solely on the difference in height between the top of the weir and the upstream water level. The depth of water below the weir (analogous to venous pressure) cannot influence the flow of water over the weir unless it rises above the height of the weir.

In the lower zone (zone 3 of *Figure 79*) of the lungs the pressure in the venous end of the capillaries is above the alveolar pressure, and under these conditions a collapsible vessel behaving like a Starling resistor will be held wide open and the flow rate will, as a first approximation, be governed by the arterial-to-venous pressure difference (the driving pressure) in the normal manner for the systemic circulation. However, as the intravascular pressure increases in relation to the alveolar pressure, the collapsible vessels will be further distended and their resistance will be correspondingly reduced. Returning to the analogy of the weir, the situation is now one in which the downstream water level has risen until the weir is completely submerged and offers little resistance to the flow of water, which is largely governed by the difference in the water level above and below the weir. However, as the levels rise further, the weir is progressively more and more submerged and what little resistance it offers to water flow is still further diminished. The concept of the weir is particularly helpful and was introduced by Permutt and Riley (1963) as the 'vascular waterfall'.

So far we have not mentioned the critical closing pressure of the pulmonary vessels (Burton, 1951). Current views suggest that the vessels of the lungs collapse at a pressure which is very close indeed to the alveolar pressure; that is to say that their critical closing pressure is extremely low (West and Dollery, 1965). The observations of these authors (and those reported by West, Dollery and Naimark in 1964) suggest that pulmonary blood flow ceases in any region where the alveolar pressure is in excess of the pressure at the arterial end of the collapsible vessels but that it recommences as soon as the vascular pressure exceeds the alveolar pressure. Simple hydrostatic considerations thus seem to define the amount of lung which is not perfused.

If the lungs are passively inflated by positive pressure, the pulmonary capillaries would clearly collapse if the pulmonary vascular pressures were to remain unchanged. In fact, the pulmonary vascular pressures normally rise by an amount almost exactly equal to the change in alveolar pressure up to inflation pressures of about 8 mm Hg (Lenfant and Howell, 1960). Beyond this the rise in intravascular pressure is less than the rise in alveolar pressure and the cut-off by the mechanism of the Starling resistor operates over a larger area of the lung field. This has been demonstrated as an increase in physiological dead space during positive pressure breathing (Bitter and Rahn, 1956; Folkow and Pappenheimer, 1955). One might therefore expect that the physiological dead space of anaesthetized patients would be greater during artificial ventilation than during spontaneous respiration; the author, however, has been unable to demonstrate this (Nunn and Hill, 1960).

Structural Factors which Influence Pulmonary Vascular Resistance

Organic obstruction of pulmonary blood vessels is important in a wide variety of conditions. Obstruction from within the lumen may be caused by emboli (thrombus, fat or gas) or by thrombosis (e.g. the chicken fat thrombus formed when death is imminent). Obstruction arising within the vessel wall is probably the cause of eventual reduction of flow through collapsed areas, and medial hypertrophy causes an increase in vascular resistance in certain cases of pulmonary hypertension due to obstruction of the outflow tract (e.g. mitral stenosis). Kinking of vessels may cause partial obstruction during extreme reduction of lung volume (*Figure 78*). Obstruction arising from outside the vessel wall may be due to a variety of pathological conditions (tumour, abscess, etc.) or to surgical manipulations during thoracotomy. Finally, vessels may be destroyed in emphysema and certain inflammatory conditions, causing a reduction in the total pulmonary vascular bed and an increase in vascular resistance.

PRINCIPLES OF MEASUREMENT OF PULMONARY CIRCULATION

Pulmonary Blood Volume

Reference has already been made to the review of Harris and Heath (1962) for methods of measurement of pulmonary blood volume. Available methods are based on the technique used for measurement of cardiac output by dye dilution (*see* page 228). In essence, the dye is injected into a central vein and its concentration is recorded in samples aspirated from some point in the systemic arterial tree. Cardiac output is determined by the method described below, and then the interval is measured between the time of the injection of the dye and the mean arrival time of the dye at the sampling point. Cardiac output is multiplied by this time interval to indicate the amount of blood lying between injection and sampling sites. Assumed values for the extrapulmonary blood are then subtracted to indicate the intrapulmonary blood volume.

It is not at all easy to obtain satisfactory results with this method. The 'mean arrival time of the dye' is difficult to determine and the correction for the extrapulmonary blood volume can be little more than an inspired guess but

may be improved by injection into the pulmonary artery with sampling from the left ventricle. It may be better to omit the correction and use the term 'central blood volume' which implies an appropriate lack of definition.

Pulmonary capillary blood volume may be measured as a byproduct of the measurement of pulmonary diffusing capacity, and the method is discussed in Chapter 10.

Pulmonary Vascular Pressures

Pressure measurements within the pulmonary circulation are almost always made with electronic differential pressure transducers. These invariably have a diaphragm which is deformed by a pressure difference across it. The movement of the diaphragm may be transduced to an electrical signal in a variety of ways. Its movement may influence special resistors of which the resistance is a function of their length (strain gauge). The diaphragm may form one plate of a capacitor of which the other plate is fixed. As the diaphragm is moved the distance between the plates changes and this alters the capacitance of the device (capacitance manometer). Finally, the diaphragm may be linked to the core of a coil whose inductance is thus altered by movements of the diaphragm (inductance manometer). It is relatively simple for changes in resistance, capacitance or inductance to be detected, amplified and displayed as indicative of the pressure across the diaphragm of the transducer.

The space on the reference side of the diaphragm is in communication with atmosphere, oesophageal balloon or left atrial blood, as the case may be (*Figure 76*). The other side of the diaphragm is filled with a liquid (usually heparinized saline) which is in direct communication with the blood of which the pressure is being measured.

If the system is to have the ability to respond to rapid changes of pressure, damping must be reduced to a minimum. This requires the total exclusion of bubbles of air from the manometer and connecting tubing, and the intravascular cannula must be unobstructed. Damping does not influence the measurement of mean pressure but reduces the apparent systolic pressure and increases the apparent diastolic pressure. The basic principles of pressure transducers have been reviewed by Leraand (1962) and sources of error in their use have been described by Crul (1962).

These methods do not measure absolute pressure and can only be used for comparison with a primary standard (such as a column of mercury of known height). Electrical signals are often used as secondary standards, but must be checked at intervals against primary standards.

Electrical manometry yields a plot of instantaneous pressure against time (*Figure 80a*). From this it is often necessary to calculate the mean pressure. This is *not* simply:

$$\frac{\text{systolic pressure} + \text{diastolic pressure}}{2}$$

since the duration of diastole is greater than that of systole and therefore the effective or integrated mean must be weighted in favour of the diastolic pressure. Mean pressure is often taken to be one-third of the way from diastolic to systolic pressure (i.e. diastolic plus one-third of pulse pressure), but it is more correctly derived from assessing the area under the instantaneous pressure

curve. A rectangle is then constructed with length equal to the duration of one cardiac cycle and area equal to the area under the pressure curve over the same time interval. The height of the rectangle indicates the mean pressure.

More simply, the mean pressure may be determined by damping the measurement (or display) of the instantaneous pressure. This may be done on the actual measurement system (e.g. by allowing the intravascular cannula to become partly occluded) or by electrical means. These methods are illustrated in *Figure 80b*. It should be noted that it is generally easier to measure mean

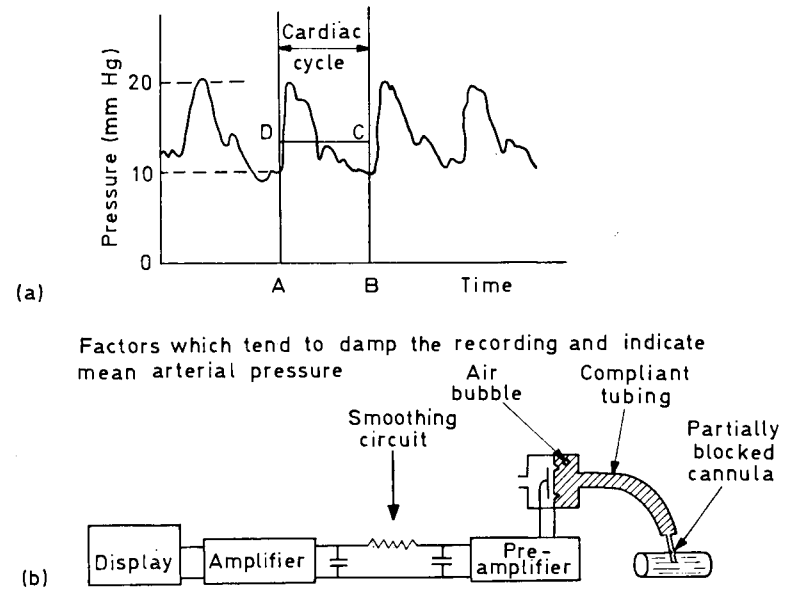


Figure 80. Determination of mean pulmonary arterial pressure. (a) An actual trace of instantaneous intravascular pulmonary arterial pressure during four cardiac cycles. For the second cycle, a rectangle has been constructed (ABCD) which has an area equal to that under the curve over the same time interval. The height of the rectangle (AD) indicates the effective integrated mean pressure. It will be seen to be approximately equal to diastolic pressure plus one-third of pulse pressure. (b) Factors which tend to damp the recording of instantaneous pressure (i.e. lower the indicated systolic pressure and raise the indicated diastolic pressure) tending towards an indication of the integrated mean pressure. Some of these factors are accidental (e.g. air bubble or blocked cannula) but others (e.g. smoothing circuit) may be employed deliberately to avoid the tedious method of calculation of mean pressure shown in (a)

pressure than instantaneous pressure. Exactly similar considerations apply to the determination of mean intrathoracic pressure (page 99). In the case of the intrathoracic pressure, the relevant cycle is, of course, that of respiration and not the heart beat.

Pulmonary Blood Flow

The total flow of blood through the pulmonary circulation may be measured by three groups of methods, each of which contains many variants (Wade and Bishop, 1962).

The Fick principle states that the amount of oxygen picked up from the respired gases equals the amount added to the blood which flows through the lungs. Alternatively, the amount of carbon dioxide exhaled equals the amount lost by the blood which flows through the lungs. In the case of oxygen it is evident that the oxygen uptake of the subject must equal the product of pulmonary blood flow and arteriovenous oxygen content difference. This is conveniently expressed in Pappenheimer symbols (see Appendix C):

$$\dot{V}o_2 = \dot{Q}\,(Ca_{o_2} - C\bar{v}_{o_2})$$

therefore

$$\dot{Q} = \frac{\dot{V}o_2}{Ca_{o_2} - C\bar{v}_{o_2}}$$

All the quantities on the right-hand side can be measured, although determination of the oxygen content of the mixed venous blood requires catheterization of the right ventricle or preferably the pulmonary artery.

Interpretation of the result is less easy. The calculated value includes the intrapulmonary arteriovenous shunt, but the situation is complicated beyond the possibility of easy solution if there is appreciable extrapulmonary admixture of venous blood (*Figure 74*).

Indirect methods avoid right heart catheterization by calculating the composition of mixed venous blood by measurement of changes in composition of rebreathed gas. This is only practicable in the case of carbon dioxide, and determination of mixed venous Pco_2 is described in Chapter 11. Unfortunately, the derivation of mixed venous CO_2 content is not sufficiently accurate for the method to be a satisfactory alternative to the direct Fick method.

One important source of error is of particular concern to the anaesthetist. Between the pulmonary capillaries and the apparatus for measurement of oxygen consumption is a large volume of gas, comprising the subject's lungs, air passages, mouthpiece, valve box, etc. The method requires that the amount of oxygen in this volume remain constant throughout the period of measurement (1–5 minutes). Clearly both the volume of the space and the composition of its contents must not be allowed to vary, and this can usually be achieved when the subject is breathing air. If the concentration of oxygen is allowed to alter during the period of measurement, a considerable error may be introduced. Thus if a patient breathing nitrous oxide and oxygen is connected to a closed-circuit spirometer containing oxygen for the measurement of oxygen uptake, nitrous oxide will pass from the patient to the spirometer and change both the total gas volume and its composition. This difficulty may be overcome, but only by quite elaborate methodology (Nunn and Pouliot, 1962). Measurement of oxygen consumption is discussed at the end of Chapter 12.

Dye dilution.—Currently the most popular technique for measurement of cardiac output is by dye dilution. Perhaps its most important virtue is that it avoids right heart catheterization. Measurement can be repeated up to at least 20 times at three-minute intervals.

An indicator substance is suddenly introduced into a large vein and its concentration is measured continuously at a sampling site in the systemic

arterial tree. *Figure 81a* shows the method as it is applied to continuous non-circulating flow as, for example, of fluids through a pipeline. In the top right-hand corner is shown the sudden injection of the bolus of dye. It is carried downstream past a sampling point where some of the fluid in the pipe is drawn

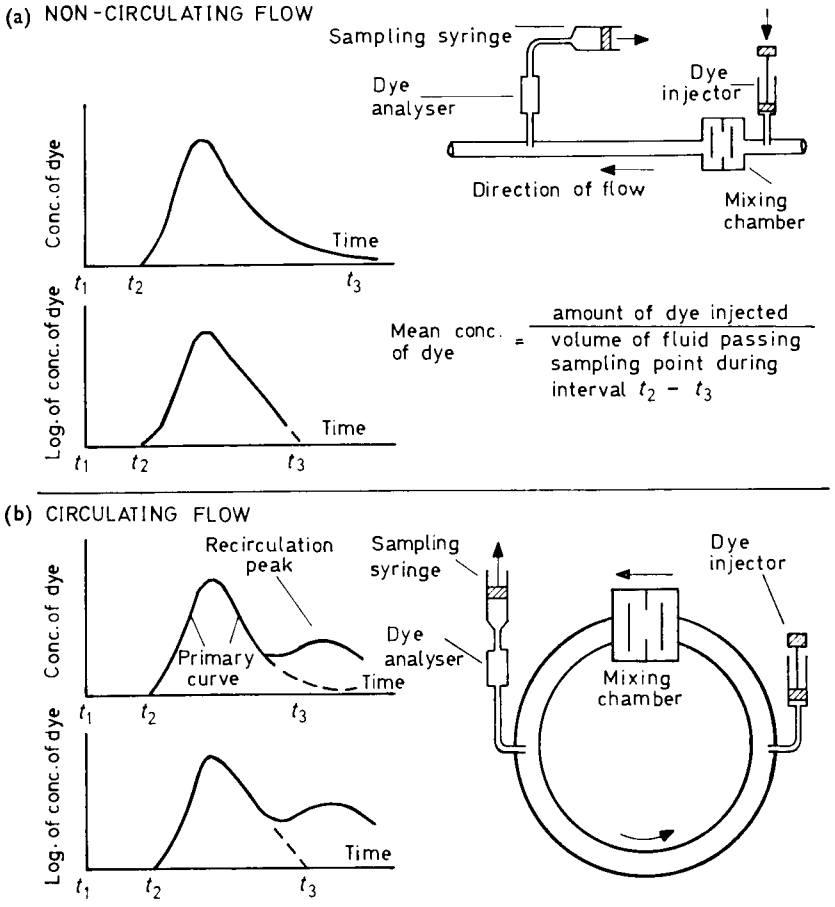


Figure 81. Measurement of flow by dye dilution. (a) shows the measurement of continuous non-circulating flow rate of fluid in a pipeline. The bolus of dye is injected upstream and its concentration is continuously monitored downstream. The relationship of the relevant quantities is shown in the equation. Mean concentration of dye is determined from the area under the curve as shown in Figure 80. (b) indicates the more complicated situation when recirculation occurs and the front of the circulating dye laps its own tail, giving a recirculation peak. Reconstruction of the primary curve is based on extrapolation of the primary curve before recirculation occurs. This is facilitated by the fact that the down curve is exponential and therefore a straight line on a logarithmic plot

through a device which performs a continuous analysis of the concentration of the dye in the fluid. The concentration is displayed on the Y axis of the graph against time on the X axis. The dye is injected at time t_1 and is first detected at the sampling point at time t_2. The uppermost curve shows the form of a typical curve. There is a rapid rise to maximum concentration followed by a decay

which is an exponential wash-out in form (see Appendix D), reaching insignificant levels at time t_3. The second graph shows the concentration (Y axis) on logarithmic co-ordinates. Under these circumstances the exponential part of the decay curve becomes a straight line (*see Figure 125*). If we consider only the part of the graph between times t_2 and t_3, it is evident that:

$$\text{mean concentration of dye} = \frac{\text{amount of dye injected}}{\text{volume of fluid flowing past sampling point during the interval } t_2 - t_3}$$

$$= \frac{\text{amount of dye injected}}{\text{flow rate of fluid} \times \text{time interval } t_2 - t_3}$$

This equation may now be rearranged to show the flow rate of the fluid:

$$\text{flow rate of fluid} = \frac{\text{amount of dye injected}}{\text{mean concentration of dye} \times \text{time interval } t_2 - t_3}$$

Now the denominator of the right-hand side will be indicated by the area under the curve, and the flow rate of the fluid may thus be readily calculated provided that the calibration of the dye analyser has been established.

Figure 81b shows the more complicated situation when fluid is flowing round a circuit. Under these conditions, the front of the dye-laden fluid may lap its own tail so that a recirculation peak appears on the graph before the primary peak has decayed to insignificant levels. This commonly occurs when cardiac output is determined in man, and steps must be taken to reconstruct the tail of the primary curve as it would have been had recirculation not taken place. To do this we make use of the fact that the exponential wash-out phase has usually been entered before the recirculation peak appears. This is clearly shown in the lowermost of the four graphs. On the logarithmic plot, it is possible to detect the point at which the recirculation peak appears and the initial part of the down curve may be extrapolated in a straight line. This is replotted on a linear scale (graph three) and the area of the reconstructed primary curve determined. For technical details of the method, reference should be made to Kinsman, Moore and Hamilton (1929), Zierler (1962) and Kelman (1966c).

Methods based on uptake of inert tracer gases.—A modified Fick method of measurement of cardiac output may be employed with fairly soluble inert gases such as acetylene (Grollman, 1929). With this technique, a single breath of a dilute acetylene mixture is taken and held. It is then exhaled and the alveolar (or more correctly end-expiratory) concentration of acetylene determined. Analysis of volume and composition of expired gas permits measurement of acetylene uptake. Since the duration of the procedure does not permit recirculation, it may be assumed that the mixed venous concentration of acetylene is zero. The Fick equation then simplifies to the following:

$$\text{acetylene uptake} = \text{cardiac output} \times \text{arterial acetylene concentration}$$

The arterial acetylene concentration is derived from the assumption that the arterial acetylene tension equals the alveolar acetylene tension which is directly measured on the expired gas. Content is derived from tension using an assumed value for the solubility coefficient of acetylene in blood. This method

entirely avoids sampling of blood and does not therefore require cannulation of vessels, a feature which appeals to the subjects.

The technique outlined above had fallen into disuse for a variety of reasons principally concerned with technical difficulties in making the various measurements. The idea behind the method has come back into prominence following the introduction of the body plethysmograph which has already been mentioned on page 108, in connection with the measurement of airway resistance. Its use in the determination of cardiac output is for the measurement of the uptake of the tracer gas (usually nitrous oxide at the present time). The subject inhales a mixture of about 15 per cent nitrous oxide, and holds his breath with his mouth open. Nitrous oxide uptake is measured directly from the fall of the pressure within the box, and the arterial nitrous oxide content is derived from the alveolar nitrous oxide tension and the solubility coefficient in blood in exactly the manner described above for acetylene (Lee and DuBois, 1955).

The methods of the third group outlined above have the following characteristics in common.

(1) They measure pulmonary capillary blood flow, excluding any flow through shunts. This is in contrast to the Fick and dye methods.

(2) The assumption that the tension of the tracer gas is the same in end-expiratory gas and arterial blood is invalid in the presence of disorders of blood and gas distribution within the lungs.

(3) Some of the tracer gas dissolves in the tissues lining the respiratory tract and is carried away by blood perfusing these tissues. The indicated blood flow is therefore higher than the actual pulmonary capillary blood flow.

When the body plethysmograph is used to measure the tracer gas uptake, it is possible to detect pulsatile uptake synchronous with systole. This is taken as evidence that pulmonary capillary blood flow is pulsatile.

CHAPTER 9

DISTRIBUTION OF THE PULMONARY BLOOD FLOW

The pulmonary blood flow is probably never distributed evenly to all parts of the lung field and the degree of non-uniformity is usually much greater than is the case for inspired gas. Uneven distribution may be present between the two lungs, between different lobes and always between successive horizontal slices of the lungs. These differences can be measured and are discussed in this chapter under the heading of 'Anatomical maldistribution' since the relevant zones of lung can be defined anatomically.

Maldistribution may also occur diffusely between tiny zones of lung which cannot be defined anatomically. The chief manifestation of this type of maldistribution is impairment of oxygenation of arterial blood, and the effect can be quantified in physiological terms although the disorder often cannot be explained in morphological terms.

ANATOMICAL MALDISTRIBUTION OF PULMONARY BLOOD FLOW

Distribution between the Two Lungs

Use of a divided airway (such as a Carlen's tube) has permitted accurate estimation of the partition of the tidal volume between the two lungs. Unfortunately, no method of comparable simplicity exists to study the partition of the pulmonary blood flow in man. It might at first sight appear that a Carlen's tube would permit solution of the Fick equation for the two lungs separately. This, however, would require sampling of the blood leaving the two lungs separately, and this could probably be contrived if it were not for the fact that each lung drains through two pulmonary veins. Representative sampling therefore requires blood to be sampled from each vein in proportion to its flow rate and this is not feasible. It is, however, possible to make a rough and ready estimate of the pulmonary venous oxygen content and this enables an approximate idea of unilateral flow to be obtained from the unilateral oxygen consumption, which is easily derived by using a Carlen's catheter and a pair of bronchospirometers.

Because of these technical difficulties, there are few reliable observations of the division of blood flow between the two lungs, and much of what there is relates to dogs. Defares and his colleagues (1960) have used an indirect method based on the Fick principle using CO_2 and obtained values for unilateral flow which agree closely with the distribution of ventilation observed by Svanberg (1957) (*Table 21*). The table also shows an important study of

artificially ventilated dogs by Rehder, Theye and Fowler (1961). This study also shows close agreement between the distribution of blood and gas between the two lungs in the supine position. In the lateral position there is a slight increase of blood flow to the dependent lung, which is fortunate since the lower lung is better ventilated than the upper lung in the lateral position during spontaneous respiration (*Figure 46*). Surprisingly, this effect was found to be reversed in dogs when the thorax was opened.

Table 21

Distribution of ventilation and blood flow between the two lungs

	Right lung		*Left lung*	
	Ventilation	*Blood flow*	*Ventilation*	*Blood flow*
Closed chest, artificial ventilation (dog)				
Supine (A)	57%	58%	43%	42%
Right lateral (A)	51%	61%	49%	39%
Left lateral (A)	67%	55%	33%	45%
Thoracotomy, artificial ventilation (dog)				
Right lateral (A)	37%	55%	63%	45%
Left lateral (A)	82%	70%	18%	30%
Closed chest, spontaneous respiration (man)				
Supine (B)	—	54%	—	46%
Supine (C)	53%	—	47%	—

(A) Data from Rehder, Theye and Fowler (1961).
(B) Data from Defares and his colleagues (1960).
(C) Data from Svanberg (1957).

Distribution in Horizontal Slices of the Lung

We have already seen in *Figure 79* that haemodynamic considerations would suggest that, in the upright posture, pulmonary blood flow would be markedly affected by gravity. One of the most important recent advances in pulmonary physiology has been the demonstration of the magnitude of this effect by West (1962), using oxygen-15-labelled CO_2.* *Figure 70* summarizes his observations on the variations in ventilation in three zones of the lungs. *Figure 82* now shows the distribution of blood flow in the same three zones and the ratio of ventilation-to-perfusion in each. The effect of this ratio on gas exchange is considered on page 247.

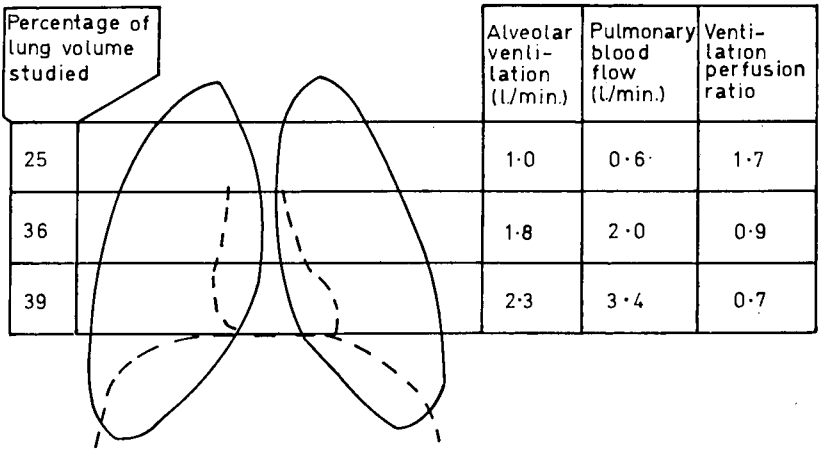
As would be expected, differences in perfusion between the upper and lower zones of the lungs disappear in the supine position (West, 1963). It is, however, probable that the craniocaudal stratification in the upright position is replaced by an antero-posterior stratification of perfusion in the supine position. It would thus be expected that, in the supine position, the areas of lung below the anterior costal wall would be underperfused while the areas bordering on the costal necks would be overperfused.† Unfortunately, there are technical difficulties in studying this problem, which is of special interest to anaesthetists.

* Many of West's studies have been collected in his monograph of 1965.

† *See* 'Note added in proof', page 265.

The normal stratification of lung perfusion can certainly be reversed by placing a patient in the Trendelenburg position, and some years ago the author saw hypostatic pneumonia and atelectasis in the upper lobe of a patient who was nursed for too long in a steep head-down position.

The concept of the effect of gravity on pulmonary perfusion is not new. In 1887 Orth, in a treatise on phthisis, suggested that the weight of the column of blood in the lung fields would tend to cause anaemia of the apices. Dock (1946) suggested that the favoured site of pulmonary tuberculosis was associated with diminished blood flow through the apices, and in the bat tuberculosis prefers the lung bases (Rothlin and Undritz, 1952). A diminished oxygen consumption of the right upper lobe in the upright position was demonstrated by Mattson and Carlens (1955), strongly suggesting a substantial reduction of blood flow.



Percentage of lung volume studied	Alveolar ventilation (l./min.)	Pulmonary blood flow (l./min.)	Ventilation perfusion ratio
25	1·0	0·6	1·7
36	1·8	2·0	0·9
39	2·3	3·4	0·7
100 Total	5·1	6·0	0·85

Figure 82. Relative ventilation and perfusion in different areas of the lungs (upright position). On the left is shown the percentage distribution of the total lung volume studied. On the right are shown the alveolar ventilation and the pulmonary blood flow of each horizontal slice. The last column indicates the ratio of the ventilation to the perfusion of each slice. Compared with the over-all ventilation/perfusion ratio of the whole lung (0·85), the upper zone is relatively overventilated (or underperfused) while the lower zone is relatively overperfused (or underventilated). (Recalculated and redrawn from West (1962))

Influence of Hypoxia on Distribution of Blood Flow

Reference has already been made to the measurement of unilateral blood flow by Defares and his colleagues (1960). In a study of the greatest technical difficulty these workers arranged that their subjects should inhale 10 per cent oxygen into the right lung while the other lung continued to breathe air. The proportion of the total pulmonary blood flow passing through the right lung then fell from 54 to 30 per cent. This experiment showed clearly that the increase in pulmonary vascular resistance caused by hypoxia (page 216) is capable of altering the distribution of the pulmonary blood flow and may

therefore be regarded as a homeostatic mechanism. The same group of workers (Arborelius and his colleagues, 1960) repeated their studies in the lateral position but were unable to detect any alteration in distribution during the unilateral inhalation of 10 per cent oxygen. They concluded that, in the lateral position, hypoxia in the lower lung was unable to overcome the effect of gravity and alter the distribution of blood between the two lungs.

VENOUS ADMIXTURE

At the beginning of Chapter 8 we briefly considered that part of the pulmonary blood flow which gained access to the pulmonary veins without passing through ventilated alveoli (*Figure 73*). This form of abnormality is very important in the management of patients who come under the care of the anaesthetist, either in the operating theatre or in the intensive care ward, where it is the main cause of arterial hypoxaemia.

There are a great many possible causes of venous admixture which may be classified in various ways (*Table 22*). In some cases the admixture is with mixed venous blood (from the pulmonary artery), while in other cases the blood is draining special structures such as myocardium or bronchi. In such cases, the blood will not necessarily have the same oxygen content as the mixed venous blood, and we shall see that it is therefore impossible to measure the precise amount of the admixture from these structures.

Table 22

Types of venous admixture

	NORMAL or physiological	*ABNORMAL or pathological*
Extrapulmonary	*Venae cordis minimae (Thebesian veins)	Congenital disease of the heart or great vessels with right-to-left shunting
Intrapulmonary	*Bronchial veins Possibly some slight degree of atelectasis *Possible flow through giant subpleural capillaries	Atelectasis *Pulmonary infection Pulmonary arteriovenous shunts *Pulmonary neoplasm including haemangioma Circulation through contused, damaged or oedematous lung

* Those forms of venous admixture marked with an asterisk involve blood which does not necessarily have the same oxygen content as mixed venous blood.

Forms of Venous Admixture

Venae cordis minimae (Thebesian veins)

Some small veins of the left heart drain directly into the chambers of the left heart and so mingle with the arterial blood. The oxygen content of this blood is probably very low and, therefore, the flow (believed to be about 0·3 per cent of cardiac output; Ravin, Epstein and Malm, 1965) causes an appreciable fall in the mixed arterial oxygen tension. It was thought by Cole and Bishop (1963)

that the venae cordis minimae constitute the major part of the venous admixture in healthy man.

Bronchial Veins

Figure 74 shows that a part of the venous drainage of the bronchial circulation passes by way of the deep true bronchial veins to reach the pulmonary veins. It is uncertain how large this component is in the healthy subject but it is probably less than 1 per cent of cardiac output. In bronchial disease and coarctation of the aorta, the flow through this channel may be greatly increased, and in bronchiectasis and emphysema may be as large as 10 per cent of cardiac output. Under these circumstances it becomes a major cause of arterial desaturation.

Congenital Heart Disease

Right-to-left shunting in congenital heart disease is the cause of the worst examples of venous admixture. In patients with pulmonary atresia, right-to-left shunting is often present at all times. When there are abnormal communications between right and left hearts without pulmonary atresia, shunting will normally be from left-to-right unless the pulmonary arterial pressure is raised above that of the systemic circulation. In that event the shunt is reversed and venous admixture occurs. Although there is usually a progressive tendency to reversal as a result of hypertrophic changes in the pulmonary arterioles, sudden reversal may occur as a result of increases in alveolar pressure. This may occur during anaesthesia, and in the author's experience has followed artificial ventilation, and straining during induction of anaesthesia with irritant inhalational agents.

*Atelectasis and Pulmonary Collapse**

It is uncertain whether there is some slight degree of atelectasis in the normal subject. Measured by modern analytical methods, the alveolar/arterial Po_2 difference can to a large extent be accounted for by the venous drainage from the Thebesian and bronchial circulation. Therefore the normal flow through atelectatic lung is likely to be very small if present at all. However, under pathological circumstances, venous admixture through collapsed areas of lung may be a large fraction of the total pulmonary blood flow and a most important cause of hypoxaemia.

Causes of collapse.—Fundamentally there are two causes of collapse. The first is loss of the pressure gradient across the wall of the alveolus, with consequent collapse of the alveolus due to its own elasticity. This is seen at thoracotomy when the intrathoracic pressure rises to atmospheric: unless the alveolar pressure is maintained above atmospheric (e.g. by artificial ventilation) the lung will quickly collapse. Less complete collapse is caused by pneumothorax or by loss of integrity of the chest wall, such as may result from thoracoplasty or crushed chest injuries.

The second cause of collapse is obstruction of the air passages with absorption of the sequestered gases. The obstruction may be due to any cause (pages 89

* The term 'atelectasis' refers to lung tissue which has never become aerated. Acquired de-aeration is therefore more correctly termed 'collapse'.

et seq.) such as retained secretions and the use of bronchial blockers. No less important is the obstruction of the smaller air passages which occurs when expiration is carried to the residual volume (*Figure 13* and page 100). Reduction of lung volume below the functional residual capacity may occur during anaesthesia as a result of expiratory muscle activity (e.g. coughing) or the use of subatmospheric airway pressures (e.g. 'negative phase' used during artificial ventilation). Velasquez and Farhi (1964) have demonstrated increased venous admixture in dogs ventilated artificially with a subatmospheric expiratory pressure, while Nunn and his colleagues (1965b) produced severe degrees of collapse in healthy conscious subjects merely by forced expiration while breathing 100 per cent oxygen.

When gases are sequestered by airway obstruction, they exchange with the gases carried in the mixed venous blood, the rate and direction of change being governed by the difference in tensions between the trapped alveolar gas and the mixed venous blood. Alveolar P_{CO_2} is normally only about 6 mm Hg below the level in the mixed venous blood. Therefore rather small quantities of carbon dioxide will pass from mixed venous blood into sequestered alveolar gas until its P_{CO_2} equals that of the mixed venous blood. The P_{O_2} of alveolar gas, on the other hand, will usually be much higher than that of mixed venous blood (*Table 37*) and therefore oxygen is rapidly absorbed from sequestered alveoli until the P_{O_2} equals that of mixed venous blood.

If the patient has been breathing 100 per cent oxygen prior to obstruction, the alveoli will contain only oxygen, carbon dioxide and water vapour. Since the last two together normally amount to less than 100 mm Hg, the alveolar P_{O_2} will usually be greater than 660 mm Hg so long as the alveoli contain any gas at all. Now, the oxygen saturation of the mixed venous blood can seldom rise above 90 per cent and its P_{O_2} is usually less than 60 mm Hg. In consequence, there will be an alveolar/mixed venous P_{O_2} gradient which is almost certainly over 600 mm Hg. Absorption of oxygen will thus be rapid and collapse will quickly occur (*Figure 83*).

The situation is much more favourable if the patient is breathing air since most of the alveolar gas is then nitrogen which is at a tension only a few mm Hg below that of mixed venous blood (Klocke and Rahn, 1961). Alveolar P_{N_2} rises above that of the mixed venous blood as oxygen is absorbed from the alveoli. Absorption is thus slow and collapse occurs more slowly.

If nitrous oxide is present in the sequestered alveoli, absorption will usually be more rapid than would be the case with the same concentration of nitrogen (*Figure 83*). There are two reasons for this. Firstly, nitrous oxide is much more soluble in blood than nitrogen, and secondly, the mixed venous tension of nitrous oxide is usually much less than the alveolar tension, except after a long period of inhalation.

When the inspired gas composition is changed *after* obstruction occurs, the pattern of absorption is altered. Consider, for example, a patient who has been breathing a nitrous oxide/oxygen mixture and who, immediately after sequestration, returns to breathing air. There will then be a gradient of tension for nitrous oxide from alveolus-to-blood and for nitrogen from blood-to-gas. Therefore, nitrous oxide will pass out of the alveolus and nitrogen will pass into it. Since, however, nitrous oxide is so much more soluble than nitrogen, the rate at which it leaves the alveolus will exceed the rate at which nitrogen passes in

and collapse will rapidly supervene. The converse is more complex. If the patient has been breathing air at the time of obstruction and the inspired gas is then changed to a nitrous oxide/oxygen mixture, the tension gradients will be the opposite of those in the preceding example. Therefore, nitrous oxide will pass into the alveolus faster than the nitrogen is absorbed. Consequently, the volume of the gas trapped in the alveolus will increase and, provided that this does not release the obstruction, the alveolus will ultimately increase to about three times the initial volume. Later on, as more nitrogen is absorbed, the nitrous oxide tension in the sequestered gases rises above its tension in the

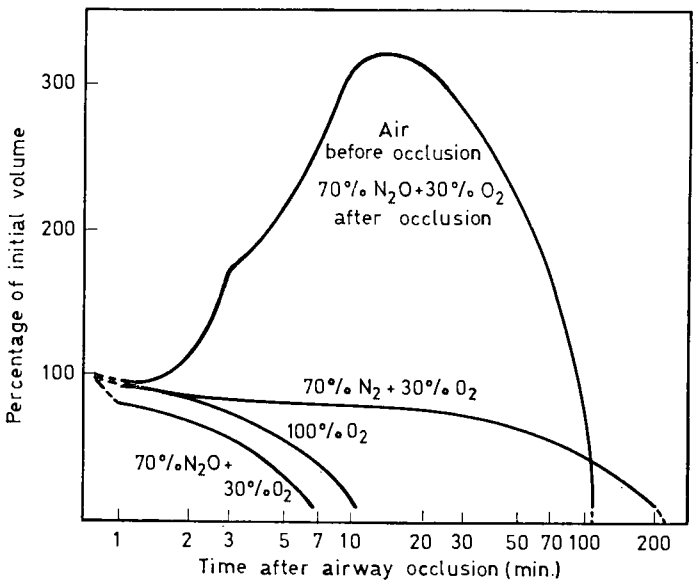


Figure 83. The lower curves show the rate of absorption of the contents of sections of the lung whose air passages are obstructed, resulting in sequestration of the contents. The upper curve shows the expansion of the sequestered gas when nitrous oxide is breathed by a patient who has recently suffered regional airway obstruction while breathing air. In all other cases, it is assumed that the inspired gas is not changed after obstruction has occurred. Similar considerations apply to gas sequestered in other parts of the body, and the data apply to pneumothorax, gas emboli and air introduced during pneumoencephalography. (Reproduced from Webb and Nunn (1967) by courtesy of the authors and the Editor of Anaesthesia)

mixed venous blood and absorption takes place, slowly at first and then more quickly until total atelectasis results. The sequence of events is shown in *Figure 83* for which the data have been prepared by forward integration (Webb and Nunn, 1967).

These changes are important to the anaesthetist. Exactly similar considerations apply to gas trapped in any part of the body including pneumothorax, air introduced in the course of pneumoencephalography and gas emboli. Changes in the volume of any of these may be of critical importance to a patient. Special attention should be paid to the possibility of loculi of air increasing in volume when a patient inhales nitrous oxide. A recent air

encephalogram is an absolute contra-indication to the use of nitrous oxide, and its use in a patient with a pneumothorax may result in a tension pneumothorax if thoracic pressures are not carefully monitored. Air emboli will increase in size and are more dangerous during the inhalation of nitrous oxide (Munson and Merrick, 1967).

The diagnosis of collapse may be made on physical signs but reliance is usually placed on chest radiography. When collapse occurs in the upright position, it is usually most marked in the basal segments where it may be detected without difficulty. However, in the supine position, collapse is more likely to occur in the dorsal parts of the lungs where the blood flow is likely to be relatively greater. Areas of collapse will thus be spread out in a plane parallel to the radiograph, and consequently difficult to recognize (Prys-Roberts and his colleagues, 1967b). Furthermore, it must be remembered that the collapse is of tissue with a very low density. Therefore a large area of lung will produce only a small area of shadow. Nor is this the whole story. Diagnosis of collapse in the unconscious patient is often made with portable x-ray apparatus, and the quality of the picture is further impaired by the inability of the patient to take a deep inspiration. These factors combine to make it extraordinarily difficult to detect collapse by radiography in an anaesthetized patient (Bendixen, Hedley-Whyte and Laver, 1963; Nunn, 1964; Hamilton and his colleagues, 1964).

Collapse diminishes the functional volume of the lung and so will reduce the compliance (page 64). A reduction in compliance has therefore been used by many groups of workers to indicate the development of collapse (Butler and Smith, 1957; Bendixen, Hedley-Whyte and Laver, 1963; Velasquez and Farhi, 1964). The practical value of compliance as an indication of collapse is limited by the wide scatter of the normal values of compliance in the anaesthetized patient. However, it is probably valid to interpret an acute fall in pulmonary compliance as an increase in the degree of collapse. Unfortunately, this requires control measurements made on the patient prior to collapse and these will seldom be available.

If we assume that pulmonary collapse is the principal cause of a very large venous admixture found during anaesthesia, then the demonstration of venous admixture is probably the simplest and most satisfactory method of diagnosing collapse under these conditions. Venous admixture is assessed by measurement of the alveolar/arterial Po_2 difference, but it must be stressed that this quantity is also influenced by the level of mixed venous oxygen content (page 342). The diagnosis of collapse is fairly certain if the alveolar/arterial Po_2 difference is diminished by hyperinflation of the lung. There is a need for an independent method of detection of pulmonary collapse and it seems possible that measurement of changes in F.R.C. might be useful.

It will be seen that the diagnosis of collapse is difficult in the unconscious patient. The special attraction of the measurement of venous admixture for the purpose of diagnosis is that it measures the functional disability. Furthermore, it permits easy calculation of the inspired oxygen concentration which is required to restore a normal level of arterial Po_2 (Chapter 12).

Pulmonary Infection

In the days when lobar pneumonia was common, it was a familiar sight to

see a patient hyperventilating but deeply cyanosed. The hypoxaemia was due to a large shunt through the lobe which was affected by the pneumonic process. It seems likely that the infection increased the blood flow through the affected lobe above its normal value.

Pulmonary Arteriovenous Shunts

Measured venous admixture frequently amounts to as much as 15 per cent of pulmonary blood flow during anaesthesia and levels of 5–10 per cent are commonplace. It is generally assumed that the admixture is from blood flow through collapsed areas of lung although these cannot usually be demonstrated by chest radiography. A possible alternative explanation is the opening of pulmonary pre-capillary arteriovenous shunts.

The existence of potential channels has been demonstrated by von Hayek (1960). The channels are 'sperr' arteries, structurally similar to those linking the pulmonary and bronchial arteries (page 211), and forming a T-network allowing blood to flow from bronchial artery to pulmonary artery, or from pulmonary artery to bronchial veins (and thence to pulmonary veins) according to the relaxation of these muscular vessels. There is also the possibility of direct shunting through the giant capillaries below the pleura. Although these possibilities exist, very little is known of the role of these vessels in the regulation of the pulmonary circulation (Krahl, 1964). It is, however, not without interest that von Hayek suggested that, when open, these communications might take as much as 20 per cent of the total pulmonary blood flow. This value accords very well with the values for venous admixture found during anaesthesia. Nevertheless, the functional significance of these potential shunts remains in doubt, but it is certain that flow through them must be negligible in the healthy conscious subject.

Evidence of passage of blood through pulmonary arteriovenous anastomoses has largely been obtained from injection of tracer substances into the pulmonary artery, clearly of limited application in anaesthetized patients. Tobin and Zariquiey (1950) have demonstrated the passage through perfused animal lungs of glass beads up to 0·5 mm. in diameter. More convincing have been *in vivo* cinefluorography studies of Thorotrast injected into the pulmonary artery of dogs (Rahn, Stroud and Meier, 1952; Rahn, Stroud and Tobin, 1952). Injected material reached the pulmonary veins so rapidly that it could not all have passed through the pulmonary capillaries. However, the significance of pulmonary arteriovenous shunts, or even their existence, has not been universally accepted and there have been a number of studies which have failed to demonstrate the passage of glass beads larger than 0·05 mm. diameter. For a review of this difficult subject the reader is referred to the monograph of Aviado (1965, page 943).

Niden and Aviado (1956) have themselves obtained evidence which strongly supports the existence of arteriovenous communications in the anaesthetized dog after embolization with glass beads. Injection into the pulmonary artery of 8 g. of glass beads (0·125 mm. diam.) resulted in a sharp rise of pulmonary arterial pressure which was due primarily to an increase in pulmonary vascular resistance, caused both by obstruction of the vascular bed and also by reflex pulmonary vasoconstriction. (Crossed circulation experiments showed an increase in pulmonary vascular resistance in a lung which

was perfused from another dog and so spared the embolization which affected the lung in the donor dog.) After embolization, beads of diameter 0·42 mm. passed through the lungs, and the ease with which they passed was directly related to the pulmonary arterial pressure. Hypoxia increased the passage of beads, presumably due to the rise in pulmonary arterial pressure which it caused. This would accord with the gross degree of shunting found by Cater and his colleagues (1963) during the ventilation of dogs with 100 per cent nitrogen. Of the greatest interest was the pulmonary venous oxygen saturation in Aviado's study. As successive injections of beads raised the pulmonary arterial pressure, there was an immediate and progressive lowering of the pulmonary venous oxygen saturation. This change could only be due to shunting and, in combination with the evidence of the passage of the glass beads, is strongly suggestive of the opening of arteriovenous shunts.

Pulmonary Haemangioma

This is a special example of a pulmonary arteriovenous shunt which enjoys the possibility of unequivocal demonstration. The condition is rare but should be considered in a patient with a degree of venous admixture which cannot be accounted for in other ways.

Scatter of Ventilation/Perfusion Ratios

The healthy lung receives each minute an alveolar ventilation of about 5 litres and a pulmonary blood flow of about 6 litres. This gives an over-all ventilation/perfusion ratio of 5/6 or about 0·85, a figure which is similar to, but should not be confused with, the respiratory exchange ratio. Not all alveoli have the same ventilation/perfusion ratio as the mean value for the lungs as a whole. *Figure 82* shows ventilation/perfusion ratios varying from 1·7 to 0·7 in three different horizontal zones of the lung and these figures do not represent the extremes. If the tips of the apices are not perfused at all (*Figure 79*), their ventilation/perfusion (V/Q)* ratio will be infinity. If other areas of the lung are atelectatic (perhaps at the bases), their V/Q ratio will be zero.

The range of possible degrees of scatter is shown diagrammatically in *Figure 84*. The top alveolus is unperfused and has a V/Q ratio of infinity. Since there is no blood flow, it makes no contribution to mixed arterial blood, but the alveolar gas from such a unit comprises alveolar dead space and forms a part of the end-expiratory gas. The second alveolus has a high V/Q ratio and the end-pulmonary capillary Po_2 is therefore higher than average. However, since the flow through such an alveolus is small, it makes only a small contribution to the mixed arterial blood. The third alveolus has a V/Q ratio equal to the mean for the lungs as a whole. The fourth alveolus has a low V/Q ratio and the end-pulmonary capillary Po_2 is lower than average. Since the flow is high this alveolus makes a disproportionately large contribution to the mixed arterial blood. At the bottom is shown a shunt which may be considered as having no ventilation at all and therefore a V/Q ratio of zero. Mixed venous blood passes through the shunt to mingle with the

* Ventilation/perfusion ratio is commonly abbreviated to V/Q (or more correctly $\dot{V}_A/\dot{Q}$) ratio. $\dot{V}_A$ stands for gas flow rate (alveolar ventilation) and $\dot{Q}$ for blood flow rate (*see* Appendix C).

arterial blood, but clearly zones of zero V/Q ratio make no contribution to the mixed alveolar (or end-expiratory) gas.

There is little doubt that the lungs contain alveoli with a continuous spectrum of V/Q ratios from about 0·6 to about 4·0. It is still uncertain what proportion of the alveoli of the supine healthy patient have V/Q ratios of zero or infinity. However, these two groups are probably present in significant proportions in healthy patients during anaesthesia.

Patterns of scatter of ventilation/perfusion ratios.—The studies of West (1962) have shown that for normal man in the upright position, gravity causes the V/Q ratio of horizontal slices to decrease from the apices towards the bases of the lungs. Two other patterns of distribution should also be considered. Farhi and

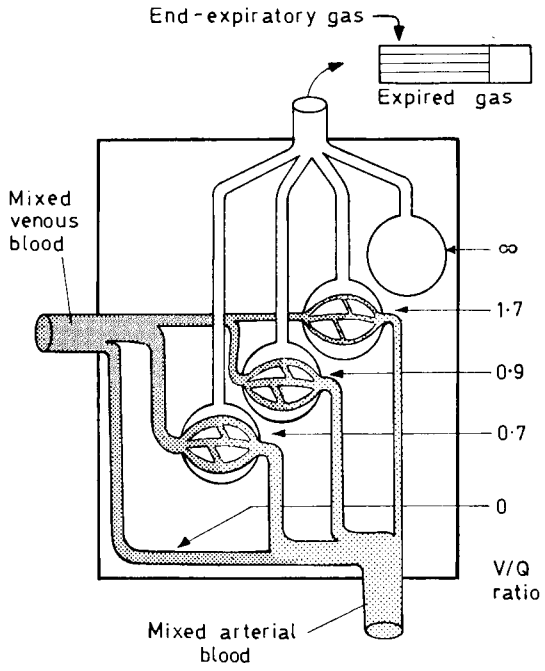


Figure 84. Abnormalities of the ventilation/perfusion ratio which occur in different parts of the lungs. At the top is shown a ventilated but unperfused alveolus, constituting alveolar dead space and with V/Q ratio infinity. Below are shown three alveoli with roughly similar ventilation but with perfusion influenced by the effect of gravity on the pulmonary circulation. All four alveoli contribute to the end-expiratory gas. At the bottom is shown a shunt which may be considered as having a V/Q ratio of zero. The three perfused alveoli and the shunt contribute to the mixed arterial blood. Effect of these abnormalities on arterial Po_2 *is considered on pages 245 et seq.*

Rahn (1955b) have suggested that V/Q ratios might be scattered in a log Gaussian distribution, this being the commonest form of biological scatter. There is no evidence that this is the case when the lungs are considered as a whole, since the effect of gravity on pulmonary blood flow produces an approximately linear pattern of distribution. However, it would be reasonable to assume a log Gaussian distribution of V/Q ratios within a horizontal slice.

Diffuse pulmonary disease, such as chronic bronchitis and emphysema, may result in a gross increase in the scatter of V/Q ratios. These conditions produce appreciable areas of lung with V/Q ratios of zero and infinity and also increase the normal spread of V/Q ratios within the finite range. Nobody can be quite certain what is the precise pattern of scatter but, as a simplification, Briscoe and Cournand (1962) have postulated a division corresponding to the fast and

slow alveoli considered in Chapter 7 (pages 200 et seq.) and earlier in *Figure 14.* The function of the two divisions was compared as shown in *Table 23.*

Table 23

Fast alveoli		*Slow alveoli*
$\frac{1}{4}$	Fraction of total lung volume	$\frac{3}{4}$
$\frac{9}{10}$	Fraction of total ventilation	$\frac{1}{10}$
$\frac{1}{2}$	Fraction of total perfusion	$\frac{1}{2}$
1·5	V/Q ratio of each group	0·2
117 mm Hg (98% saturation)	Po_2 of pulmonary end-capillary blood while breathing air	45 mm Hg (80% saturation)

Note that blood leaving the slow alveoli contains little more oxygen than does mixed venous blood (Po_2, 40 mm Hg; saturation, 75 per cent). The effects will thus be very similar to those of a true shunt. It is thought that, in many forms of chronic lung disease, the distribution of slow and fast alveoli is random throughout the lung fields with the two types lying alongside each other.

Nomenclature of Venous Admixture

Venous admixture refers to the degree of admixture of mixed venous blood with pulmonary end-capillary blood which would be required to produce the observed difference between the arterial and pulmonary end-capillary Po_2. (Pulmonary end-capillary Po_2 is usually taken as equal to ideal alveolar Po_2—*see* Chapter 10.) The calculation is shown in *Figure 85.* Note that the venous admixture is not the *actual* amount of venous blood which mingles with the arterial blood but the *calculated* amount which would be required to produce the arterial blood-gas picture. The difference is due to the contribution to the arterial blood of blood from alveoli having a V/Q ratio of more than zero but less than the normal value. The strict quantitative basis of the calculation is also destroyed by the admixture of bronchial and Thebesian venous blood of unknown oxygen content. *Venous admixture* is thus a convenient index but does not define the anatomical pathway of shunt.

Anatomical shunt, frank shunt or shunt (unqualified).—These terms refer to the amount of venous blood which mingles with the pulmonary end-capillary blood on the arterial side of the circulation. The terms embrace bronchial and Thebesian venous blood flow and also admixture of mixed venous blood caused by actelectasis, bronchial obstruction, congenital heart disease with right-to-left shunting, etc. This excludes blood draining any alveoli with a V/Q ratio of more than zero.

Pathological shunt is sometimes used to describe the forms of anatomical shunt which do not occur in the normal subject.

Physiological shunt is, unfortunately, used in two senses. In the first sense it is used to describe the degree of venous admixture which occurs in a normal

healthy subject. Differences between the actual measured venous admixture and the 'physiological shunt' thus indicate the amount of venous admixture which results from the disease process. In its alternative sense, physiological

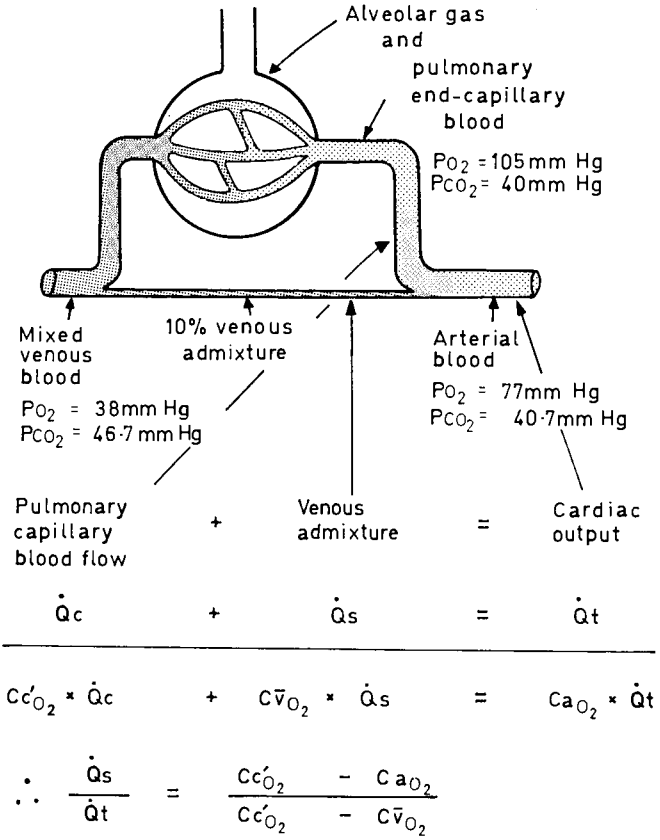


Figure 85. A schematic representation of venous admixture. It makes the simplifying assumption that all the arterial blood has come either from alveoli with normal V/Q ratio or from venous admixture. This is never true but it forms a convenient method of quantifying venous admixture and can be used as a basis for oxygen therapy. The shunt equation is similar to the Bohr equation and is based on the axiomatic relationship that the total amount of oxygen in one minute's flow of arterial blood equals the sum of the amount of oxygen in one minute's flow through the pulmonary capillaries and the amount of oxygen in one minute's flow through the shunt. Amount of oxygen in one minute's flow of blood equals the product of the blood flow rate and the concentration of oxygen in the blood. $\dot{Q}t$, *total cardiac output;* $\dot{Q}c$, *pulmonary capillary blood flow;* $\dot{Q}s$, *flow of blood through shunt;* Ca_{O_2}, *concentration of oxygen in arterial blood;* Cc'_{O_2}, *concentration of oxygen in pulmonary end-capillary blood;* $C\bar{v}_{O_2}$, *concentration of oxygen in mixed venous blood*

shunt is synonymous with venous admixture and is derived from the mixing equation (*Figure 85*) in a manner exactly analogous to the derivation of the physiological dead space from Bohr's equation. It is then possible to subtract the anatomical shunt from the physiological shunt and so derive some idea of

the malfunction due to abnormal ventilation/perfusion ratios. This is comparable to the derivation of alveolar dead space.

Physiological dead space	Physiological shunt (calculated venous admixture)
=	=
anatomical dead space	anatomical shunt
+	+
alveolar dead space ('dead-space-like effect' due to areas of increased ventilation/perfusion ratio).	'shunt-like effect' due to areas of decreased ventilation/perfusion ratio.

The author tends to retreat in the face of alternative definitions of important terms. In this case, there is no hardship in avoiding the term 'physiological shunt'. In its first sense 'normal degree of venous admixture' seems unequivocal, while in its second sense it can easily be replaced by 'calculated venous admixture', both terms being self-explanatory.

Effects of Venous Admixture

Qualitatively, it will be clear that venous admixture reduces the over-all efficiency of gas exchange and results in arterial blood-gas tensions which are closer to those of mixed venous blood than would otherwise be the case. Quantitatively, the effect is simple provided that we consider the *contents* of gases in blood. Considering a simple anatomical shunt such as that shown in *Figure 85* we may take as an example:

pulmonary end-capillary oxygen content	20 vols. per cent
mixed venous blood oxygen content	10 vols. per cent

It will be clear that a 50 per cent venous admixture will result in an arterial oxygen content of 15 vols. per cent, a 25 per cent venous admixture will result in an arterial oxygen content of 17·5 vols. per cent, and so on. The calculation is based on the conservation of mass:

the amount of oxygen flowing in the arterial system in each minute	=	the amount of oxygen leaving the pulmonary capillaries in each minute	+	the amount of oxygen flowing through the venous admixture in each minute

For each term in this equation the amount of blood flowing per minute may be expressed as the product of the blood flow rate and the oxygen content of the blood flowing in the vessel. In the case of the pulmonary capillary blood flow, this equals $\dot{Q}c$ *times* Cc'_{O_2} and so on (the symbols are explained in *Figure 85* and Appendix C). *Figure 85* shows how the equation may be cleared and solved for the ratio of the venous admixture to the cardiac output. The final equation has a form similar to that of the Bohr equation for the physiological dead space (page 191).

To calculate the venous admixture, it is first necessary to determine the gas contents of the arterial, pulmonary end-capillary and mixed venous blood. In practice these are usually measured or calculated as oxygen tensions, and content is then derived from the oxygen dissociation curve and the oxygen

capacity of the blood, allowance being made for dissolved oxygen. Conversely, if we know the degree of venous admixture, the effect on arterial blood-gas *contents* may be easily calculated. If, however, we require to know the effect on arterial blood P_{O_2}, we must undertake the tiresome calculation of tension from content using the oxygen dissociation curve and the oxygen capacity of the blood.*

The shape of the oxygen dissociation curve looms very large in any consideration of venous admixture. If a normal subject has a pulmonary end-capillary P_{O_2} of 105 mm Hg (the normal value) and a venous admixture of 5 per cent of his cardiac output, the consequent reduction of his arterial oxygen content or saturation is too small to be measured easily (*Table 24*). However, due to the flatness of the oxygen dissociation curve in this range, there is a considerable fall in arterial P_{O_2} which may be detected without difficulty.

The effect of this degree of venous admixture on arterial CO_2 content is similar in magnitude to that of oxygen content. However, due to the relative steepness of the CO_2 dissociation curve in this range the effect on arterial P_{CO_2} is also very small and is far less than the change in arterial P_{O_2} (*Table 24*). Two conclusions may be drawn.

(1) Arterial P_{O_2} is the most useful blood-gas measurement for the detection of venous admixture.

(2) Venous admixture reduces the arterial P_{O_2} markedly, but has relatively little effect on arterial P_{CO_2} or the content of either CO_2 or O_2, unless the venous admixture is large.

Table 24

Effect of 5 per cent venous admixture on the difference between arterial and pulmonary end-capillary blood levels of carbon dioxide and oxygen

	Pulmonary end-capillary blood	*Arterial blood*
CO_2 content (vols. %)	49·7	50·0
P_{CO_2} (mm Hg)	39·7	40·0
O_2 content (vols. %)	19·9	19·6
O_2 saturation (%)	97·8	96·8
P_{O_2} (mm Hg)	105	90

It has been assumed that the arterial/venous oxygen content difference is 4·5 vols. per cent and that the haemoglobin concentration is 14·9 g. per cent. Typical changes in P_{O_2} and P_{CO_2} have been shown for a 10 per cent venous admixture in Figure 85

Quite large degrees of venous admixture are needed to produce clinically recognizable reduction of arterial oxygen content, and elevations of P_{CO_2} are seldom seen. It is, in fact, more usual for venous admixture to *lower* the P_{CO_2} indirectly since the resultant lowering of the P_{O_2} commonly causes hyperventilation, which more than compensates for the slight elevation of P_{CO_2} which would otherwise result from the venous admixture.

* These calculations may be expedited by the use of the computer-written tables produced by Kelman and Nunn (1968).

Since the effect of venous admixture on arterial P_{O_2} is so markedly influenced by the slope of the dissociation curve, it will clearly depend upon the section of the dissociation curve which is concerned in a particular situation. Thus if the pulmonary end-capillary P_{O_2} is high (above 300 mm Hg where the curve is flat), venous admixture causes a very marked fall in arterial P_{O_2} (approximately 17 mm Hg for 1 per cent venous admixture). If, however, the pulmonary end-capillary P_{O_2} is low (below 70 mm Hg where the curve is steep), venous admixture has relatively little effect on arterial P_{O_2}. It would probably be wrong to consider this from the teleological standpoint, but it is nevertheless convenient to remember that a given degree of venous admixture causes a greater fall of P_{O_2} in the better oxygenated patients and a smaller fall in the less well oxygenated patients. Discussion of the magnitude of these changes is postponed to Chapter 12.

Scatter of V/Q Ratio considered as Venous Admixture

Figure 82 shows the lungs divided into three horizontal slices, each with its own V/Q ratio. The alveolar (and end-pulmonary capillary) oxygen tensions within similar slices vary according to the V/Q ratio, and it now remains to consider the effect of this scatter of V/Q ratios on the difference between the P_{O_2} and P_{CO_2} of alveolar gas and arterial blood.

Figure 86 shows three alveoli with V/Q ratios similar to those of the three horizontal slices of lung in *Figure 82*. The contribution that each alveolus makes to the mixed alveolar gas and the arterial blood is also the same as in *Figure 82*, and these contributions are expressed as percentages in *Figure 86*. The P_{O_2} of the alveolar gas in each group has been calculated from the V/Q ratio* and it is assumed that the pulmonary end-capillary P_{O_2} equals the alveolar P_{O_2} in each group. The pulmonary end-capillary oxygen saturation of each group has then been determined from the oxygen dissociation curve. Saturation can easily be converted into content, and the saturation of the mixed arterial blood has been determined making allowance for the different volume contributions of blood from the three zones. Arterial P_{O_2} was derived from the arterial saturation, using the dissociation curve. Mixed alveolar P_{O_2} was determined by a similar procedure but without the necessity of using the dissociation curve (since P_{O_2} of a gas is directly proportional to the oxygen content provided that the barometric pressure remains constant).

It will be seen that the saturation of the mixed arterial blood (97·4 per cent) is less than the arithmetic mean of the saturations from the three groups (97·7 per cent). This is partly due to the curvature of the oxygen dissociation curve (*see* below) but also because the group of alveoli with the lowest saturation makes the largest contribution to the arterial blood. As a result of these two effects the arterial P_{O_2} is always less than the alveolar P_{O_2}, and in this example there is an alveolar/arterial P_{O_2} difference of 5 mm Hg. In contrast, the scatter of P_{CO_2} between the three groups of alveoli is small and alveolar/arterial P_{CO_2} difference is only 0·6 mm Hg. This is mainly because the mixed venous/arterial P_{CO_2} difference is small.

* The imaginary patient is breathing air and the mixed venous blood has the normal gas contents.

It is only possible to measure the V/Q ratios of different parts of the lung by the use of sophisticated techniques. Most investigators in this field can only make a simplified assessment based on measurement of the following oxygen levels: (1) alveolar P_{O_2}; (2) arterial P_{O_2} and saturation; (3) mixed venous P_{O_2} and saturation; (4) oxygen capacity of the patient's blood.

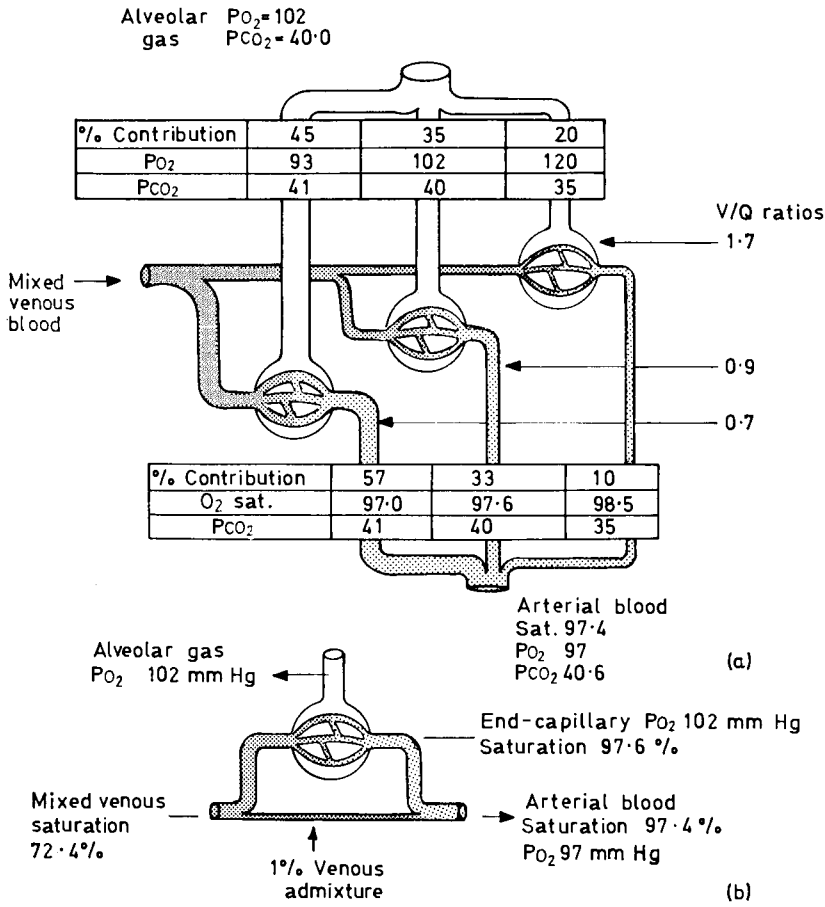


Figure 86. Alveolar/arterial P_{O_2} *difference caused by scatter of V/Q ratios and its represenation by an equivalent degree of venous admixture. (a) shows scatter of V/Q ratios corresponding roughly to the three zones of the lung in the normal upright subject. Mixed alveolar gas* P_{O_2} *is calculated with allowance for the volume contribution of gas from the three zones. Arterial saturation is similarly determined and the* P_{O_2} *derived. There is an alveolar/arterial* P_{O_2} *difference of 5 mm Hg. (b) shows an entirely imaginary situation which would account for the difference. This is a useful method of quantifying the functional effect of scatter of V/Q ratios but should be carefully distinguished from the actual situation*

These measurements are not by themselves sufficient to calculate the spatial scatter of V/Q ratios as shown in *Figure 86a*. Therefore, there has arisen a useful convention according to which the investigator *pretends* that all functioning alveoli have the same V/Q ratio but that there is a shunt (zero V/Q ratio). This *entirely imaginary* situation is shown in *Figure 86b*. In this example a calculated

venous admixture of 1 per cent has been shown, which would produce the same alveolar/arterial P_{O_2} difference that results from the scatter of V/Q ratios shown in the real situation in *Figure 86a*. This is a useful method of quantifying the functional effect of scatter of V/Q ratios but should be carefully distinguished from the true situation. The calculation of the 1 per cent venous admixture in *Figure 86b* is not a measurement of true shunt in the patient, but is a calculation of *the amount of venous admixture which would be required to produce the observed alveolar/arterial* P_{O_2} *difference*, which is actually caused by the scatter of V/Q ratios shown in *Figure 86a* and which, in most laboratories, cannot be measured directly.

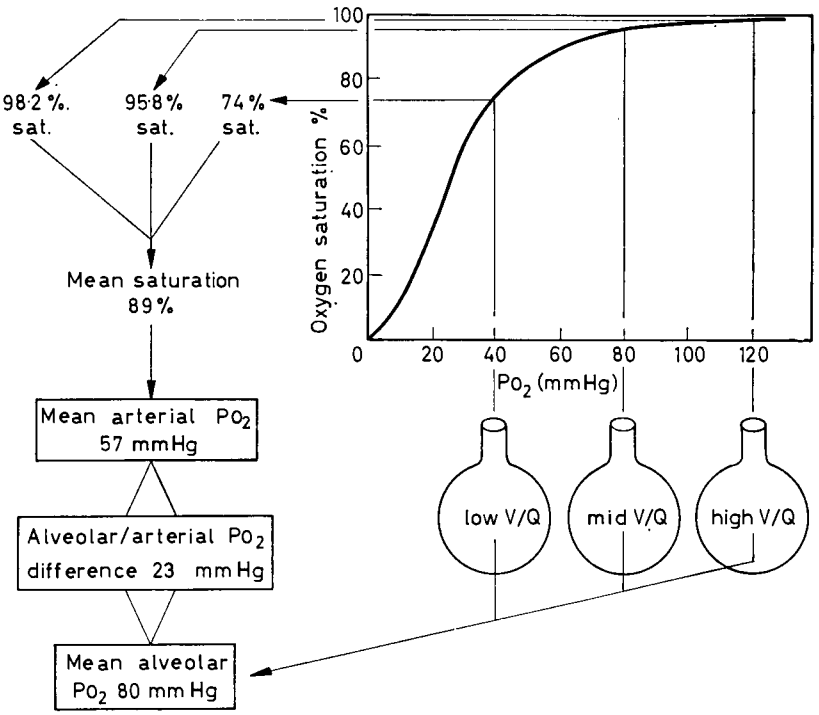


Figure 87. Alveolar/arterial P_{O_2} *difference caused by scatter of V/Q ratios resulting in oxygen tensions around the bend of the oxygen dissociation curve. This diagram shows the effect of three groups of alveoli with* P_{O_2} *values of 40, 80 and 120 mm Hg. Ignoring the effect of the different volumes of gas and blood contributed by the three groups, the mean alveolar* P_{O_2} *is 80 mm Hg. However, due to the bend of the dissociation curve, the saturations of the blood leaving the three groups are not proportional to their* P_{O_2}. *The mean arterial saturation is, in fact, 89 per cent and the* P_{O_2} *therefore is 57 mm Hg. The alveolar/arterial* P_{O_2} *difference is thus 23 mm Hg. The actual difference would be somewhat greater since gas with a high* P_{O_2} *would make a relatively greater contribution to the alveolar gas, and blood with a low* P_{O_2} *would make a relatively greater contribution to the arterial blood. In this example a calculated venous admixture of 27 per cent would be required to account for the scatter of V/Q ratios in terms of the measured alveolar/arterial* P_{O_2} *difference, at an alveolar* P_{O_2} *of 80 mm Hg*

Effect of mean alveolar P_{O_2}.—Overventilated alveoli fail to compensate for underventilated alveoli in the maintenance of the arterial oxygen level. There are two reasons for this. The first is clearly shown in *Figure 86* and arises from the

fact that the relatively underventilated alveoli usually contribute more blood than the relatively overventilated alveoli to the mixed arterial blood. The second reason is that, due to the shape of the oxygen dissociation curve, the overventilated alveoli cannot return blood with a saturation of much more than 98·5 per cent saturation, and so cannot offset the contribution of desaturated blood from the underventilated alveoli. Asmussen and Nielsen (1960) have pointed out that this effect will be more pronounced if the mean alveolar P_{O_2} is depressed to the tension corresponding to the bend of the dissociation curve. This is a P_{O_2} of about 50 mm Hg, which is encountered only in fairly severe underventilation or during the inhalation of oxygen mixtures of less than 20 per cent. This effect is illustrated in *Figure 87* where the mean alveolar P_{O_2} is reduced to 80 mm Hg.

It follows from the latter consideration that the degree of calculated venous admixture which is equivalent in effect to a fixed degree of scatter of V/Q ratio will depend upon the actual level of the alveolar P_{O_2}. At high levels of alveolar P_{O_2} the effect of V/Q scatter will be small since blood from all alveoli will be close to 100 per cent saturation, even if the V/Q ratios vary widely. At normal levels of alveolar P_{O_2} the situation is as shown in *Figure 86*. When the alveolar P_{O_2} is less than normal, scatter of V/Q ratios appears as an ever larger venous admixture as the alveolar P_{O_2} falls towards 50 mm Hg. In the example in *Figure 87* (alveolar P_{O_2} 80 mm Hg), the scatter of V/Q ratios produces an effect equivalent to a venous admixture of 27 per cent.

Combined Effects of Alveolar Dead Space, Scatter of V/Q Ratios and Shunt

Most of the patients who come under the care of anaesthetists do not have a single disorder of distribution. Almost all show an increase in alveolar dead space; most have more than the normal degree of shunt and it appears likely that the scatter of V/Q ratios is at least as great as in the healthy conscious subject.

Figure 88 portrays an imaginary but typical anaesthetized patient breathing gas containing 21 per cent oxygen. Ten per cent of the alveolar ventilation is distributed to unperfused alveoli where the V/Q ratio is infinity. This alveolar dead space gas mingles with gas from perfused alveoli during expiration. The mixed alveolar gas from the three perfused alveoli has a composition whose derivation has been shown in *Figure 86*. The end-expiratory gas consists of mixed gas from perfused alveoli diluted with air from the alveolar dead space during expiration. *Figure 86* also showed the derivation of the gas tensions of the mixed pulmonary end-capillary blood and the values are the same as those in *Figure 88*.

The alveolar/arterial gas tension gradients have been considered in *Figure 86*. Further gas tension gradients exist between mixed pulmonary end-capillary blood and arterial blood; these gradients are due to the shunt which has the value of 10 per cent of pulmonary blood flow in this example; the influence of the shunt on P_{CO_2} and P_{O_2} has been explained in *Figure 85*.

The whole series of gradients of P_{CO_2} and P_{O_2} between air and arterial blood have been tabulated below *Figure 88*. The following general conclusions may be drawn.

(1) *Ambient gas/end-expiratory* P_{O_2} and P_{CO_2} gradients are of comparable magnitude and are influenced primarily by ventilation, being low at high minute volume.

(2) *End-expiratory/mixed alveolar* P_{O_2} and P_{CO_2} gradients are of comparable magnitude and are influenced mainly by alveolar dead space ventilation.

(3) *Mixed alveolar/mixed end-capillary* P_{CO_2} gradient is usually negligible. The

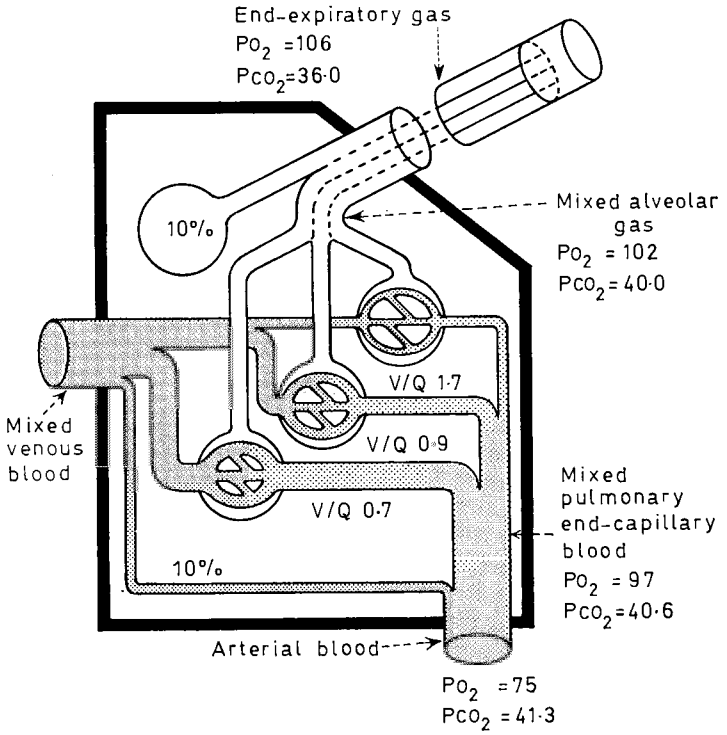


Figure 88. Schematic representation of an imaginary but typical anaesthetized patient breathing air, to show combined functional effects of alveolar dead space, scatter of V/Q ratios and shunt. Ten per cent of the alveolar ventilation is distributed to unperfused alveoli (V/Q infinity); 10 per cent of the mixed venous blood passes through unventilated spaces (V/Q zero). Ventilated and perfused alveoli are considered as falling into three groups whose ventilation/perfusion ratios vary as in the normal upright subject. Gas tensions show a continuous gradient from air to arterial blood, but the effects of the different abnormalities on P_{CO_2} *and* P_{O_2} *show striking quantitative differences*

	P_{O_2} (*mm Hg*)	P_{CO_2} (*mm Hg*)
Air	150	0
End-expiratory gas	106	36·0
Mixed alveolar gas (not contaminated with alveolar dead space gas)	102	40·0
Mixed pulmonary end-capillary blood (not contaminated with shunted blood)	97	40·6
Arterial blood	75	41·3

P_{O_2} gradient is appreciable and a function of scatter of V/Q ratios (*Figures 86 and 87*).

(4) *Mixed end-capillary/arterial* P_{CO_2} gradient is usually negligible unless the shunt is very large. The P_{O_2} gradient is appreciable and a function of the magnitude of the shunt* (*Figure 85*).

It is impossible to sample the mixed alveolar gas from the perfused alveoli (uncontaminated with gas from the alveolar dead space), and similarly mixed pulmonary end-capillary blood can only be sampled after admixture with shunted blood to form arterial blood. Therefore, direct measurement of P_{CO_2} and P_{O_2} of mixed alveolar gas and mixed end-capillary blood is not possible. This is shown in *Figure 88* as a black box from within which samples cannot ordinarily be collected. The internal workings of the black box must be deduced from samples taken from outside it, that is to say, mixed venous and arterial blood, inspired, expired and end-expiratory gas.

The 'Riley' Method of Analysis of Distribution Abnormalities

Without sampling from within the black box, it might appear an impossible task to quantify the errors of distribution shown in *Figure 88*. However, Riley and his co-workers, in a brilliant series of papers, have suggested an approach which is of great practical value although it does not pretend to offer a precise definition of the nature of malfunction (Riley, Lillienthal, Proemmel and Franke, 1946; Riley and Cournand, 1949; Riley and Cournand, 1951; Riley, Cournand and Donald, 1951).

The 'Riley' approach ignores the scatter of V/Q ratios and considers the lung as a three-compartment model—ventilated but unperfused alveoli (alveolar dead space), perfused and ventilated alveoli ('ideal' alveoli), and perfused but unventilated alveoli (venous admixture or shunt) (*Figure 89*). The small gradient in P_{CO_2} caused by scatter of V/Q ratio and shunt is ignored and it is assumed that the 'ideal' alveolar P_{CO_2} equals the arterial P_{CO_2}. The 'ideal' alveolar P_{O_2} may then be calculated on the assumption that the respiratory exchange ratios of 'ideal' alveolar and expired gas are the same (the latter may easily be measured). This calculation is performed with any of a number of forms of the alveolar air equation (*see* pages 262 et seq.).†

If we embark on a 'Riley' analysis of the imaginary patient in *Figure 88*, we start by assuming that the 'ideal' alveolar P_{CO_2} is 41·3 mm Hg. This is, in fact, too high but by an insignificant amount. We next calculate the 'ideal' alveolar P_{O_2} to be 101 mm Hg, a value which is very close to the mixed alveolar P_{O_2}. Using these values in conjunction with the measured end-expiratory gas tension, we would calculate the alveolar dead space ventilation to be 13 per cent of the alveolar ventilation. Similarly, by comparing our calculated 'ideal' alveolar P_{O_2} with the measured arterial P_{O_2} we would derive a calculated venous admixture of 11 per cent of pulmonary blood flow. Each of these estimates is higher than the corresponding malfunctions built into the model. However, the 'Riley' analysis makes no estimate of the scatter of V/Q ratios,

* The end-capillary/arterial P_{O_2} gradient is also increased when the mixed venous/arterial P_{O_2} gradient is increased and this is a function of low cardiac output in relation to O_2 consumption.

† This paragraph constitutes the definition of the 'ideal' alveolar gas.

and the enhanced values of calculated alveolar dead space and shunt include the equivalent effect of the scatter of V/Q ratios which is not measured. *Table 25* shows how very accurately this is done.

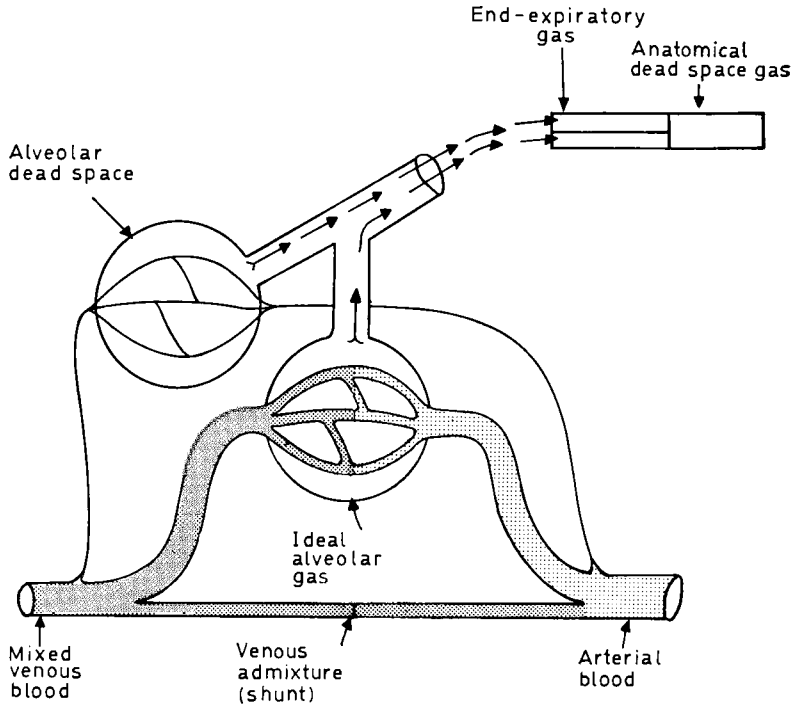


Figure 89. The assessment of the efficiency of gas exchange in the lungs considered as a black box. The lung is imagined to consist of three functional units: (1) alveolar dead space, (2) 'ideal' alveoli, and (3) venous admixture or shunt. Gas exchange occurs only in the 'ideal' alveoli. The measured alveolar dead space consists of true alveolar dead space together with a component caused by V/Q scatter. The measured venous admixture consists of true venous admixture (shunt) together with a component caused by V/Q scatter. Note that 'ideal' alveolar gas is exhaled contaminated with alveolar dead space gas (if present). Under such circumstances it is not possible to sample 'ideal' alveolar gas, the P_{O_2} of which is therefore derived indirectly

Table 25

Detection of pulmonary maldistribution by the 'Riley' method of analysis

	Malfunction built into the model patient shown in Figure 88	*Malfunction which would be indicated by 'Riley' method of analysis*
Alveolar dead space ventilation	10%	13%
Scatter of V/Q ratios	Approx. equal to that found in normal upright subjects	Not estimated
Shunt	10%	11%

The scatter of V/Q ratios which is not estimated by the 'Riley' method of analysis, appears as enhanced values for dead-space-like effect and shunt effect.

Although the 'Riley' analysis does not give a precise estimate of what is going on inside the black box of the lungs, it gives a most valuable quantification of the degree of abnormality as though it were all due to alveolar dead space or shunt. It is then reasonable to go ahead and treat the patient on this basis. Thus the minute volume may be increased to allow for ventilation which is wasted in the alveolar dead space, and the inspired oxygen concentration may be increased to restore the arterial Po_2 when this has been decreased by 'shunt effect'. This is done by raising the oxygen content of the pulmonary end-capillary blood until there is sufficient surplus oxygen to saturate the shunted blood. Full restoration of arterial Po_2 by this means is not possible if the shunt is large (page 346).

Distinction between Shunt and Scatter of V/Q Ratios

The 'Riley' analysis described in the section above makes no distinction between shunt and scatter of V/Q ratios. The great majority of publications on venous admixture in clinical practice similarly draw no distinction and authors may attribute their findings to either shunt or scatter of V/Q ratios, often with little evidence to support their preference. In fact, the distinction is far from simple and has been attempted by very few workers.

The most satisfactory approach would be to measure the scatter of V/Q ratios directly by the isotope techniques which have been mentioned earlier in this chapter. However, these methods are elaborate and few workers possess the facilities for their use. Instead it is commoner to measure the calculated venous admixture at different levels of alveolar Po_2 and, from these results, to attempt a deduction of the relative contribution of shunt and scatter of V/Q ratios to the total calculated venous admixture measured at the different values of alveolar Po_2.

The distinction is made possible by the difference in slope of the oxygen dissociation curve at different values of Po_2. This is the reason why a given degree of scatter of V/Q ratios appears as though it were a venous admixture of different magnitude at different levels for alveolar Po_2. As an example, let us consider a patient with particularly gross scatter of V/Q ratios in whom, while breathing air, 65 per cent of the arterial blood is derived from alveoli with Po_2 70 mm Hg, and 10 per cent from alveoli with Po_2 140 mm Hg. This gross degree of scatter of V/Q ratios would produce an alveolar/arterial Po_2 gradient of about 27 mm Hg. If this gradient were due to a shunt, it would correspond to a shunt of about 10 per cent. Now if the patient were to breathe an oxygen concentration of 60 per cent or more, blood leaving even the worst ventilated alveoli would still be almost fully saturated and the functional defect would then correspond to a shunt of only 1 per cent. If, however, the patient were to breathe about 16 per cent oxygen, the alveolar/arterial Po_2 gradient would then correspond to a shunt of about 50 per cent. Thus if measurements of the calculated venous admixture were found to be 50 per cent while breathing 16 per cent oxygen, 10 per cent while breathing air and 1 per cent while breathing 100 per cent oxygen, we might reasonably infer the patient had hardly any true shunt but a serious degree of scatter of V/Q ratio. If, alternatively, the calculated venous admixture were found to be 10 per cent regardless of the concentration of oxygen inspired, we could infer that this was a true shunt and there was no appreciable scatter of V/Q ratios. It is more likely that we should

find a calculated venous admixture of (say) 60 per cent during the inhalation of 16 per cent oxygen, 20 per cent while breathing air and 11 per cent while inhaling 100 per cent oxygen. We could then infer that there was a true shunt of about 10 per cent together with a serious degree of scatter of V/Q ratio.

This approach rests upon an assumption of doubtful validity, that the true shunt is uninfluenced by the concentration of oxygen which the patient is breathing. Clearly, the Po_2 may influence the pulmonary vasculature and also the presence of 100 per cent oxygen may result in absorption atelectasis. Furthermore, from the practical point of view the procedure is laborious and few estimates of this nature have been performed. Cole and Bishop (1963) and Nunn and Bergman (1964) showed, in conscious subjects, a significant increase in calculated venous admixture at lower values of alveolar Po_2 and their results accord roughly with the degree of scatter of V/Q ratios which is believed to occur in man. In anaesthetized man breathing spontaneously, Nunn (1964) showed raised values for calculated venous admixture with low values for alveolar Po_2, and this suggests the presence of a significant degree of scatter of V/Q ratios under these conditions.

VENOUS ADMIXTURE ASSOCIATED WITH ANAESTHESIA

Venous admixture is important to the anaesthetist since it is the major cause of arterial hypoxaemia, both during anaesthesia and in patients undergoing intensive care. However, our knowledge of the subject is still far from complete. In most of the studies which are cited below, the venous admixture was derived from measurements of alveolar/arterial Po_2 difference using an assumed value for the mixed venous oxygen content. It now seems likely that in many cases the mixed venous oxygen must have been less than was thought, and that reported values for venous admixture are too high (Kelman and his colleagues, 1967).

In 1958, Campbell, Nunn and Peckett showed an increase in the venous admixture of three patients out of six, 12 minutes after induction of anaesthesia, intubation and artificial ventilation; venous admixture was unaltered in the remaining three patients. The following year, Frumin and his colleagues showed substantial increases in alveolar/arterial Po_2 differences in a number of anaesthetized patients who were ventilated artificially. In 1960, Stark and Smith measured the alveolar/arterial Po_2 difference in anaesthetized patients who were breathing mixtures containing a high concentration of oxygen. They reported high values of venous admixture and, under the conditions of their study, such venous admixture should be considered as true shunt.

These pioneer studies were carried out before the general introduction of the polarographic method of measurement of Po_2 (page 380) and used techniques which were probably stretched to the limit of their accuracy. The advent of polarography ushered in a new generation of studies in which arterial Po_2 was measured more expeditiously and probably more accurately. The findings of some of these studies are summarized in *Table 26.*

Range of venous admixture during anaesthesia is generally from 5 to 20 per cent of total pulmonary blood flow, although reported values range from zero to 50 per cent.

Table 26

Studies of venous admixture during anaesthesia

	Studies near normal arterial P_{O_2}		*Studies at high* P_{O_2}	
	Alveolar P_{O_2} (*mm Hg*)	*Venous admixture* (%)	*Alveolar* P_{O_2} (*mm Hg*)	*Venous admixture* (%)
Anaesthesia with spontaneous respiration				
Stark and Smith (1960)	—	—	584	17·8
Nunn (1964)	97	21·0	660	13·5
	149	11·3		
Anaesthesia with artificial ventilation				
Campbell, Nunn and Peckett (1958)	102	9·3	—	—
Stark and Smith (1960)	—	—	615	22·7
Sykes, Young and Robinson (1965)*				
Group I	133	10·7	—	—
Group II	133	8·6	—	—
Nunn, Bergman and Coleman (1965)	155	9·3	662	10·8
Some comparable studies in conscious man				
Campbell, Nunn and Peckett (1958)	102	6·2	—	—
Cole and Bishop (1963)	107	3·6	653	1·2
Nunn and Bergman (1964)	106	5·7	665	1·3

* In Sykes, Young and Robinson (1965) Group II patients enjoyed a higher tidal volume than patients in Group I.

To facilitate comparisons, all calculations of venous admixture in this table are based on an assumed arterial/venous oxygen content difference of 3·5 vols. per cent, but in certain cases the original authors have not chosen this value. If the reader prefers to assume an arterial/venous content difference of 5 vols. per cent, values in this table should be reduced by about 25 per cent.

Additional studies have been reviewed by Cole and Bishop (1963) for conscious man, and by Laver and Seifen (1965) for those during anaesthesia.

The effect of age of the patient is quite marked, with more severe venous admixture occurring in the older patients (*Figure 90*). This appears to be a general effect not confined to anaesthesia, and many workers have reported a significant negative correlation between age and arterial P_{O_2} in normal conscious man and in the post-operative period (*see* below). This subject has been reviewed by Nunn (1965).

Pre-operative changes in arterial P_{O_2} are considered in some detail in Chapter 12 (page 376). The changes are small and have not been found by all investigators. It therefore seems unlikely that premedication or preparation for surgery causes any serious change in the degree of venous admixture.

The influence of time on venous admixture during anaesthesia.—Young healthy patients who are adequately ventilated do not as a rule show a progressive increase of their venous admixture during anaesthesia, while older patients often do so (Nunn, Bergman and Coleman, 1965). Bendixen, Hedley-Whyte and Laver (1963) showed a strong relationship between the progressive increase in venous

admixture and the ventilation (indicated as P_{CO_2}). Progressive falls of P_{O_2} do not, however, occur in all patients during anaesthesia. Theye and Tuohy (1964a) have studied changes in P_{O_2} during anaesthesia and did not observe any pattern of change in alveolar/arterial P_{O_2} gradients with time in individual patients. Askrog and his colleagues (1964) have reported serial changes during anaesthesia and, although they do not define the limits within which they controlled the concentration of oxygen in the inspired gas, their results, prolonged over 150 minutes, did not show progressive falls of arterial P_{O_2} of the type reported by Bendixen and his colleagues. Additional evidence has now been obtained by Sykes, Young and Robinson (1965). Patients in their Group I were maintained at reasonably constant levels of ventilation, arterial P_{CO_2} and alveolar P_{O_2}, but showed no change in alveolar/arterial P_{O_2} gradient with time (42 mm Hg at 25 minutes and 41·6 mm Hg at 80 minutes). Panday and Nunn (1968) reported stability of arterial P_{O_2} in most patients of a series breathing spontaneously during anaesthesia.

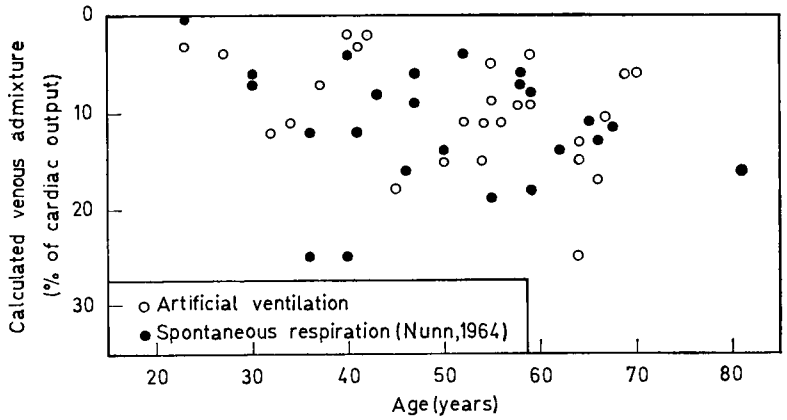


Figure 90. Calculated venous admixture during anaesthesia plotted against age shows an increase which approached the 95 per cent limit of confidence in the study of Nunn, Bergman and Coleman (1965). Values in this diagram were measured or interpolated at 30 minutes after the induction of anaesthesia. (Reproduced by courtesy of the Editor of the British Journal of Anaesthesia)

In the post-operative period venous admixture is one of the causes of the arterial hypoxaemia which is often present. Sometimes it is evident that venous admixture is due to shunting through collapsed lung. However, in the early post-operative period there may also be appreciable venous admixture which cannot be shown to be due to collapsed lung. A study by Bay, Nunn and Prys-Roberts (1968) showed that post-operative hypoxaemia due to an increased alveolar/arterial P_{O_2} difference was not always due to increased venous admixture but might be due to excessive desaturation of mixed venous blood which could cause arterial hypoxaemia when the venous admixture was within the normal limit. Many factors influence the arterial P_{O_2} in the post-operative period and they are considered in Chapter 12 (page 375).

Hyperinflation of the lungs may diminish venous admixture during anaesthesia

(Bendixen, Hedley-Whyte and Laver, 1963). This effect was shown by Butler and Smith in 1957 during the artificial ventilation of a patient with poliomyelitis. Further data have been reported by Bendixen and his colleagues (1964) and Nunn, Bergman and Coleman (1965). Pressures as high as 40 cm H_2O are usually required and, even then, the manœuvre is not always successful. Inflations to lower pressure are seldom effective.

The nature of the inspired gas has surprisingly little effect on the venous admixture which develops during anaesthesia. One hundred per cent oxygen, N_2O/O_2 mixtures and N_2/O_2 mixtures all produce venous admixture of the same order, suggesting that the solubility of the alveolar gas in blood is of little importance under these circumstances (Nunn, Bergman and Coleman, 1965; Webb and Nunn, 1967).

The relative contribution of shunt and V/Q scatter is difficult to assess during anaesthesia. Studies at high levels of inspired oxygen measure only frank shunt, and such studies have indicated a level of venous admixture which is clearly sufficient to account for the venous admixture reported during the inhalation of 30 per cent oxygen (*Table 26*). The effect of V/Q scatter would only be expected to become fully apparent at lower levels of alveolar P_{O_2} for the reason illustrated in *Figure 87*. Only one study has reported values of alveolar P_{O_2} less than 100 mm Hg and this has shown a significantly larger venous admixture at an alveolar P_{O_2} of 97 mm Hg than at an alveolar P_{O_2} of 149 mm Hg (Nunn, 1964). This suggests that pronounced scatter of V/Q ratios occurs during anaesthesia, but does not permit direct quantification of the magnitude of the effect.

A Comparison between Emphysema and Anaesthesia

This is invited by the similarity of physiological dead space and venous admixture in the two conditions (Donald and his colleagues, 1952). At first sight, it might be thought that anaesthesia produces a reversible emphysema-like state of the lungs. However, this outlook is untenable for the following reasons. Firstly, the changes in physiological dead space and venous admixture during anaesthesia are dissociated from one another. The data of Nunn, Bergman and Coleman (1965) combined with those of Nunn (1964) have been examined to determine the correlation between physiological dead space and venous admixture in individual patients. There is none. Secondly, the distribution of inspired gas has now been found to be normal during anaesthesia (Bergman, 1963b) and defects of distribution are a consistent finding in patients with severe emphysema. Finally, the slope of the expired CO_2 concentration (plotted against expired volume) is practically normal during anaesthesia (Nunn and Hill, 1960). This is in contrast to patients with emphysema in whom the capnogram is steeply sloping and characteristic of their condition (page 205).

The Cause of the Venous Admixture during Anaesthesia

It is generally assumed that venous admixture during anaesthesia consists largely of flow through collapsed lung. I have considered above (page 240) the possibility of arteriovenous shunts contributing to the total venous admixture. This gains some support from the observation of Webb and Nunn (1967) that the avoidance of 100 per cent oxygen and N_2O/O_2 mixtures (both highly

soluble in blood) does nothing to reduce the venous admixture during anaesthesia. Furthermore, there are patients with a large venous admixture which cannot be reduced by hyperinflation of the lungs. It is, however, difficult to distinguish between pulmonary collapse and other forms of pulmonary arteriovenous shunting. Further light on the cause of venous admixture will probably require a fresh approach using new methods. It is also important to discard the belief that all increases in the alveolar/arterial Po_2 difference of anaesthetized patients must be due to venous admixture. It is now clear that venous desaturation (due to a cardiac output which is insufficient for the oxygen consumption) can cause a substantial increase in the alveolar/arterial Po_2 difference in the presence of normal venous admixture.

Venous Admixture in Other Conditions which are of Interest to the Anaesthetist

Increased venous admixture features in almost all the conditions in which the anaesthetist plays a part in therapy. Types of venous admixture are listed in *Table 22* and are discussed on pages 235 et seq. However, venous admixture in a patient may be caused by more than one physiological malfunction at a time. In pulmonary oedema, the pulmonary vessels may course through oedematous tissue through which gas exchange is not possible. On the other hand, alveoli may be flooded to the extent of preventing ventilation and, if their circulation persists, it will constitute venous admixture.

Reference has already been made to the loss of 'surfactant' lipoprotein in the respiratory distress syndrome of the newborn (hyaline membrane disease) and in the somewhat similar condition which occasionally follows open heart surgery performed with the aid of a pump oxygenator (Tooley, Finley and Gardner, 1961). In the latter condition, the histological picture in the lungs of dogs consists of patchy collapse, perivascular oedema and haemorrhage, all of which could contribute to the venous admixture which is found (Nahas and his colleagues, 1965a and b).

Pulmonary embolus probably causes venous admixture for a wide variety of reasons. In the first place, it is likely that some alveoli are blocked with exudation and haemorrhage which may proceed to frank collapse of large areas. In addition, there is the possibility of the opening of pulmonary arteriovenous anastomoses secondary to the pulmonary hypertension caused by the embolization (page 240).

Reference has been made to the venous admixture which follows collapse caused by obstruction of the air passages. It is usual for the Po_2 of the sequestered gas to equilibrate with that of mixed venous blood before complete collapse actually occurs (page 236). Blood flowing through these regions will then constitute venous admixture (Nunn and his colleagues, 1965b), and it is difficult to distinguish between this effect and true collapse. The latter is, however, less easy to reverse.

Crushed chest injuries also present multiple causes of venous admixture. Reid and Baird (1965) report disruption of alveolar structure, interstitial and intra-alveolar haemorrhage and collapse due to plugging of bronchioles with secretions and debris. It is hardly surprising that all investigators report severe interference with arterial oxygenation in this condition.

Any of the patients treated by an anaesthetist may suffer from concomitant lung disease featuring venous admixture. The causes of this venous admixture include excessive bronchial venous drainage into the pulmonary veins, all grades of collapse and extreme degrees of scatter of V/Q ratios.

Acute myocardial infarction has been shown to result in substantial arterial hypoxaemia. This is not usually associated with a rise of P_{CO_2} and the alveolar/arterial P_{O_2} difference is enlarged, corresponding to high values for calculated venous admixture. The calculated venous admixture is much diminished during the breathing of oxygen, suggesting that the main disorder is increased scatter of V/Q ratios rather than true shunting (Valentine and his colleagues, 1966). A high alveolar/arterial P_{O_2} difference, suggesting increased venous admixture, has been reported in patients with severe head injuries (Froman, 1968).

Most patients seen in the intensive care unit have an abnormal degree of venous admixture. It will seldom be possible to pinpoint the precise cause of the venous admixture, although this should not discourage an active study of the ability of the patient to oxygenate his arterial blood. The results of such investigations will be valuable for prognosis and therapy, and it is not essential to know the precise cause of venous admixture for its alleviation by oxygen therapy. Firmer diagnosis is, of course, required if attempts are to be made to re-expand frank areas of collapse. This is usually obtainable by radiography.

PRINCIPLES OF ASSESSMENT OF DISTRIBUTION OF PULMONARY BLOOD FLOW

Measurement of Unilateral Pulmonary Blood Flow

Reference has been made to the considerable difficulty of measuring unilateral blood flow in the intact subject. Direct measuring devices may be attached to, or inserted into, the left and right pulmonary arteries, but clearly such methods are of limited application to the human subject. Most attempts to measure unilateral pulmonary blood flow in the human subject are based on an endeavour to apply the Fick principle using oxygen as the indicator gas. Divided airway techniques such as the Carlen's catheter enable the investigator to measure unilateral oxygen uptake and unilateral ventilation.

The pulmonary arterial blood is common to both lungs and the only remaining problem is the measurement of the oxygen content of the blood draining each lung separately. This cannot be determined directly. Even if it were feasible to cannulate pulmonary veins, it would not be possible to sample proportionately from the two pulmonary veins which drain each lung. Their flow rate and oxygen content are both likely to be different, at least in the upright position. The usual approach is to measure the end-expiratory P_{O_2} and assume that the pulmonary venous P_{O_2} is less than this by a certain amount. Alternatively, the 'ideal' alveolar P_{O_2} may be calculated for each lung indirectly from its end-expiratory P_{CO_2}. Clearly these approaches are very indirect, although it is feasible to calculate the likely error of the technique. The error is less than might be imagined since the shape of the oxygen dissociation curve limits the likely range of pulmonary venous oxygen content (in

contrast to tension). Elaborate attempts have been made to assess the validity of observations which have been made (Defares and his colleagues, 1960).

On a simpler plane, some estimate of blood flow may be obtained from measurements of unilateral ventilation and oxygen uptake. Clearly, if the ventilation of the two lungs is similar and the oxygen uptake differs, it may be assumed that the blood flow rates differ by approximately the same extent. However, because ventilation and blood flow alter the pulmonary venous oxygen content, it is impossible to make a precise assessment of blood flow from the simple measurements made with the bronchospirometer.

It is possible to deflect the pulmonary blood flow away from one lung, and so to study the ability of the other lung to take the whole of the pulmonary circulation. This may be achieved by inflation of a balloon on the end of a cardiac catheter within one branch of the pulmonary artery (Carlens, Hanson and Nordenström, 1951). It is also possible to combine this procedure with bronchial occlusion and so to reproduce the cardio-respiratory effects of pneumonectomy (Nemir and his colleagues, 1953).

Measurement of Pulmonary Lobar Blood Flow

By intubation, the right upper lobe bronchus may be isolated in man (Mattson and Carlens, 1955), and the oxygen consumption of this lobe may therefore be estimated. It is found to be considerably less than proportionate to its ventilation and this indicates a low rate of perfusion.

End-expiratory gases sampled from different lobes at bronchoscopy will give some qualitative indication of blood flow, although precise calculation of flow is not possible. A simple estimate of ventilation/perfusion ratio may be obtained from the respiratory exchange ratio (Armitage and Taylor, 1956). A more complete assessment has been made by the simultaneous analysis of a number of gases exhaled from various bronchi, using a mass spectrometer at bronchoscopy (Hugh-Jones and West, 1960).

Measurement of Perfusion of Horizontal Slices of the Lung

Reference has already been made to the measurement of ventilation of horizontal slices of the lung with the aid of radioactive isotopes (page 233). The same technique permits measurement of perfusion in the same slices. The most suitable isotope is oxygen-15 from which carbon dioxide may be prepared. If a gas mixture containing labelled carbon dioxide is inhaled, the rate of increase of local counts will indicate the regional ventilation. When the breath is held in inspiration, the labelled carbon dioxide rapidly passes into the pulmonary blood and so the decay of the count (the biological component not the physical component) will indicate the circulation. It is not immediately apparent why the labelled carbon dioxide should be taken up by the blood. Although there is a *net* transfer of carbon dioxide from blood to gas, there is in fact a free exchange of molecules in both directions. For the labelled carbon dioxide there is a large tension gradient from gas to blood, and therefore there is a rapid uptake. Details of the technique and the method of counting are given by West and his colleagues (1962).

The use of oxygen-15 is curtailed by the fact that the half-life is only a few minutes. Samples are therefore prepared in a cyclotron as required. An

alternative is provided by xenon-133 which has a much longer half-life and therefore is more convenient to handle. Xenon-133 may be inhaled to study the spatial distribution of ventilation or it may be administered intravenously (dissolved in saline) for study of regional perfusion of the lung (Ball and his colleagues, 1962).

Measurement of Venous Admixture

The usual method of calculation of venous admixture is by solution of the equation shown in *Figure 85*. It has been explained above that when the alveolar P_{O_2} is less than about 200 mm Hg, scatter of V/Q ratios contributes appreciably to the total calculated venous admixture. This effect is maximal when the alveolar P_{O_2} is within the range 50–80 mm Hg. When the subject breathes a high oxygen concentration, the calculated venous admixture contains only a small component due to scatter of V/Q ratios. Nevertheless, the calculated quantity still does not indicate the precise value of shunted blood since some of the shunt consists of blood of which the oxygen content is unknown (e.g. from bronchial veins and venae cordis minimae). The calculated venous admixture is thus at best an index rather than a precise measurement of contamination of arterial blood with venous blood.

In the equation shown in *Figure 85*, some of the quantities on the right-hand side are amenable to direct measurement. The arterial and mixed venous oxygen contents may be derived by sampling and analysis. Arterial blood may be drawn from any convenient systemic artery, but the mixed venous blood must be withdrawn from the right ventricle or pulmonary artery. Blood in the right atrium is not perfectly mixed, and blood from inferior and superior venae cavae and coronary sinus forms separate streams. The major problem is, however, measurement of alveolar P_{O_2}. If *Figure 89* is studied in conjunction with *Figure 85*, it will be seen that the 'alveolar' P_{O_2} required for measurement of venous admixture is the 'ideal' alveolar P_{O_2} and not the end-expiratory P_{O_2} since the end-expiratory gas is contaminated with alveolar dead space gas if this is present.

The alveolar air equation.—'Ideal' alveolar gas cannot be sampled and its P_{O_2} must be derived by indirect means (page 252). Derivation of the 'ideal' alveolar P_{O_2} was first suggested by Benzinger (1937) and later by Rossier and Méan (1943). It was finally formulated with greater precision by Riley and his colleagues (1946).

Derivation of the 'ideal' alveolar P_{O_2} is based on the following considerations.

(1) Quite large degrees of venous admixture or V/Q scatter cause relatively little difference between P_{CO_2} of 'ideal' alveolar gas (or pulmonary end-capillary blood) and arterial blood (*Table 24*). Therefore 'ideal' alveolar P_{CO_2} is approximately equal to arterial P_{CO_2}.

(2) The respiratory exchange ratio of ideal alveolar gas (in relation to inspired gas) equals the respiratory exchange ratio of mixed expired gas (again in relation to inspired gas).

From these considerations it is possible to derive an equation which indicates the 'ideal' alveolar P_{O_2} in terms of arterial P_{CO_2}, inspired gas P_{O_2}, respiratory exchange ratio or related quantities. As a very rough approximation, the

oxygen and carbon dioxide in the alveolar gas replace the oxygen in the inspired gas. Therefore, very approximately:

$$\underset{P_{O_2}}{\text{alveolar}} \fallingdotseq \underset{P_{O_2}}{\text{inspired}} - \underset{P_{CO_2}}{\text{arterial}}$$

This is not sufficiently accurate for use except in the special case considered below. In practice three corrections are required to overcome errors due to the following factors: (*a*) usually, less CO_2 is produced than oxygen is consumed (respiratory exchange ratio); (*b*) the respiratory exchange ratio produces a secondary effect due to the fact that the expired volume does not equal the inspired volume; (*c*) the inspired and expired gas volumes may also differ because of inert gas exchange.

We may now see how corrections are applied to produce successive improvements in the accuracy of the equation.

(1) The simplest practicable form of the equation is that suggested by Benzinger (1937) and Rossier and Méan (1943). It makes correction for the principal effect of the respiratory exchange ratio (*a*), but not the small supplementary error due to the difference between the inspired and expired gas volumes which results from the respiratory exchange ratio (*b*):

$$\text{alveolar } P_{O_2} = \text{inspired } P_{O_2} - \frac{\text{arterial } P_{CO_2}}{\text{respiratory exchange ratio}}$$

This form is suitable for rapid bedside calculations of alveolar P_{O_2}, when great accuracy is not required.

(2) One stage more complicated is an equation which allows for differences in the volume of inspired and expired gas due to the respiratory exchange ratio, but still does not allow for differences due to the exchange of inert gases. This equation exists in various forms, all algebraically identical:

$$\underset{P_{O_2}}{\text{alveolar}} = P_{I_{O_2}} - \frac{Pa_{CO_2}}{R}(1 - F_{I_{O_2}}(1 - R))^*$$

(derived from Riley and his colleagues, 1946)

This equation is suitable for use whenever the subject has been breathing the inspired gas mixture long enough for the inert gas to be in equilibrium. It is unsuitable for use when the inspired oxygen concentration has recently been changed, when the ambient pressure has recently been changed (e.g. during hyperbaric oxygen therapy), or when the inert gas concentration has recently been changed (e.g. soon after the start or finish of a period of inhaling nitrous oxide. It will thus be clear that this form of the alveolar air equation has only limited application to those patients with whom the anaesthetist is likely to be concerned. These considerations have been discussed in detail by Nunn (1963).

(3) Perhaps the most satisfactory form of the alveolar air equation is that which was advanced by Filley, MacIntosh and Wright (1954). This equation makes no assumption that inert gases are in equilibrium and allows for the difference between inspired and expired gas from whatever cause. It also

* Symbols are listed in Appendix C.

proves to be very simple in use and does not require the calculation of the respiratory exchange ratio:

$$\overset{\text{alveolar}}{P_{O_2}} = P_{I_{O_2}} - Pa_{CO_2} \frac{P_{I_{O_2}} - P\bar{E}_{O_2}}{P\bar{E}_{CO_2}}$$

If the alveolar P_{O_2} is calculated separately according to the last two equations, the difference (if any) will be that due to inert gas exchange. This affords a method of study of such phenomena as so-called diffusion anoxia (Fink, Carpenter and Holaday, 1954).

Calculation of alveolar P_{O_2} *of a patient breathing 100 per cent oxygen.*—When the inspired oxygen concentration approximates to 100 per cent, the 'ideal' alveolar gas contains only oxygen and carbon dioxide. Under these special circumstances a very simplified form of the alveolar air equation is applicable:

$$\overset{\text{alveolar}}{P_{O_2}} = \overset{\text{inspired}}{P_{O_2}} - \overset{\text{arterial}}{P_{CO_2}}$$

In general this form should only be used when the inspired oxygen concentration exceeds 90 per cent. It is also applicable to patients breathing air who have a respiratory exchange ratio of exactly 1·0.

The critical reader will have seen that the measurement of venous admixture is a very artificial affair, based on a number of simplifications and assumptions which are only partly true. Before dismissing the whole subject in scorn, it should be realized that this approach, imperfect though it may be, has opened an extremely difficult field to quantification. It will be seen in Chapter 12 that, even if we do not know quite what we are measuring, the measurement of venous admixture is of very considerable practical value in prognosis and therapy.

Distinction between Shunt and the Effect of V/Q Scatter

Shunt and scatter of V/Q ratios will each produce an alveolar/arterial P_{O_2} difference from which a value for venous admixture may be calculated. It is, however, often impossible to say from the measurements whether the disorder is a true shunt or else an excessive scatter of V/Q ratios. Two methods are available for distinction between the two conditions.

If the inspired oxygen concentration is altered, the effect on the arterial P_{O_2} will depend upon the nature of the disorder. If oxygenation is impaired by shunt, the arterial P_{O_2} will always rise by less than the inspired P_{O_2}. If, however, the disorder is due to scatter of V/Q ratios, the arterial P_{O_2} will rise by approximately the same amount as the inspired P_{O_2}. This subject is discussed in some detail in Chapter 12 in relation to oxygen therapy (page 345).

Measurement of the alveolar/arterial P_{N_2} difference is a specific method for quantification of V/Q scatter, since the P_{N_2} difference is entirely uninfluenced by a true shunt. The method has not proved attractive to anaesthetists, mainly because their patients are seldom in a state of complete nitrogen equilibrium which is a prerequisite of the method. Furthermore, the method is technically difficult, requiring the measurement of P_{N_2} to an accuracy which is not easily obtainable. The method is lucidly presented by Rahn and Farhi (1964).

Spread of Ventilation/Perfusion Ratios during Anaesthesia

Since the manuscript for this book was submitted, it has been possible to study the effect of anaesthesia on the spread of ventilation/perfusion ratios between horizontal slices of the lung fields (*Figure 82*, pages 241 et seq. and 247 et seq.).

The study was carried out at Hammersmith Hospital as a joint venture between the Respiratory Research Group and the Division of Anaesthesia (both of the Medical Research Council). Investigators included G. H. Hulands, R. E. Greene, Miss L. C. Iliff and the author. The study was initiated under the guidance of Dr. J. B. West.

Four supine subjects were investigated before and after induction of anaesthesia. Xenon-133 was used to label pulmonary blood flow and inspired gas for vertically moving scans in a transverse section of the thorax at the level of the sixth thoracic vertebra. Scanning was carried out at a lung volume one litre above the functional residual capacity.

When the subjects were conscious, the posterior part of the lung fields (i.e. the dependent zone) was found to be relatively overventilated and overperfused although the differences were much less than those reported between the upper and lower lung zones of subjects in the upright position. These results may be compared with those of Kaneko and his colleagues (1966). Ventilation/perfusion ratios were marginally greater in the anterior layers of the lung fields but the spread of values was small in comparison with the upright position (*Figure 82*).

Following the induction of anaesthesia with thiopentone, neuromuscular blockade with curare, and intubation, the patients were ventilated artificially with 0·7 per cent halothane in oxygen, allowing sufficient rebreathing to maintain the end-expiratory P_{CO_2} at about 40 mm Hg. Scans were repeated and it was found that there were no consistent or significant changes in the pattern of ventilation or perfusion as shown by the technique which was employed. There was no reduction in the relative perfusion of the anterior (uppermost) part of the lung field, as might be caused by pulmonary hypotension. The distribution of ventilation/perfusion ratios was virtually unchanged in all except one patient who showed an increased spread of ratios. However, even this patient did not show a greater spread than is present in the normal conscious subject in the upright position.

This type of anaesthesia does not seem to alter the spread of ventilation/perfusion ratios in horizontal slices of the lung in any way which might account for the increase in alveolar dead space, or the increased alveolar/arterial P_{O_2} difference which is usually observed during anaesthesia. The study did not exclude the possibility that anaesthesia might increase the scatter of ventilation/perfusion ratios within small lung units.

CHAPTER 10

DIFFUSION

FUNDAMENTALS OF THE DIFFUSION PROCESS

Diffusion of a gas is a process by which a net transfer of molecules takes place from a zone in which the gas exerts a high partial pressure to a zone in which it exerts a lower partial pressure. The mechanism of transfer is the random movement of molecules and the term excludes transfer by mass movement of gas in response to a total pressure difference (as occurs during expiration). The partial pressure (or tension) of a gas in a gas mixture is the pressure which it would exert if it occupied the space alone (equal to total pressure multiplied by fractional concentration). The tension of a gas in solution in a liquid is defined as being equal to the tension of the same gas in a gas mixture which is in equilibrium with the liquid.

Typical examples of diffusion are shown in *Figure 91.* In each case there is a net transfer of oxygen from one zone to another in response to a tension gradient. We may note certain points which are common to all three examples.

(1) Total pressure differences play no significant part in gas transfer.

(2) Gas transfer results from the random movement of the molecules and is therefore dependent on temperature.

(3) Gas molecules pass in each direction but at a rate proportional to the tension of the gas in the zone which they are leaving. The *net* transfer of the gas is the difference in the number of molecules passing in each direction, and is thus proportional to the difference in tension between the two zones.

(4) In a static situation, such as the example in *Figure 91a,* the process of diffusion proceeds to equilibrium, when there will be no difference between the tension of the gas in the two zones. There will then be no *net* transfer of the gas, although molecules will continue to pass in both directions but at the same rate.

Conditions are not static for oxygen and carbon dioxide in the living body since oxygen is constantly being consumed while carbon dioxide is being produced. Therefore, static equilibrium cannot be attained as in the case of the open bottle of oxygen in *Figure 91a.* Instead, a dynamic equilibrium is attained with a cascade of oxygen tensions from 160 mm Hg in dry air, down to a few millimetres of mercury at the site of consumption in the mitochondria (*see* Chapter 12). The maintenance of these tension gradients is, in fact, a characteristic of life.

These considerations do not apply to gases and vapours which are not metabolized, such as nitrogen, nitrous oxide and volatile anaesthetic agents. In these cases, there is always a tendency towards a static equilibrium at which all tissue tensions become equal to the tension of the particular gas in the

inspired air. This is attained in the case of nitrogen and would also be attained with an inhalational agent if it were administered for a very long time.

Resistance to Diffusion

In each of the examples shown in *Figure 91*, there is a finite resistance to the

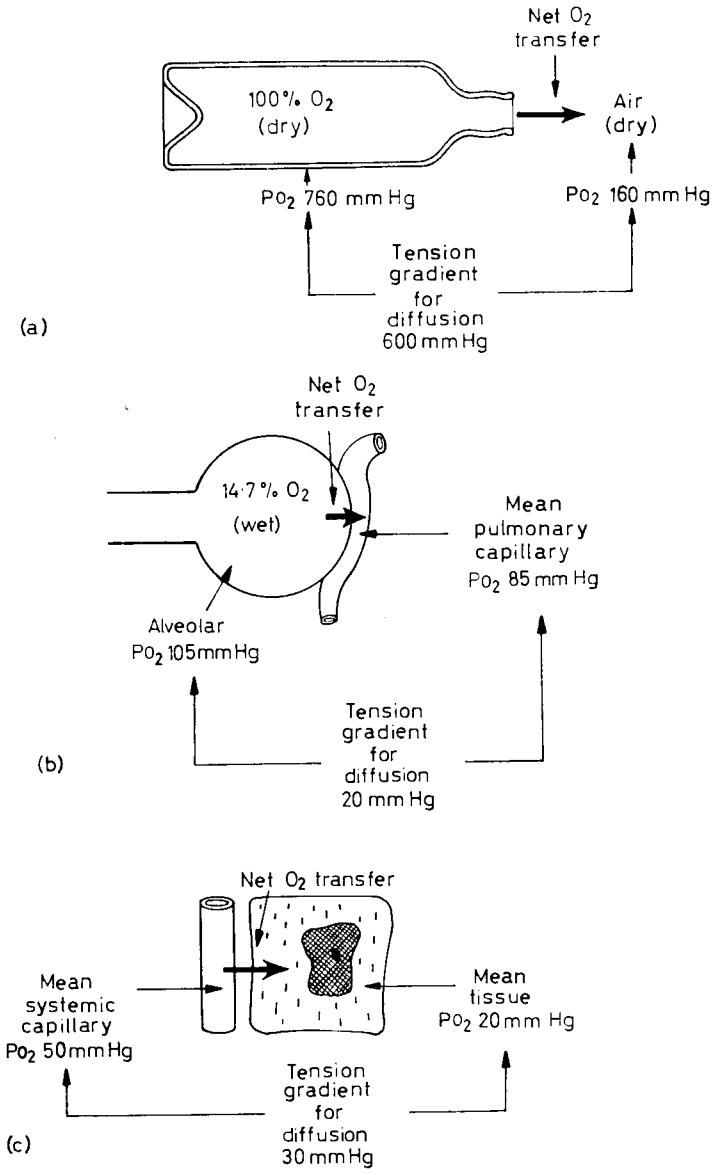


Figure 91. Three examples of diffusion of oxygen. In each case there is a net transfer of oxygen from left to right in accord with the tension gradient. (a) Oxygen passes from one gaseous phase to another. (b) Oxygen passes from a gaseous phase to a liquid phase. (c) Oxygen passes from one liquid phase to another

transfer of the gas molecules. In *Figure 91a*, the resistance is concentrated at the restriction in the neck of the bottle. Clearly, the narrower the neck, the slower will be the process of equilibration with the outside air. In *Figure 91b*, the site of the resistance to diffusion is less circumscribed but includes the alveolar-capillary membrane, the diffusion path through the plasma, and the delay in combination of oxygen with the reduced haemoglobin in the erythrocyte. In *Figure 91c*, the resistance commences with the delay in the release of oxygen by haemoglobin, and includes all the interfaces between the erythrocyte cell membrane and the site of oxygen consumption in the cell (the mitochondria). There may then be an additional component in the rate at which oxygen enters into chemical combination.

There is a clear analogy between the diffusion of gases in response to a partial pressure gradient and the passage of an electrical current in response to a potential difference in an electrical circuit. Diffusing capacity is analogous to conductance (inverse of resistance):

$$\text{diffusing capacity} = \frac{\text{net rate of gas transfer (ml./min.)}}{\text{partial pressure gradient (mm Hg)}}$$

$$\text{conductance} = \frac{\text{current flow (amps)}}{\text{potential difference (volts)}}$$

It will be recalled that the unit of electrical conductance is the *mho*. The usual biological unit of diffusing capacity is ml./min./mm Hg.

The size of gas molecules limits their ability to diffuse, and small molecules diffuse more easily than large molecules. Graham's law states that the rate of diffusion of a gas is inversely proportional to the square root of its density. This means that only large differences in density have any marked effect on the rate of diffusion within a gas phase. Thus, nitrous oxide has a density of 1·4 times that of oxygen, but the rate of gaseous diffusion of oxygen is only 1·2 times that of nitrous oxide.

When a gas is diffusing into or through an aqueous phase, the solubility of the gas in water becomes an important factor and the diffusing capacity under these circumstances is considered to be directly proportional to the solubility. Nitrous oxide would thus be expected to have about 20 times the diffusing capacity of oxygen in crossing a gas/water interface. High solubility does not confer an increased 'agility' of the gas in its negotiation of an aqueous barrier, but simply means that, for a given tension, more molecules of the gas are present in the liquid.

Apart from these factors, inherent in the gas, the resistance to diffusion is related directly to the length of the diffusion path and inversely to the area of interface which is available for diffusion. In the case of the lungs, for example, the diffusion path extends from the gas side of the alveolar membrane to some unspecified reference point within the erythrocyte. The area of interface probably corresponds to the total area of pulmonary capillary endothelium in contact with alveolar lining membrane. It is important to remember that the pulmonary diffusing capacity is as much a measure of the area of the interface as it is of the thickness of the tissues which comprise the diffusion path.

It has recently been shown that the diffusing capacity of oxygen in the lung is markedly influenced by the rate of combination of oxygen with reduced

haemoglobin. Clearly, if this is slow, it will retard the whole process of oxygen transfer and similar considerations apply to release of carbon dioxide from chemical combination.

Tension and Concentration Gradients

In gas mixtures at the same total pressure, the tension of any component gas is directly proportional to its concentration. Therefore, when we consider a gas diffusing from one gas mixture to another, the tension gradient of the gas between the two mixtures will be directly proportional to the concentration gradient. This is not the case when a gas in solution in a liquid diffuses into a different liquid. When gases are in solution, the tension they exert is directly proportional to their concentration in the solvent but inversely to the solubility of the gas in the solvent. Thus, if water and oil have the same concentration of nitrous oxide dissolved in each, the tension of nitrous oxide in the oil will be only one-third of the tension in the water since the oil/water solubility ratio is about 3:1. If the two liquids are shaken up together, there will be a net transfer of nitrous oxide from the water to the oil until the tension in each phase is the same. At that time the concentration of nitrous oxide in the oil will be about three times the level in the water. Under all circumstances, the direction and rate of diffusion are governed by tension gradients and it is therefore more useful to consider *tensions* rather than *concentrations* in relation to movement of gases and vapours from one compartment of the body to another. The same units of pressure may be used in gas, liquid and lipoid phases.

DIFFUSION OF OXYGEN WITHIN THE LUNGS

It is now widely accepted that oxygen passes from the alveoli into the pulmonary capillary blood by a passive process of diffusion according to physical laws. For a long time this view was contested by a school of thought which believed that oxygen was actively secreted into the blood. A similar process was known to occur in the swim-bladders of certain fish, so the postulated mechanism was certainly feasible, but proof of secretion depended on the demonstration of an arterial Po_2 which was higher than the alveolar Po_2. In the earlier years of this century a great controversy raged, with active secretion being upheld by Bohr and Haldane while the Kroghs and Barcroft took the opposite view. Much of the difficulty hinged on the analytical problems and on the sampling of representative alveolar gas, particularly under the conditions of exercise. Finally the day was won by the diffusion school although it was for some time contended that secretion might play a part in adaptation to altitude.

There is now strong evidence for believing that diffusion equilibrium is very nearly achieved for oxygen during the normal pulmonary capillary transit time in the resting subject.* Therefore, under these circumstances, the uptake of oxygen is limited by pulmonary blood flow and not by diffusing capacity. However, under conditions of exercise while breathing gas mixtures deficient in oxygen, the diffusing capacity becomes important and may actually limit the oxygen uptake.

* In the resting subject, blood passes through the pulmonary capillaries in about 0·75 seconds. Transit time decreases as the cardiac output rises (*Table 27*).

The Diffusion Path

The Gas Space within the Alveolus

In the past there has been some doubt as to the degree of gas mixing which occurs within the alveolus. Some believed that gaseous diffusion would not be sufficiently rapid to maintain equality of gas composition between the core (freshly charged with inspired gas) and the periphery of the alveolus (where the oxygen concentration would be lowest, due to uptake by the pulmonary capillaries). 'Layering' of gas would clearly be a factor limiting the uptake of oxygen, and would impose a tension gradient between the centre of the alveolus and the alveolar-capillary membrane.

It is now generally believed that the non-uniformity of gas within a single alveolus is negligible. At functional residual capacity, the diameter of the average human alveolus is of the order of 200 μ (Weibel and Gomez, 1962), and it is likely that mixing is almost instantaneous over the very small distance from the centre to the periphery. Precise calculations are impossible on account of the complex geometry of the alveolus, but the over-all efficiency of gas exchange within the lungs suggests that mixing must be complete within less than 10 milliseconds (Forster, 1964b). Therefore, in practice it is usual to consider alveolar gas as uniformly mixed within a single alveolus.

The Alveolar-capillary Membrane

Electron microscopy has revealed details of the actual path between alveolar gas and pulmonary capillary blood, shown diagrammatically in *Figure 3*. Each alveolus is completely lined with epithelium which, with its basement membrane, is about 0·2 μ thick, except where its nuclei bulge into the alveolar lumen. Beyond the basement membrane is a tissue space which is very thin where it overlies the capillaries: elsewhere it is thicker and contains collagenous and elastic fibres and lymphatics. The pulmonary capillaries are lined with endothelium, also with its own basement membrane, which is approximately the same thickness as the alveolar epithelium, except where it is expanded to enclose the endothelial nuclei. The total thickness of the greater part of the alveolar-capillary membrane is thus about 0·5 μ. The beautiful picture of rat lung published by Weibel (1964) shows how the nuclei tend to be sited in the space between adjacent capillaries, where they cause minimal interference with gas exchange. This arrangement is also shown in *Figure 3*.

Pulmonary Capillaries

Weibel (1962) has suggested a mean diameter of 7 μ for the human pulmonary capillary. This is similar to the diameter of the erythrocyte which is therefore forced into close proximity with the alveolar-capillary membrane. The pulmonary capillary network is seen by studying thick sections, which will occasionally reveal a face view of an alveolar septum. We may then marvel at the delicate lattice structure which is so well adapted to its function. The space between the capillaries is normally less than the diameter of the capillaries themselves (*Figure 3*).

Diffusion within the Blood

Since the diameter of the erythrocytes is so close to that of the capillaries, the diffusion path through plasma may be very short indeed. Furthermore, since the diameter of the erythrocyte is about 14 times the thickness of the alveolar-capillary membranes, it is clear that the diffusion path within the erythrocyte is likely to be much longer than the path through the alveolar-capillary membrane, although the shape of the erythrocyte does tend to concentrate the cell mass at the periphery. Even so, the rim has a thickness of about 2·5 μ, and the diffusion path within it is still large compared with the alveolar-capillary membrane. Once within the cell, diffusion of oxygen is aided by mass movement of the haemoglobin molecules caused by the deformation of the erythrocyte as it passes through the capillary bed. Other factors may be involved since oxygen diffuses through a layer of haemoglobin solution more rapidly than through a layer of water which might be expected to offer less resistance (Hemmingsen and Scholander, 1960).

Uptake of Oxygen by Haemoglobin

The greater part of the oxygen which is taken up in the lungs enters into chemical combination with haemoglobin. This chemical reaction takes a finite time and forms an appreciable part of the total resistance to the transfer of oxygen. Indeed, it now appears that the reaction of oxygen with haemoglobin is sufficiently slow to be the limiting factor in the rate of transfer of oxygen from the alveolar gas into chemical combination within the erythrocyte. This important discovery by Staub, Bishop and Forster in 1961 resulted in an extensive reappraisal of the whole concept of diffusing capacity, since it followed that measurements of 'diffusing capacity' did not necessarily give an indication of the degree of permeability of the alveolar-capillary membrane. It will be seen below that methods exist for analysing the diffusing capacity of carbon monoxide into two components, one through the alveolar-capillary membrane and the other within the pulmonary blood. The latter component is determined by the pulmonary capillary volume and the rate of chemical combination of carbon monoxide with haemoglobin.

Quantification of the Diffusing Capacity for Oxygen

Diffusing capacity of a gas is defined as the rate of its transfer, divided by the tension gradient across the interface. The rate of transfer of oxygen is simply the oxygen uptake, which may be easily measured. The tension gradient is from alveolar gas to pulmonary blood where the relevant tension is the mean pulmonary capillary P_{O_2}.

$$\text{Oxygen diffusing capacity} = \frac{\text{oxygen uptake}}{\text{alveolar } P_{O_2} - \text{mean pulmonary capillary } P_{O_2}}$$

The alveolar P_{O_2} can be derived with some degree of accuracy (page 262) but there are serious problems in estimating the mean capillary P_{O_2}.

Changes of P_{O_2} *in the Pulmonary Capillary*

It is clearly impossible to take a direct measurement of the mean P_{O_2} of the pulmonary capillary blood, and therefore attempts have been made to derive

this quantity indirectly from the presumed changes of P_{O_2} which occur as blood passes through the pulmonary capillaries.

The earliest analysis of the problem was made by Bohr (1909). He made the assumption that, at any point along the pulmonary capillary, the rate of diffusion of oxygen was proportional to the P_{O_2} difference between the alveolar gas and the pulmonary capillary blood at that point. If, for example, the alveolar P_{O_2} is 100 mm Hg and blood enters the pulmonary capillaries at P_{O_2} of 40 mm Hg, the rate of transfer of oxygen at the arterial end of the capillary will be 60 times as great as it will be at that point in the capillary where the P_{O_2} has reached 99 mm Hg. Using this approach it is possible to construct a graph of capillary P_{O_2}, plotted against the time the blood has been in the pulmonary capillary, provided that the following quantities are known: (1) alveolar P_{O_2}; (2) pulmonary arterial P_{O_2} (= mixed venous P_{O_2}); (3) pulmonary end-capillary P_{O_2}; (4) haemoglobin dissociation curve.

Once the curve has been drawn (*Figure 92*), it is relatively easy to derive the effective or integrated mean pulmonary capillary P_{O_2}. This is similar to the technique for the determination of the effective mean intrathoracic or arterial blood pressure, and the graphical method of determination has already been shown in *Figure 32*. The mean pulmonary capillary P_{O_2} is the height of a rectangle whose area is equal to that under the curve and whose length corresponds to the total pulmonary capillary transit time. The actual procedure for deriving the curve is known as the Bohr integration procedure and, for reasons given below, is now largely of historical interest. Those who are interested in the actual mechanics of the operation will find it expounded by Comroe and his colleagues (1962, page 353). Alternatively, graphs have been prepared to do the arithmetic. These graphs are not published but are referred to by Riley, Cournand and Donald (1951).

The Bohr integration procedure was shown to be invalid when it was found that the fundamental assumption was untrue. The rate of transfer of oxygen is *not* proportional to the alveolar/capillary P_{O_2} gradient at any point along the capillary. It would no doubt be true if the transfer of oxygen were a purely physical process (as in the case of nitrous oxide, for example) but the transfer is actually limited by the chemical combination of oxygen with haemoglobin, which is sufficiently slow to comprise the greater part of the total resistance to transfer of oxygen.

In vitro studies of the rate of combination of oxygen with haemoglobin have shown that this is not directly proportional to the P_{O_2} gradient for two distinct reasons.

(1) The combination of the fourth molecule of oxygen with the haemoglobin molecule ($Hb_4(O_2)_3 + O_2 \rightleftharpoons Hb_4(O_2)_4$) has a much higher velocity constant than that of the combination of the other three molecules (Staub, Bishop and Forster, 1961). This is discussed further on page 351.

(2) As the capillary oxygen saturation rises, the number of molecules of reduced haemoglobin diminishes and the velocity of the forward reaction must therefore diminish by the law of mass action. This depends upon the haemoglobin dissociation curve and is therefore not a simple exponential function of the actual P_{O_2} of the blood.

When these two factors are combined it is found that the resistance to

'diffusion' due to chemical combination of oxygen within the erythrocyte is fairly constant up to a saturation of about 80 per cent (Po_2, 45 mm Hg). Thereafter, it falls very rapidly to become zero at full saturation (Staub,

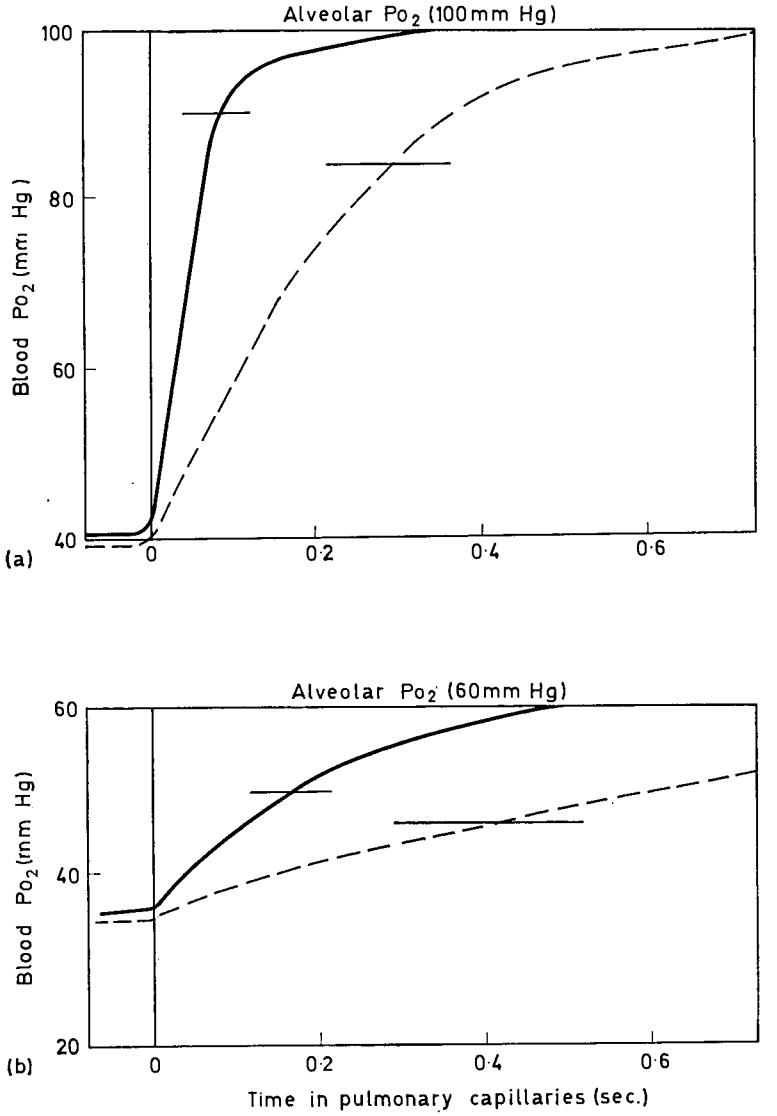


Figure 92. Each graph shows the rise in blood Po_2 *as blood passes through the pulmonary capillaries. The horizontal line at the top of the graph indicates the alveolar* Po_2 *which the blood* Po_2 *is approaching. In (a) the patient is breathing air, while in (b) the patient is breathing about 14 per cent oxygen. The broken curve shows the rise in* Po_2 *calculated according to the Bohr procedure on an assumed value for the alveolar/end-capillary* Po_2 *gradient. The continuous curve shows the values obtained by forward integration (Staub, 1963a). Horizontal bars indicate mean pulmonary capillary* Po_2 *calculated from each curve*

Bishop and Forster, 1962). These authors proceeded to elaborate the Bohr integration procedure to allow for changes in the rate of combination of haemoglobin with oxygen. Assuming traditional values for the alveolar/end-capillary P_{O_2} difference, they obtained a curve lying to the left of the original Bohr curve shown in *Figure 92*. This indicated a mean pulmonary capillary P_{O_2} higher than had previously been believed, and therefore an oxygen diffusing capacity which was substantially higher than the accepted value. The situation is actually one degree more complicated still, since quick-frozen sections prepared by Staub have shown that the colour of haemoglobin is beginning to alter to the red colour of oxyhaemoglobin within the pulmonary arterioles before the blood has entered the pulmonary capillaries.

Uncertainties about the Pulmonary End-capillary P_{O_2}

Both the classical and the modified Bohr integration procedures for calculation of mean capillary P_{O_2} depend critically on the precise value of the pulmonary end-capillary P_{O_2}, and the constructed curve is considerably influenced by very small variations in the value which is assumed. It is therefore appropriate to consider how this value is derived, because it can never be measured directly. Some readers may be content with the simple statement that it is now realized that the pulmonary end-capillary P_{O_2} *cannot* be satisfactorily derived from the arterial P_{O_2}. Others may be interested to read the following paragraphs which explain how it was once thought that it could be done.

The previous chapter has explained how a shunt causes a difference between the P_{O_2} of pulmonary end-capillary and arterial blood. This difference falls to very small values when the alveolar P_{O_2} is reduced to less than about 70 mm Hg. Now it happens that the alveolar/end-capillary P_{O_2} difference caused by resistance to diffusion behaves in exactly the opposite way. When the alveolar P_{O_2} is low, the mixed venous P_{O_2} is not reduced by an equal amount because it falls along the steep part of the dissociation curve. Therefore the alveolar/mixed venous P_{O_2} difference is much less than it is when the patient has a normal alveolar P_{O_2}. Consequently, the transfer of oxygen is slower and the alveolar/end-capillary P_{O_2} difference is greater when the alveolar P_{O_2} is low. Riley and his colleagues (1946) therefore suggested that alveolar and arterial P_{O_2} should be compared when the subject was breathing first air and then 11 per cent oxygen. At the alveolar P_{O_2} of the first pair of observations, the component of the alveolar/arterial P_{O_2} difference due to resistance to diffusion would be small and the total difference would thus be largely due to venous admixture: under the conditions of the second pair of observations, the component of the difference due to venous admixture would become small while the difference due to resistance to diffusion would be appreciable. It was assumed that both the diffusing capacity and the venous admixture would remain the same while breathing air and 11 per cent oxygen. Typical normal values obtained by this approach were as follows.

	breathing air	*breathing 11% oxygen*
Venous admixture component	9 mm Hg	1 mm Hg
'Diffusion' component	1 mm Hg	9 mm Hg
Total alveolar/arterial P_{O_2} difference	10 mm Hg	10 mm Hg

Unfortunately, the two-level oxygen study made two assumptions which are now known to be incorrect. Firstly, the component of the alveolar/arterial P_{O_2} difference

due to venous admixture does not fall to small values when the alveolar P_{O_2} is reduced, because a considerable part of it is now known to be due to regional scatter of ventilation/perfusion ratios (*Figure 86*), and this component actually increases as the alveolar P_{O_2} falls (*Figure 87*).

The second fallacy is that the resistance to diffusion should be uninfluenced by the actual level of the arterial P_{O_2}. It has been explained above that the major part of the resistance to 'diffusion' is due to the rate of chemical combination of oxygen with haemoglobin and we have seen that the rate of combination is very markedly influenced by the actual level of P_{O_2}.

The present position of the two-level oxygen method may be summarized as follows.

(1) It is not possible to derive the alveolar/end-capillary P_{O_2} gradient by the two-level method or, indeed, by any other known method.

(2) Were it possible to derive the alveolar/end-capillary P_{O_2} gradient, it would still be very difficult to derive the mean pulmonary capillary P_{O_2} because of the important and variable influence of the rate of combination of oxygen with haemoglobin.

We are thus at least two stages away from the possibility of measuring the mean pulmonary capillary P_{O_2} and therefore cannot, in the present state of knowledge, measure the diffusing capacity for oxygen. Measurements reported in the earlier literature were based on false assumptions and cannot therefore be regarded as valid.

'*Forward Integration and Let the Chips Fall where They May*' (Staub, personal communication)

The preceding paragraphs have brought us to the position where we can appreciate that it might be possible to derive the mean pulmonary capillary P_{O_2} if we knew the end-capillary P_{O_2}. However, we cannot derive the end-capillary P_{O_2} and seem unlikely to be able to do so in the foreseeable future. A new and entirely opposite approach was made by Staub in a most important paper in 1963 (a). Staub started from what was known about the behaviour of oxygen in the pulmonary capillary and, beginning at the pulmonary arterial end, calculated the P_{O_2} of the capillary blood progressively along the capillary until he was able to give an estimate of the remaining alveolar/capillary P_{O_2} gradient at the end of the capillary. This procedure of forward integration was thus the reverse of the classical approach which, starting from the alveolar/end-capillary P_{O_2} gradient, worked backwards to see what was happening along the capillary.

It is useful to list Staub's assumptions.

(1) The ability of oxygen to penetrate the alveolar-capillary membrane was taken to be 1·23 times that of carbon monoxide, which is measured more readily (*see* page 286). The ratio of 1·23 expresses the difference in density and water solubility of the two gases.

(2) The volume of blood in the pulmonary capillaries was taken to be 86 ml. in resting subjects, the value being derived from studies with carbon monoxide (*see* below).

(3) Staub used his own previously published data on the rate of uptake of oxygen by blood (Staub, Bishop and Forster, 1961 and 1962).

(4) It was assumed that distribution of ventilation and perfusion was ideal.

Staub's forward integrations gave startling results. They suggested that alveolar/end-capillary P_{O_2} gradients were very much smaller than had previously been thought. Papers by Asmussen and Nielsen (1960) and Thews (1961) had presaged much of Staub's conclusion and, at the time of writing, there is no strong dissent from his view which is a radical departure from what was believed prior to 1963. The results of Staub's calculations are summarized in *Table 27.*

Table 27

Values for the alveolar/end-capillary P_{O_2} *gradient suggested by the Forward Integration Procedure of Staub (1963a).*

Conditions	*Capillary transit time (sec.)*	*Alveolar/end-capillary* P_{O_2} *gradient (mm Hg)*
Resting subject		
($\dot{V}_{O_2}$ = 270 ml./min.)		
Breathing air ($P_{A_{O_2}}$ = 100 mm Hg)	0·760	0·000,000,01
Breathing low oxygen ($P_{A_{O_2}}$ = 47 mm Hg)	0·636	0·2
Moderate exercise		
($\dot{V}_{O_2}$ = 1,500 ml./min.)		
Breathing low oxygen ($P_{A_{O_2}}$ = 55 mm Hg)	0·476	4·0
Heavy exercise		
($\dot{V}_{O_2}$ = 3,000 ml. min.)		
Breathing air ($P_{A_{O_2}}$ = 120 mm Hg)	0·496	< 0·001
Breathing low oxygen ($P_{A_{O_2}}$ = 59 mm Hg)	0·304	16·0

Abbreviations: $\dot{V}_{O_2}$, oxygen consumption; $P_{A_{O_2}}$, alveolar P_{O_2}.

Reduction in capillary transit time is a major factor in the development of the end gradient during exercise, but a decreased transit time is an inevitable accompaniment of raised cardiac output.

Within the limitations of Staub's assumptions we may draw the following conclusion:

> 'Impaired diffusing capacity is unlikely to result in measurable reduction of arterial P_{O_2} provided that a normal level of alveolar P_{O_2} is maintained and the patient remains in the resting state.'

Thus, under the conditions in which a patient comes under the care of an anaesthetist, it is unlikely that impairment of diffusing capacity will be an important factor in the causation of arterial hypoxaemia.

The Cause of Hypoxaemia Previously Thought to be Due to Alveolar/Capillary Block

These iconoclastic views on the magnitude of the alveolar/end-capillary P_{O_2} gradient demand some explanation of the reported cases of arterial hypoxaemia which were previously ascribed to defective diffusing capacity or

alveolar/capillary block. It must be realized that the extent of the regional scatter of ventilation/perfusion ratios has only recently been appreciated and in the past it was usual to think of distribution disturbances as due solely to shunt or alveolar dead space, as in the model shown in *Figure 89*. Finley, Swenson and Comroe (1962) have studied a group of patients previously thought to have pure alveolar/capillary block, and found that in each case the arterial hypoxaemia could be explained by disturbances of distribution without the need to invoke an alveolar/end-capillary P_{O_2} gradient.

The present position regarding the diffusion of oxygen within the lung may be summarized as follows.

(1) There is no acceptable method for measurement of the oxygen diffusing capacity.

(2) Impairment of oxygen diffusing capacity is unlikely to cause a significant reduction of the arterial P_{O_2} in the resting patient with a normal alveolar P_{O_2}.

DIFFUSION OF CARBON MONOXIDE WITHIN THE LUNGS

The diffusion of carbon monoxide has been studied in detail because it is one of the few gases for which measurement of the diffusing capacity is feasible. Furthermore, the uptake of carbon monoxide is *diffusion limited* in contrast to oxygen uptake which is normally *perfusion limited.*

By an elaboration of the technique for measurement of the diffusing capacity of carbon monoxide, it is possible to arrive at an estimate of the resistance to diffusion afforded by the alveolar capillary membrane. This value may give a valuable indication of the general functional state of the lung and may also be extrapolated to derive the resistance to diffusion of oxygen. However, it is now believed that the carbon monoxide diffusing capacity, as usually measured, embraces wider aspects of pulmonary function than just diffusion. Furthermore, it is recognized that alveolar/capillary resistance to diffusion is less important for arterial oxygenation than was formerly believed. For these reasons the popularity of measurement of carbon monoxide diffusing capacity has not risen in Great Britain and there are many centres in which the measurement is not routinely made.

The outstanding difficulty in the measurement of the oxygen diffusing capacity is derivation of the mean pulmonary capillary P_{O_2}. Turning away from this intractable problem, it was reasonable to consider measuring the diffusing capacity of carbon monoxide as a substitute for oxygen, since the affinity of carbon monoxide for haemoglobin is so high that, for all practical purposes, the tension of the gas in the pulmonary capillary blood remains at zero throughout the usual procedures for measurement of the carbon monoxide diffusing capacity. The formula for calculation of this quantity then simplifies to the following:

$$\text{diffusing capacity for carbon monoxide} = \frac{\text{carbon monoxide uptake}}{\text{alveolar } P_{CO}}$$

(Compare with equation for oxygen, page 271.) The mean pulmonary capillary P_{CO} is deleted from the equation because it is equal to zero. There are no insuperable difficulties in the measurement of either of the quantities on

the right-hand side of the equation, and the methods are outlined at the end of the chapter.

The Diffusion Path for Carbon Monoxide

Diffusion of carbon monoxide within the alveolus, through the alveolar-capillary membrane and through the plasma is governed by the same factors which apply to oxygen and have been outlined above. The quantitative difference is due to the different vapour density and water solubility of the two gases. These factors indicate that the rate of diffusion of oxygen up to the point of entry into the erythrocyte is 1·23 times the corresponding rate for carbon monoxide. It will be remembered that the rate of diffusion is directly proportional to water solubility of the gas and inversely to the square root of the vapour density (Graham's law).

Uptake of Carbon Monoxide by Haemoglobin

At equilibrium the *affinity* of haemoglobin for carbon monoxide is about 250 times as great as for oxygen. Nevertheless, it does not follow that the *rate* of combination of carbon monoxide with haemoglobin is faster than the rate of combination of oxygen with haemoglobin and it is, in fact, rather slower (Forster, 1964a). The reaction is slower still when oxygen is displaced from oxyhaemoglobin according to the equation:

$$CO + HbO_2 \longrightarrow O_2 + HbCO$$

Thus the reaction rate of carbon monoxide with haemoglobin is reduced when the oxygen saturation of the haemoglobin is high. The inhalation of different concentrations of oxygen thus causes changes in the reaction rate of carbon monoxide with the haemoglobin of a patient. Use has been made of this fact to study the different components of the resistance to diffusion of carbon monoxide in man.

Quantification of the Components of the Resistance to Diffusion of Carbon Monoxide

When two resistances are arranged in series, the total resistance of the pair is equal to the sum of the two individual resistances. Diffusing capacity is analogous to conductance, which is the reciprocal of resistance. Therefore when considering the diffusing capacity of a pair of structures in series, both of which offer resistance to diffusion, the reciprocal of the diffusing capacity of the total system equals the sum of the reciprocals of the diffusing capacities of the two components:*

$$\frac{1}{\text{total diffusing capacity for CO}} = \frac{1}{\text{diffusing capacity of CO through the alveolar-capillary membrane}} + \frac{1}{\text{'diffusing capacity' of CO within the erythrocyte}}$$

The second component on the right-hand side is not really a matter of diffusion,

* Adding of reciprocals has already been encountered in the summation of compliances (page 67).

since the limiting factor to the passage of carbon monoxide within the erythrocyte is the rate of chemical combination with haemoglobin (exactly as in the case of oxygen). This 'diffusing capacity' within the erythrocyte is equal to the product of the pulmonary capillary blood volume and the rate of reaction of carbon monoxide with haemoglobin (θCO), a parameter which varies with the oxygen saturation of the haemoglobin. The equation may now be rewritten:

$$\frac{1}{\begin{matrix}\text{total}\\ \text{diffusing}\\ \text{capacity}\\ \text{of CO}\end{matrix}} = \frac{1}{\begin{matrix}\text{diffusing capacity}\\ \text{of CO through the}\\ \text{alveolar-capillary}\\ \text{membrane}\end{matrix}} + \frac{1}{\left(\begin{matrix}\text{pulmonary}\\ \text{capillary}\\ \text{blood}\\ \text{volume}\end{matrix}\right) \times \left(\begin{matrix}\text{reaction rate}\\ \text{of CO with}\\ \text{haemoglobin}\\ (\theta\text{CO})\end{matrix}\right)}$$

The total diffusing capacity for carbon monoxide may be readily measured by the techniques outlined at the end of this chapter; θCO may be determined, at different values of oxygen saturation, by *in vitro* studies. This leaves two unknowns—the diffusing capacity through the alveolar-capillary membrane and the pulmonary capillary blood volume. By repeating the measurement of total diffusing capacity at different values of θCO (obtained by inhaling different concentrations of oxygen and so varying the oxygen saturation of the haemoglobin), it is possible to obtain two simultaneous equations with two unknowns. It is then possible to solve and derive values for the following.

(1) Total diffusing capacity of carbon monoxide at different levels of oxygenation of the blood.
(2) Diffusing capacity of the alveolar-capillary membrane (presumably independent of oxygenation).
(3) Pulmonary capillary blood volume.
(4) The 'diffusing capacity' of carbon monoxide within the erythrocyte at different values of oxygen saturation.

This elegant approach was introduced by Roughton and Forster (1957). Although the original data appear to undergo an unreasonable amount of manipulation, confidence in the whole operation is engendered by the observed fact that the total diffusing capacity for carbon monoxide is undoubtedly reduced by the inhalation of high concentrations of oxygen. Furthermore, the change occurs very quickly and it would be unreasonable to expect that it was due to changes in the alveolar-capillary membrane. The technique yields normal values for pulmonary capillary blood volume within the range 60–110 ml. These appear astonishingly small, but morphometric studies by Weibel (1962) have indicated a value of about 100 ml. at a lung volume of 2·5 litres. This approximates to the functional residual capacity of the human lung in the supine position.

Normal values obtained by various methods of measurement of the carbon monoxide diffusing capacity have been collected by Forster (1964b) as shown in *Table 28.*

Factors which Influence the Carbon Monoxide Diffusing Capacity

It should not be imagined that the membrane component of the CO diffusing capacity is solely a measure of the thickness or impermeability of the

Table 28

Values obtained by various methods of measurement of diffusing capacity (transfer factor) of carbon monoxide (data from Forster, 1964b)

Technique of measurement	*Total diffusing capacity for CO (ml./min./mm Hg)*	*Membrane diffusing capacity (ml./min./mm Hg)*	*Pulmonary capillary blood volume (ml.)*
Steady state	15	26	73
Single breath	30	57	79
Rebreathing	27	40	110

alveolar-capillary membrane. It is easy to visualize a hard, thick and leathery membrane which is blocking the transfer of gases, but such a condition is by no means the only cause of a reduction of the membrane component of the CO diffusing capacity. Alternative causes for this finding are as follows.

(1) *Reduction in the total surface area available for diffusion.* Clearly a destructive disease such as emphysema will reduce the area for diffusion as the pulmonary capillary bed is destroyed. However, the effective diffusion interface will also be reduced by disorders of distribution. As an extreme example, if the ventilation were restricted to the left lung and the perfusion to the right lung, there would be no effective area of interface and the diffusing capacity would be zero. It is, in fact, meaningless to distinguish between extreme disorders of distribution and diffusion.

(2) *Pulmonary capillary congestion* could impede the uptake of carbon monoxide (or oxygen) into the cell if the capillaries were dilated to the point at which the erythrocytes passed through the capillaries abreast of one another. However, small increases in pulmonary blood volume induced by drugs have been found to increase the diffusing capacity (Lewis and his colleagues, 1960).

Pulmonary oedema is often advanced as a possible cause of reduction in diffusing capacity. Again, it is easy to visualize a thick, waterlogged alveolar-capillary membrane which offers a serious impedance to the passage of gases, but it is doubtful whether interstitial oedema alone is ever sufficiently severe to result in a significant Po_2 gradient between alveolar gas and the blood leaving the pulmonary capillary. More severe pulmonary oedema results in flooding of the alveolus and the blood perfusing such an alveolus is more correctly considered as a shunt, although some might prefer to consider it as localized extreme reduction of diffusing capacity. The distinction is really only semantic. Williams (1953) has suggested that, in an experimental dog preparation, pulmonary oedema caused arterial hypoxaemia as a result of venous admixture. Fortunately, the treatment of a gross reduction in diffusing capacity and a shunt would be the same as regards oxygen therapy.

Body size influences diffusing capacity directly. This is inevitable since alveolar/capillary gas tension gradients are not greatly different in different species or in different-sized individuals while, of course, gas exchange volumes vary directly with size.

Exercise results in an increase in diffusing capacity and some workers believe

that the increase proceeds to a plateau value which is known as the maximal diffusing capacity (Riley and his colleagues, 1954).

Age results in a diminution of both the diffusing capacity and the maximal diffusing capacity.

Posture.—Diffusing capacity is substantially increased when the subject is supine rather than standing or sitting (Ogilvie and his colleagues, 1957). This change is explained in part by the increase in pulmonary blood volume, and the improvement in the uniformity of distribution of perfusion of the lungs.

Maldistribution.—There appears to be no solution to the technical problems involved in the measurement of diffusing capacity in the presence of maldistribution. It is clear that the condition must introduce grave difficulties into the measurement of the alveolar CO level since this is unlikely to be uniform throughout the lungs. It has already been mentioned that gross maldistribution will reduce the effective area for gas exchange and so result in a reduction of the measured 'diffusing capacity'.

Cotes (1965) has presented an excellent exposition of the problem of gas exchange across the alveolar-capillary membrane. He points out that the term 'diffusing capacity' was coined before it was appreciated that chemical reaction rates and scatter of ventilation/perfusion ratios played a significant part in the over-all process of transfer of gas from alveolus to blood. He therefore suggests that 'transfer factor' is a more appropriate term to describe the whole process, although 'diffusing capacity' may still be applied to the alveolar/capillary membrane component of the total transfer factor.

DIFFUSION OF CARBON DIOXIDE WITHIN THE LUNGS

Carbon dioxide has a much higher water solubility than oxygen and, although its vapour density is greater, it may be calculated to penetrate an aqueous membrane about 20 times as rapidly as oxygen. Therefore it was formerly believed that diffusion problems could not exist for carbon dioxide because the patient would have succumbed from hypoxia before hypercapnia could attain measurable proportions. All of this ignored the fact that chemical reactions of the respiratory gases were sufficiently slow to limit the rate of diffusion. Attention was therefore turned to the rate of release of carbon dioxide from its chemical combination in the pulmonary arterial blood.

The carriage of carbon dioxide in the blood is discussed in Chapter 11, but for the moment it is sufficient to say that the essential reactions in the release of carbon dioxide in the pulmonary capillaries are as follows.

(1) Release of some carbon dioxide from carbamino carriage.
(2) Conversion of bicarbonate ions to carbonic acid followed by dehydration to release molecular carbon dioxide.

It will be remembered that the latter reaction involves the movement of bicarbonate ions across the erythrocyte membrane (Hamburger effect) but its rate is probably limited by the dehydration of carbonic acid. This reaction would be very slow indeed if it were not catalysed by carbonic anhydrase which is present in abundance in the erythrocyte. The important limiting role of the

rate of this reaction was elegantly shown in a study by Cain and Otis (1961) of the effect on carbon dioxide transport of inhibition of carbonic anhydrase. This resulted in a large increase in the arterial/alveolar P_{CO_2} gradient corresponding to a gross decrease in the apparent 'diffusing capacity' of carbon dioxide.

Although the rate of release of carbon dioxide from whole blood is not precisely known, it is likely to be of the same order as for oxygen (Forster, 1964b).

Equilibrium is probably very nearly complete within the normal pulmonary capillary transit time. However, even if it were not so, it would be of little significance since the mixed venous/alveolar P_{CO_2} difference is itself quite small (about 6 mm Hg). Therefore an end gradient as large as 20 per cent of the initial difference would still be too small to be of any importance and, indeed, could hardly be measured by modern analytical methods.

Hypercapnia is, in fact, never caused by decreased 'diffusing capacity' except when carbonic anhydrase is inhibited by drugs. Under pathological conditions, hypercapnia may always be explained by other causes, usually an inadequate alveolar ventilation for the metabolic rate of the patient.

The assumption that there is no measurable difference between the P_{CO_2} of the alveolar gas and the pulmonary end-capillary blood is used when the alveolar P_{CO_2} is assumed equal to the arterial P_{CO_2}. The assumption is also made that there is no measurable difference between end-capillary and arterial P_{CO_2}. We have seen in the last chapter (page 245) that this is only partly true and a large shunt will cause an arterial/end-capillary P_{CO_2} gradient of a few millimetres of mercury.

DIFFUSION OF 'INERT' GASES WITHIN THE LUNGS

In the biological sense, inert gases are those which do not undergo chemical changes within the body. This definition includes nitrogen, helium and most of the anaesthetic gases and vapours. Diffusion of these gases is as important to the diver as it is to the anaesthetist, and is an essential consideration in the pharmacokinetics of the inhalational anaesthetic agents.

Since these substances are carried in the blood by purely physical means, their diffusing capacity consists only of the membrane component and there is no limitation due to chemical reaction as in the case of oxygen, carbon monoxide and carbon dioxide. Their diffusing capacities are therefore governed primarily by their water solubilities, and the diffusing capacities of the anaes thetic agents are therefore all very much higher than for oxygen. Heavy molecules such as chloroform, halothane and methoxyflurane result in a high vapour density, but the effect of this is more than offset by their water solubility which is also very high and influences the diffusing capacity in direct proportion. It will be remembered that vapour density only affects diffusing capacity inversely according to its square root, so that its influence is relatively unimportant. Physical properties influencing diffusing capacity are set out in *Table 29.*

Whatever the small differences between the diffusing capacity of different anaesthetic agents, the important point is that they are all high enough for there to be virtually complete equilibrium between alveolar and end-capillary anaesthetic gas tensions at all times during induction of anaesthesia and recovery. It may therefore be assumed that the end-capillary anaesthetic tension

is equal to the alveolar tension, and the actual value of the pulmonary diffusing capacity is thus irrelevant to the pharmacokinetics of the agent. Uptake from the lungs is *blood-flow limited* rather than *diffusion limited.* In this way they differ from carbon monoxide and resemble oxygen and carbon dioxide.

Table 29

The influence of physical properties on the diffusion of gases through a gas/liquid interface

Gas	*Density relative to oxygen*	*Water solubility relative to oxygen*	*Diffusing capacity relative to oxygen*
Oxygen	1·00	1·00	1·00
Carbon monoxide	0·88	0·75	0·80
Nitrogen	0·88	0·515	0·55
Carbon dioxide	1·37	24·0	20·5
Nitrous oxide	1·37	16·3	14·0
Helium	0·125	0·37	1·05
Ether	2·30	580	380
Halothane	5·07	27·3	12·1

Since the diffusing capacity of anaesthetic agents is irrelevant to their rate of uptake, it follows that relative insolubility in no way slows down the rate of onset of anaesthesia. In fact, on the contrary, the more soluble the agent, the greater the quantity which must be transferred to the arterial blood to build up the required tension for narcosis. Therefore, contrary to what might be expected from considerations of diffusing capacity, the more soluble an anaesthetic agent, the slower will be the induction of anaesthesia and recovery.

DIFFUSION OF GASES IN THE TISSUES

In the case of oxygen there is a series of tension gradients from ambient air to the mitochondria of the cells, the site of oxygen consumption and the point at which the Po_2 is lowest (page 331). The series of tension gradients for carbon dioxide is in the reverse direction with the highest values in the mitochondria and the lowest in ambient air.

During induction, anaesthetic gases and vapours diffuse outwards from the capillaries until the tissues reach tension-equilibrium with the incoming blood. During recovery, gases and vapours leave the tissues until zero tension is attained.

Oxygen

Oxygen leaves the systemic capillaries by the reverse of the processes by which it entered the pulmonary capillaries. After leaving the tissue capillaries, oxygen passes to its site of utilization in the mitochondria by diffusion, although possibly aided by protoplasmic streaming.

Diffusion paths are much longer in tissues than in the parenchyma of the lung. In well vascularized tissue, such as brain, each capillary serves a zone of radius about 20 μ, but the comparable distance is about 200 μ in skeletal muscle and greater still in fat and cartilage.

It is impracticable to talk about mean tissue Po_2 since this varies from one

organ to another and must also depend on perfusion in relation to metabolic activity. Furthermore, within an organ there must be some cells occupying favourable sites towards the arterial ends of capillaries, while others must be content with accepting oxygen from the venous ends of the capillaries where the Po_2 is lower. This is well demonstrated in the liver where the centrilobular cells must exist at a lower Po_2 than their fellows at the periphery of the lobule. Even within a single cell, there is no uniformity of Po_2. Not only are there 'low spots' around the mitochondria, but those mitochondria nearest to the capillaries presumably enjoy a higher Po_2 than those lying further away.

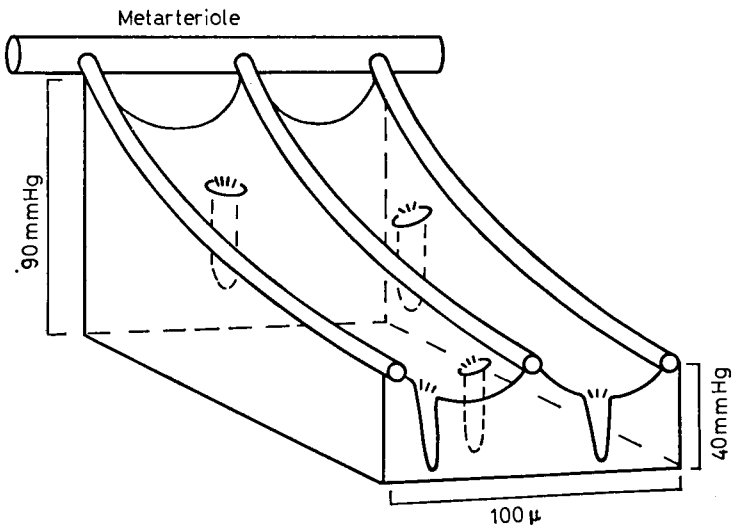


Figure 93. Graphic representation of Po_2 *within the tissues. The vertical axis represents the actual* Po_2*; in the horizontal plane is represented the course of three parallel capillaries from the metarteriole to the point of entry into the venule (not shown). The* Po_2 *falls exponentially along the course of each capillary with a trough of* Po_2 *between the capillaries. The pits represent the low spots of* Po_2 *in the vicinity of the mitochondria. This diagram shows the very wide range of tissue* Po_2 *from about 90 mm Hg in the tissue close to the arterial end of the capillaries down to a few millimeters of mercury at the mitochondria near the venous end of the capillaries. This is the simplest of many possible models of tissue perfusion*

Figure 93 shows a model in which an area of tissue is perfused by three parallel capillaries. Vertical height indicates Po_2 which falls exponentially along the line of the capillaries, with troughs lying in between the capillaries. Five 'low spots' corresponding to mitochondria are shown. This diagram makes no pretence to histological accuracy but merely illustrates the difficulty of talking about the 'mean tissue Po_2' which is not an entity like the arterial or mixed venous Po_2.

There is uncertainty about the actual Po_2 within a mitochondrion. It is known that oxidative phosphorylation will continue down to a Po_2 of about 1 mm Hg (page 329) and some mitochondria may habitually operate at this level. Others, particularly those close to the arterial end of the capillaries, may

have a much higher Po_2. Capillary/tissue Po_2 gradients probably range from about 20 to over 40 mm Hg.

Since the oxygen consumption of a mitochondrion is probably fairly constant and the geometric layout of its diffusion path for oxygen is also relatively static, it follows that the Po_2 gradient from capillary to a particular mitochondrion must also remain fairly constant. This follows from the general equation for diffusing capacity. Nevertheless, there must be a broad spectrum of different Po_2 gradients for the many mitochondria of a cell.

Carbon Dioxide

Little is known about the magnitude of carbon dioxide gradients between the mitochondria and the tissue capillaries. It is, however, thought that the tissue/venous Pco_2 gradient can be increased by two methods. The first is by inhibition of carbonic anhydrase which blocks the uptake of carbon dioxide by the blood. The second is by hyperoxygenation of the arterial blood caused by breathing 100 per cent oxygen at high pressures. If the Po_2 of the arterial blood exceeds about 2,000 mm Hg, the dissolved oxygen will be sufficient for the usual tissue requirements. Therefore no significant amount of oxyhaemoglobin will be dissociated and reduced haemoglobin is not available for the carbamino carriage of carbon dioxide, for which it is more efficient than oxyhaemoglobin. This results in partial blocking of the uptake of carbon dioxide by the blood. This theory was advanced by Gessell (1923) as an explanation of the cause of oxygen convulsions. However, it seems likely that the alternative method of carbon dioxide carriage as bicarbonate would be able to function quite adequately in the absence of the facilitated carbamino carriage.

Inert Gases and Anaesthetic Agents

Inert gases will ultimately attain equilibrium in the tissues because, unlike oxygen, they are not constantly being consumed which would result in permanent tension gradients.* The rate of attaining equilibrium with inert gases depends upon the perfusion of the tissue relative to its bulk and the solubility of the agent in the tissue. There is an important distinction between well perfused and poorly perfused tissues. The former are those tissues in which all parts of the cells come into rapid equilibrium with the inert gas carried in the arterial blood, so that the tension of the gas in blood leaving the tissue may be considered equal to the mean tension of the gas in the tissue. Well perfused tissues include brain, heart and liver. Poorly perfused tissues are those in which inert gases tend to diffuse slowly, forming tension gradients in the form of the cylinders and cones which were considered in the case of oxygen, above. Less well perfused tissues include fat, cartilage and, to a certain extent, resting muscle. The practical importance is that the tension of the gas in the venous blood draining the tissue does not give a representative value for the mean tissue tension, being higher during loading and lower during unloading of the agent. This greatly complicates measurement of exchange and also theoretical consideration of long-term changes in tissue levels. Appreciation of this problem

* It now appears that halothane is less inert than was formerly supposed. Some 14 per cent apparently is metabolized and there must be tension gradients at its site of metabolism (Rehder and his colleagues, 1967).

has been of the greatest importance in establishing techniques for avoidance of bends after prolonged dives.

PRINCIPLES OF METHODS OF MEASUREMENT OF CARBON MONOXIDE DIFFUSING CAPACITY

All the methods are based on the general equation:

$$D_{CO} = \frac{\dot{V}_{CO}}{P_{A_{CO}} - P\bar{c}_{CO}}$$

In each case it is usual to assume that the mean tension of carbon monoxide in the pulmonary capillary blood ($P\bar{c}_{CO}$) is effectively zero. It is, therefore, only necessary to measure the carbon monoxide uptake ($\dot{V}_{CO}$), and the alveolar carbon monoxide tension ($P_{A_{CO}}$). The diffusing capacity indicated (D_{CO}) is the total diffusing capacity including that of the alveolar capillary membrane and the component due to the reaction of carbon monoxide with haemoglobin.

The Steady State Method

The subject breathes a gas mixture containing about 0·3 per cent carbon monoxide for about a minute. After this time, expired gas is collected when the alveolar P_{CO_2} is steady but the mixed venous P_{CO} has not yet reached a level high enough to require consideration in the calculation.

The carbon monoxide uptake ($\dot{V}_{CO}$) is measured in exactly the same way as oxygen consumption by the open method (page 382): the amount of carbon monoxide expired ($\dot{V}_E \times F\bar{E}_{CO}$) is subtracted from the amount of carbon monoxide inspired ($\dot{V}_I \times F_{I_{CO}}$). The alveolar P_{CO} is calculated from the form of the alveolar air equation derived by Filley, MacIntosh and Wright (1954):

$$P_{A_{CO}} = P_{I_{CO}} - P_{A_{CO_2}} \frac{F_{I_{CO}} - F\bar{E}_{CO}}{F\bar{E}_{CO_2}}$$

Rewritten for oxygen, this equation has proved of great value for the calculation of the alveolar P_{O_2} under the circumstances of general anaesthesia, and is discussed in Chapter 9 (page 263). Measurement of inspiratory and expiratory carbon monoxide and expiratory carbon dioxide concentrations presents no serious difficulty, and infra-red analysis has proved satisfactory. Measurement of alveolar P_{CO_2} is more difficult and is discussed in Chapter 11.

For present purposes, it is sufficient to say that the usual method is to sample arterial blood and assume that the alveolar P_{CO_2} is equal to the arterial P_{CO_2}. We have seen (page 245) that this is not strictly true in the presence of maldistribution. As an alternative, some workers measure the end-expiratory P_{CO_2} although this, too, does not equal the arterial P_{CO_2} in the presence of maldistribution (page 251). Finally, it is possible to derive the alveolar P_{CO_2} from the mixed venous P_{CO_2} by the rebreathing technique, assuming a reasonable value for the mixed venous/alveolar P_{CO_2} difference (page 324).

The Single-breath Method

This method has a long history of progressive refinement. The patient is first required to exhale maximally. He then draws in a vital-capacity breath of a gas mixture containing about 0·3 per cent carbon monoxide and about 10 per

cent helium. The breath is held for 10 seconds and a gas sample is then taken after the exhalation of the first 750 ml., which is sufficient to wash out the patient's dead space.

It is assumed that no significant amount of helium has passed into the blood and, therefore, the ratio of the concentration of helium in the inspired gas to the concentration in the end-expiratory gas, multiplied by the volume of gas drawn into the alveoli during the maximal inspiration, will indicate the total alveolar volume during the period of breath holding. The alveolar P_{CO} at the commencement of breath holding is equal to the same ratio multiplied by the P_{CO} of the inspired gas mixture. The end-expiratory P_{CO} is measured directly.

From these data, together with the time of breath holding, it is possible to calculate the carbon monoxide uptake and the mean alveolar P_{CO}. A neat mathematical solution is available, and the interested reader is referred to Cotes (1965).

The Rebreathing Method

Somewhat similar to the single-breath method is the rebreathing method by which a gas mixture containing about 0·3 per cent carbon monoxide and 10 per cent helium is rebreathed rapidly from a rubber bag. The bag and the patient's lungs are considered as a single system, with gas exchange occurring in very much the same way as during breath holding. The calculation proceeds in a similar way to that for the single-breath method.

Measurement of Oxygen Diffusing Capacity

For reasons which were developed in this chapter, it now appears that the measurement of oxygen diffusing capacity is based on assumptions which can no longer be considered valid. Therefore, the method is not described here but reference may be made to Comroe and his colleagues (1962).

CHAPTER 11

CARBON DIOXIDE

Carbon dioxide is the end product of aerobic metabolism. It is produced in the cells and almost entirely in the mitochondria where the P_{CO_2} is highest. From its point of origin there are a series of tension gradients as carbon dioxide passes through the cytoplasm, and the extracellular fluid into the blood. In the lungs the P_{CO_2} of the blood entering the pulmonary capillaries is higher than the alveolar P_{CO_2}, and therefore carbon dioxide diffuses from the blood into the alveolar gas. Carbon dioxide finally passes into the expired air where it mixes with the ambient air.

CARRIAGE OF CARBON DIOXIDE IN BLOOD

Carbon dioxide is present in body fluids in different forms and passes readily from one to another until equilibrium is achieved according to a number of physico-chemical laws.

Forms in which Carbon Dioxide is Carried

In Physical Solution

Carbon dioxide belongs to the group of gases with moderate solubility in water. This group includes many of the anaesthetic gases, and the solubility of carbon dioxide is rather greater than that of nitrous oxide. According to Henry's law of solubility:

$$P_{CO_2} \times \text{solubility coefficient} = CO_2 \text{ concentration in solution} \quad \ldots(1)$$

For present purposes, solubility of carbon dioxide is most conveniently quantified in units of millimoles per litre per millimetre of mercury P_{CO_2} (mM/l./mm Hg), and for plasma approximates to 0·03m M/l./mm Hg, the precise value depending on temperature (*Table 30*). Approximately 1·2 mM/l. of carbon dioxide is carried in plasma at the normal arterial P_{CO_2} of 40 mm Hg.

As Carbonic Acid

In solution carbon dioxide hydrates to form carbonic acid:

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \quad \ldots(2)$$

Some physiological texts have given the impression that this reaction proceeds to an equilibrium far to the right with almost all the carbon dioxide being present in the form of carbonic acid. This, however, is not the case and only

about one molecule of carbon dioxide in 700 is hydrated. According to the law of mass action, this may be expressed in the form:

$$[H_2CO_3] = \frac{[CO_2] \times [H_2O]}{L'} \quad ...(3)$$

where $[H_2O]$ is constant and close to unity, and the constant L' is approximately 700. The square brackets indicate the concentration of the substance within the brackets.

Table 30

Values for solubility of carbon dioxide in plasma and for pK′ at different temperatures (values from Severinghaus, Stupfel and Bradley, 1956a and b)

Temperature (°C)	*Solubility of* CO_2 *in plasma* (*mM/l./mm Hg*)	*pK′*		
		(*at pH 7·6*)	(*at pH 7·4*)	(*at pH 7·2*)
40	0·0288	6·07	6·08	6·09
39	0·0294	6·07	6·08	6·09
38	0·0301	6·08	6·09	6·10
37	0·0308	6·08	6·09	6·10
36	0·0315	6·09	6·10	6·11
35	0·0322	6·10	6·11	6·12
33	0·0337	6·10	6·11	6·12
30	0·0362	6·12	6·13	6·14
25	0·0413	6·15	6·16	6·17
20	0·0478	6·17	6·19	6·20
15	0·0554	6·20	6·21	6·23

It would be theoretically more correct to indicate the thermodynamic activities rather than concentrations, the two quantities being related as follows:

$$\frac{\text{activity}}{\text{concentration}} = \text{activity coefficient}$$

At infinite dilution the activity coefficient is unity but, in physiological concentrations, it is significantly less than unity. In practice it is usual to work in concentrations,* and values for the various equilibrium constants are adjusted accordingly, as indicated by a prime after the symbol thus—L' and K'. This is one of the reasons why these 'constants' are not in fact constant but vary slightly under physiological conditions.

The concentration of carbonic acid in normal arterial blood is of the order of 0·0017 mM/l. at P_{CO_2} 40 mm Hg. Many medical writers make the statement that the concentration is 1·2 mM/l. which is the normal concentration of dissolved carbon dioxide. They are following a rather misleading medical convention which indicates carbon dioxide as though it were all hydrated to the form of carbonic acid.

The reaction of carbon dioxide with water (equation 2) is non-ionic and slow, requiring a period of minutes for equilibrium to be attained. This would be far too long for the time available for gas exchange in pulmonary and systemic

* The glass electrode responds to hydrogen ion activity and not concentration.

capillaries were the reaction not speeded up enormously in both directions by the enzyme carbonic anhydrase which is present in erythrocytes but not in plasma.

As Bicarbonate Ion

The largest fraction of carbon dioxide in the blood is in the form of bicarbonate ion which is formed by ionization of carbonic acid:

$$H_2CO_3 \rightleftharpoons \underset{\text{first dissociation}}{H^+ + HCO_3^-} \rightleftharpoons \underset{\text{second dissociation}}{2\,H^+ + CO_3^{--}} \qquad ...(4)$$

The second dissociation occurs only at high pH (above 9) and is not a factor in the carriage of carbon dioxide by the blood. The first dissociation is, however, of the greatest importance within the physiological range.

According to the law of mass action:

$$\frac{[H^+] \times [HCO_3^-]}{[H_2CO_3]} = K_1' \qquad ...(5)$$

where K_1' is the equilibrium constant of the first dissociation. The subscript 1 indicates that it is the first dissociation, and the prime indicates that we are dealing with concentrations rather than the more correct activities.

Rearrangement of equation (5) gives the following:

$$[H^+] = K_1' \frac{[H_2CO_3]}{[HCO_3^-]} \qquad ...(6)$$

The left-hand side is the hydrogen ion concentration, and this equation is the non-logarithmic form of the Henderson–Hasselbalch equation (Henderson, 1909). Practical use of the equation requires one slight modification which has often caused confusion in the past. The term $[H_2CO_3]$ cannot be directly measured and is therefore replaced with $[CO_2]$, the relationship between these two quantities being constant ($[CO_2] = L' \times [H_2CO_3]$; equation 3). Therefore the equation may be rewritten as:

$$[H^+] = \frac{K_1'}{L'} \times \frac{[CO_2]}{[HCO_3^-]} \quad \text{or} \quad K' \times \frac{\alpha \times P_{CO_2}}{[HCO_3^-]} \qquad ...(7)$$

where a new constant K' replaces K_1'/L' and is the *apparent* first dissociation constant of carbonic acid when the dissolved carbon dioxide takes the place of carbonic acid in the equation.

α is the solubility coefficient of CO_2 in plasma (usually in units of mM/l./mm Hg). When multiplied by the P_{CO_2}, the product is the concentration of carbon dioxide in solution in the plasma (mM/l.).

$$\alpha \times P_{CO_2} = [CO_2] \quad \text{(equation 1)}$$

The equation is now in a useful form and substitution of values which have been experimentally derived gives the following:

$$[H^+] = 24 \times \frac{P_{CO_2}}{[HCO_3^-]} \qquad ...(8)$$

The constant 24 only applies if the following units are employed:

$[H^+]$ = hydrogen ion concentration in nanomoles (10^{-9} moles) per litre. (nanomoles are sometimes called micromillimoles)
P_{CO_2} = carbon dioxide tension in mm Hg
$[HCO^-]$ = bicarbonate ion concentration of plasma in millimoles per litre.

Normal values are as follows:

$$40 = 24 \times \frac{40}{24}$$

This equation is very simple to use and has been strongly recommended by Campbell (1962).

Those who prefer to use the pH scale may follow the approach of Hasselbalch (1916) and take logarithms of the reciprocal of each term in equation (7) with the following familiar result:

$$pH = pK' + \log \frac{[HCO_3^-]}{\alpha P_{CO_2}} = pK' + \log \frac{[CO_2] - \alpha P_{CO_2}}{\alpha P_{CO_2}} \qquad ...(9)$$

where pK' has an experimentally derived value of the order of 6·1 but variable with temperature and pH (*Table 30*).

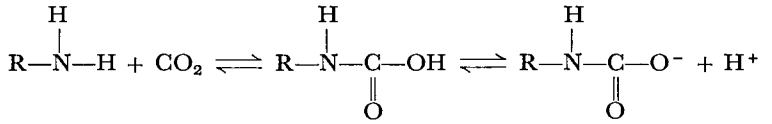
It is sometimes useful to clear equation (9) for P_{CO_2}:

$$P_{CO_2} = \frac{[CO_2]}{\alpha\{\text{antilog } (pH - pK') + 1\}} \qquad ...(10)$$

It is important to remember that $[CO_2]$ refers to the carbon dioxide concentration in plasma and not whole blood.

Carbamino Carriage

Amino groups have the ability to combine directly with carbon dioxide thus:



In a protein, the amino groups involved in the peptide linkages between amino-acid residues cannot combine with carbon dioxide. Carbamino carriage is therefore restricted to the one terminal amino group in each protein and to the side chain amino groups in lysine and arginine. The terminal amino groups are the most effective at physiological pH, and one binding site per protein molecule is more than sufficient to account for the quantity of carbon dioxide carried as a carbamino compound.

Only very small quantities of carbon dioxide are carried in carbamino compounds with plasma protein. Almost all is carried by haemoglobin, and reduced haemoglobin is about 3·5 times as effective as oxyhaemoglobin (*Figure 94*). The actual P_{CO_2} has very little effect upon the quantity of carbon dioxide carried in this manner, throughout the physiological range of P_{CO_2} (Ferguson, 1936).

The Haldane effect.—Although the amount of carbon dioxide carried in the blood in carbamino carriage is small (*Table 31*), the *difference* between the amount

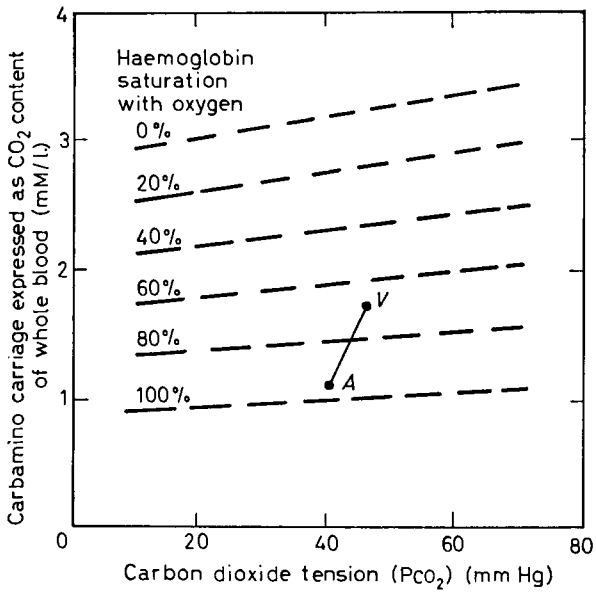


Figure 94. The broken lines on the graph indicate the carbamino carriage of carbon dioxide at different levels of saturation of haemoglobin with oxygen (15 g. Hb/100 ml. blood). It will be seen that this has a far greater influence on carbamino carriage than the actual Pco_2 *(abscissa). A represents arterial blood (95 per cent saturation and* Pco_2 *40 mm Hg); V represents mixed venous blood (70 per cent saturation and* Pco_2 *46 mm Hg). Note that the arterial/venous difference in carbamino carriage is large in relation to the actual level of carbamino carriage, and accounts for about a third of the total arterial/venous blood* CO_2 *content difference (see Table 31). (These values have not been drawn from a single publication but present the mean of values reported from a number of studies)*

Table 31

Normal values for carbon dioxide carriage in blood

	Arterial blood (Hb 95% sat.)	*Mixed venous blood (Hb 70% sat.)*	*Arterial/venous difference*
Whole blood			
pH	7·40	7·367	−0·033
Pco_2 (mm Hg)	40·0	46·0	+6·0
Total CO_2 (mM/l.)	21·5	23·3	+1·8
(vols. %)	48·0	52·0	+4·0
Plasma (mM/l.)			
Dissolved CO_2	1·2	1·4	+0·2
Carbonic acid	0·0017	0·0020	+0·0003
Bicarbonate ion	24·4	26·2	+1·8
Carbamino CO_2	Negligible	Negligible	Negligible
Total	25·6	27·6	+2·0
Erythrocyte fraction of 1 litre of blood			
Dissolved CO_2	0·44	0·51	+0·07
Bicarbonate ion	5·88	5·92	+0·04
Carbamino CO_2	1·10	1·70	+0·60
Plasma fraction of 1 litre of blood			
Dissolved CO_2	0·66	0·76	+0·10
Bicarbonate ion	13·42	14·41	+0·99
Total in 1 litre of blood (mM/l.)	21·50	23·30	+1·80

These values have not been drawn from a single publication but represent the mean of values reported in a large number of studies.

carried in venous and arterial blood is about a third of the total arterial/venous difference. This accounts for the major part of the Haldane effect which is the difference in the quantity of carbon dioxide carried, at constant P_{CO_2}, in oxygenated and reduced blood (*Figure 95*). The remainder of the effect is due to the increased buffering capacity of reduced haemoglobin which is discussed below. It is interesting to recall that when the Haldane effect was described by Christiansen, Douglas and Haldane (1914) they believed that the whole effect

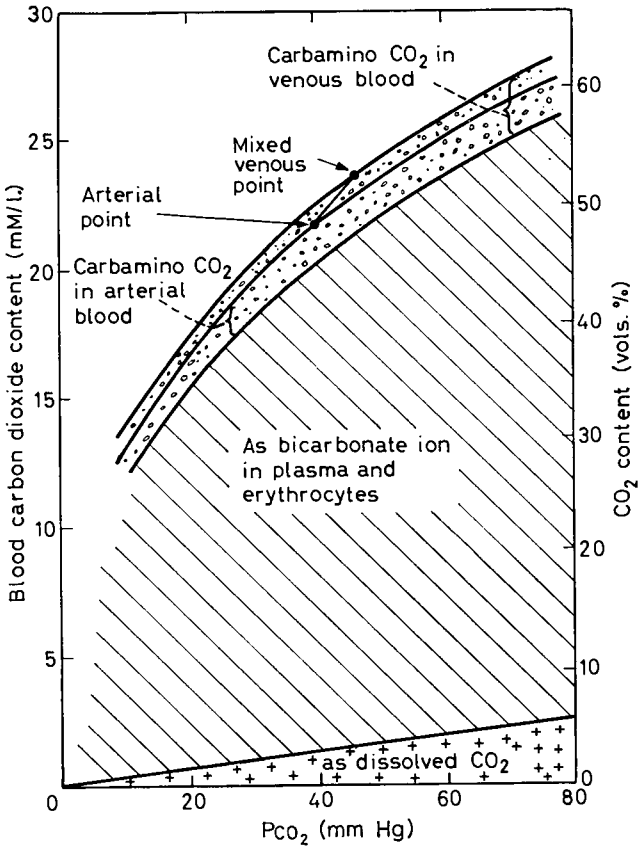


Figure 95. Components of the carbon dioxide dissociation curve for whole blood. Dissolved CO_2 and bicarbonate ion vary with P_{CO_2} but are little affected by the state of oxygenation of the haemoglobin. (Increased basic properties of reduced haemoglobin cause slight increase in formation of bicarbonate ion.) Carbamino carriage of CO_2 is strongly influenced by the state of oxygenation of haemoglobin but hardly at all by P_{CO_2}. (These values have not been drawn from a single publication but represent the mean of values reported in a large number of studies)

was due to altered buffering capacity: carbamino carriage was not proved until much later (Ferguson and Roughton, 1934).

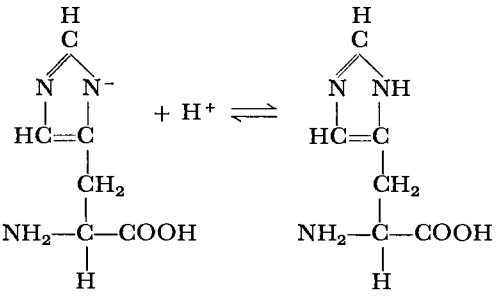
Formation of carbamino compounds does not require the dissolved carbon

dioxide to be hydrated and so is independent of carbonic anhydrase. The reaction is very rapid and would be of particular importance in a patient who had received a carbonic anhydrase inhibitor. The arterial/venous difference in carbamino carriage is lost in certain regions of the body when a patient inhales 100 per cent oxygen at a pressure of about 3 atmospheres absolute, since the oxygen dissolved in the arterial blood is then sufficient for metabolic requirements and very little reduced haemoglobin appears in the venous blood. Gessell (1923) suggested that the loss of the arterial/venous difference in carbamino carriage of carbon dioxide under these conditions resulted in tissue retention of carbon dioxide, and was a major factor in the cerebral toxic effects produced by high tensions of oxygen. It is, however, unlikely that this would cause a rise of tissue P_{CO_2} greater than a few millimetres of mercury, and it is known that such a rise can be tolerated without any of the symptoms characteristic of oxygen toxicity. Furthermore, administration of carbonic anhydrase inhibitors does not produce a condition resembling oxygen toxicity.

The reader who is interested in advances in carbamino carriage is referred to the excellent review by Roughton (1964).

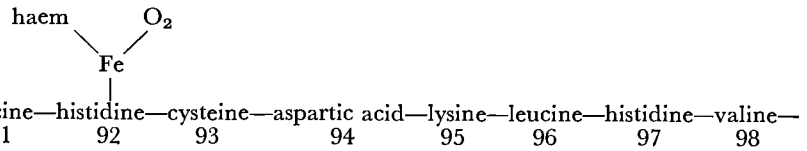
Effect of Buffering Power of Proteins on Carbon Dioxide Carriage

Amino and carboxyl groups concerned in peptide linkages have no buffering power. Neither have most side chain groups (e.g. in lysine and glutamic acid) since their pK values are far removed from the physiological range of pH. In contrast is the imidazole group of the amino acid histidine which is almost the only effective buffer in the normal range of pH. Imidazole groups constitute the major part of the considerable buffering power of haemoglobin, each molecule of which contains 38 histidine residues. The buffering power of plasma proteins is less and is proportional to their histidine content.



Basic form of histidine *Acidic form of histidine*

The four haem groups of a molecule of haemoglobin are attached to the corresponding four amino-acid chains by means of one of the histidine residues on each chain (page 350). The following is a section of a β chain of human haemoglobin:



The figures indicate the position of the amino-acid residue in the chain. The

histidine in position 92 is one to which a haem group is attached. The histidine in position 97 is not. Both have buffering properties but the dissociation constant of the imidazole groups of the four histidine residues to which the haem groups are attached is strongly influenced by the state of oxygenation of the haem. Reduction causes the corresponding imidazole group to become more basic. The converse is also true: in the acidic form of the imidazole group of the histidine, the strength of the oxygen bond is weakened. Each reaction is of great physiological interest and both effects were noticed many decades before their mechanisms were elucidated.

(1) *The reduction of haemoglobin causes it to become more basic.* This results in increased carriage of carbon dioxide as bicarbonate, since hydrogen ions are removed permitting increased dissociation of carbonic acid (first dissociation of equation 4). This accounts for a part of the Haldane effect, the other and greater part being due to increased carbamino carriage (*see* above).

(2) *Conversion to the basic form of histidine causes increased affinity of the corresponding haem group for oxygen.* This is, in part, the cause of the Bohr effect (page 349).

Total reduction of the haemoglobin in blood would raise the pH by about 0·03 pH units if the P_{CO_2} were held constant at 40 mm Hg, this would correspond roughly to the addition of 3 mEq. of base to 1 litre of blood. The normal degree of desaturation in the course of the change from arterial to mixed venous blood is about 25 per cent, corresponding to a pH rise of about 0·007 if P_{CO_2} remained constant. In fact, P_{CO_2} rises by about 6 mm Hg, which would cause a fall of pH of 0·040 units if the oxygen saturation were to remain the same. The combination of a rise of P_{CO_2} of 6 mm Hg and a fall of saturation of 25 per cent thus results in a fall of pH of 0·033 units (*Table 31*).

Transfer of Carbon Dioxide across Cell Membranes

It may readily be demonstrated in the laboratory that membranes made of most plastic materials (e.g. polytetrafluorethylene or Teflon) permit the free diffusion of carbon dioxide, but will not permit the passage of hydrogen ions. This is, in fact, the principle of the CO_2-sensitive electrode (page 324).

Selectivity of a somewhat similar type exists across cell membranes in the living body. These membranes are relatively impervious to hydrogen ions, but permit the rapid diffusion of carbon dioxide. Therefore, the intracellular hydrogen ion concentration is relatively uninfluenced by changes in extracellular pH, but can be altered by perfusion with a solution containing dissolved carbon dioxide. The carbon dioxide passes through the membrane and inside the cell is able to hydrate and ionize, thus producing hydrogen ions. This property is unique to carbon dioxide which is the only substance, normally present in the blood, able to alter the intracellular pH in this manner.

The passage of carbon dioxide through the cell membrane to release hydrogen ions within the cell is reminiscent of the seige of Troy (Virgil, 19 B.C.). The city of Troy is analogous to the cell and its walls were impervious to Greek soldiers (hydrogen ions). However, the wooden horse (carbon dioxide) passed through the walls without difficulty and once within the city (cell) was able to release the Greek soldiers (hydrogen ions).

This effect of carbon dioxide is of immense physiological importance, and probably accounts for many of the effects of carbon dioxide which are thought to be specific, in contrast to its effect of reducing the blood pH. Chapter 2 describes how this mechanism is thought to underlie the effect of carbon dioxide on the respiratory centre.

Distribution of Carbon Dioxide within the Blood

Table 31 shows the form in which carbon dioxide is carried in normal arterial and mixed venous blood. Although the amount carried in solution is small, most of the carbon dioxide enters and leaves the blood in this form (*Figure 96*).

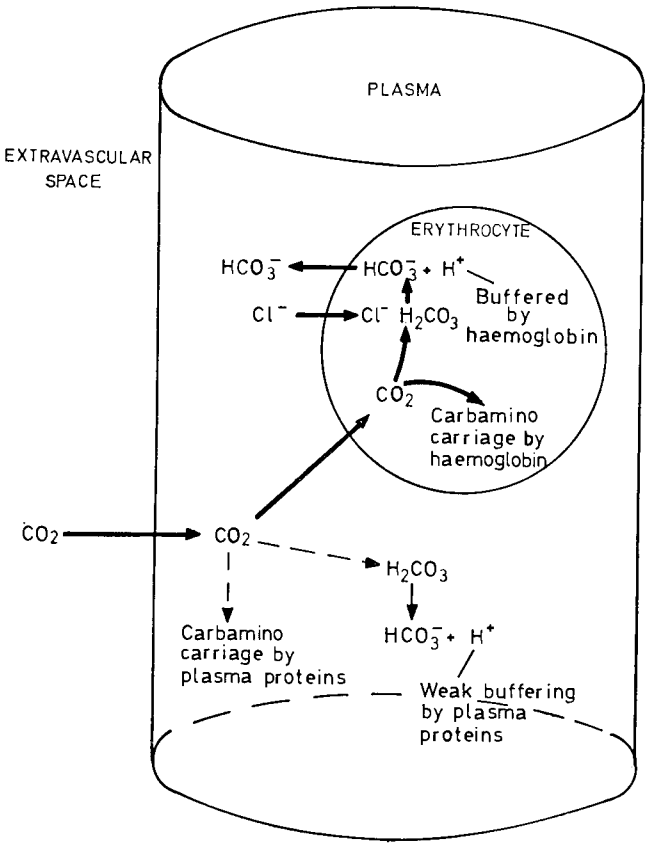


Figure 96. This diagram shows how carbon dioxide enters the blood in molecular form. Within the plasma, there is only negligible carbamino carriage and dissociation, due to the structure of the plasma proteins and the absence of carbonic anhydrase. The greater part of the carbon dioxide diffuses into the erythrocytes where conditions for carbamino carriage are much more favourable. In addition, hydration to carbonic acid occurs easily in the presence of carbonic anhydrase and subsequent ionization is promoted by the buffering capacity of haemoglobin for the hydrogen ions.

Within the plasma there is little combination of carbon dioxide for three reasons. Firstly, there is no carbonic anhydrase in plasma and therefore carbonic acid is only formed very slowly. Secondly, there is little buffering power in plasma to promote the dissociation of carbonic acid. Thirdly, it is thought that the formation of carbamino compounds by plasma proteins is not great, and is presumably almost identical for arterial and venous blood.

Carbon dioxide can, however, diffuse freely into the erythrocyte where two courses are open. Firstly, carbamino compounds may be formed with haemoglobin, not so much because the P_{CO_2} is raised, but rather because the oxygen saturation is likely to be reduced at the same time as the P_{CO_2} is rising (*see* above). The second course is hydration and dissociation. Hydration is greatly facilitated by the presence of carbonic anhydrase in the erythrocyte, and dissociation is facilitated by the presence of the imidazole groups on the histidine residues of the haemoglobin, particularly reduced haemoglobin. In this way considerable quantities of bicarbonate ion are formed and these are able to diffuse into the plasma in exchange for chloride ions which diffuse in the opposite direction (Hamburger, 1918).

Dissociation Curves of Carbon Dioxide

Figure 95 shows the original form of the dissociation curve of carbon dioxide relating blood content to tension. Recently, there has been much greater interest in curves which relate any pair of the following: (1) plasma bicarbonate concentration; (2) P_{CO_2}; (3) pH. These three quantities are related by the Henderson–Hasselbalch equation and therefore the third variable can always be derived from the other two. For this reason the three possible plots may be used interchangeably and selection is largely a matter of custom or convenience. There is some doubt about the nomenclature of the plots. A plot of plasma $[CO_2]$ against P_{CO_2} is not really a dissociation curve, and a plot of plasma $[HCO_3^-]$ against pH (*Figure 97*) is not really a titration curve since in each case the relevant concentration is in plasma and not blood. The difference, however, is not very great, and the general shape of the curve is much the same as when the ordinate is expressed as concentration in blood. With current analytical techniques a plot of P_{CO_2} (logarithmic) against pH has special attractions (*Figure 98*), and is best described as a CO_2 equilibration curve (Siggaard-Andersen, 1964).

It is important to appreciate that, if the P_{CO_2} of an entire patient is altered, the pH changes are not the same as those of a blood sample whose P_{CO_2} is altered *in vitro*. This is because the blood of a patient is in continuity with the extracellular fluid (of very low buffering capacity) and also with the intracellular fluid (of high buffering capacity). Bicarbonate ions pass rapidly and freely across the various interfaces, and experimental studies have shown the following changes to occur in the arterial blood of an intact subject when the P_{CO_2} is acutely changed.

(1) The arterial pH reaches a steady state within minutes of establishment of the new level of P_{CO_2}.

(2) The change in arterial pH is intermediate between the pH changes obtained *in vitro* with plasma and whole blood after the same change in P_{CO_2}.

That is to say, the *in vivo* change in pH is greater than the *in vitro* change in the patient's blood when subjected to the same change in P_{CO_2}.

Numerous studies have been carried out in animals, and there is indication of some species differences (Shaw and Messer, 1932). Studies in conscious man show *in vivo* changes close to the *in vitro* changes obtained in plasma (Cohen, Brackett and Schwartz, 1964). Prys-Roberts, Kelman and Nunn (1966)

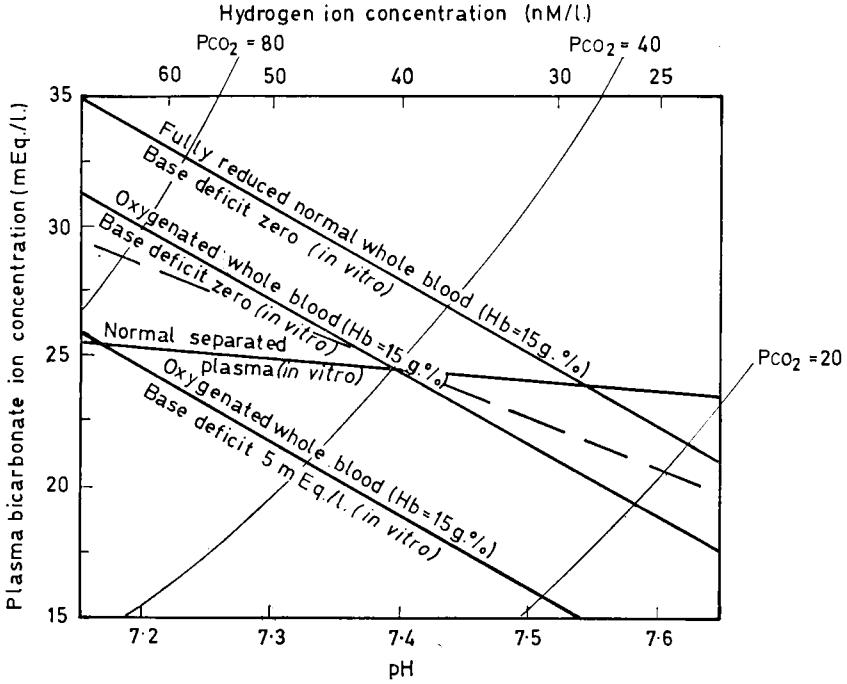


Figure 97. This graph shows a number of CO_2 equilibration curves plotted on the co-ordinates $pH/[HCO_3^-]$. (Isobars are shown for P_{CO_2} 80, 40 and 20 mm Hg.) For most biological fluids, the plot is linear over the physiological range. pH = 7·40, P_{CO_2} = 40 mm Hg and HCO_3^- = 24·4 mEq./l. is the accepted normal point through which all curves for normal oxygenated blood or plasma pass. The steepest curve passing through that point is the curve of normal oxygenated whole blood; the flattest is that of plasma, both curves being obtained in vitro. *The broken curve describes blood of haemoglobin 10 g. per cent, equilibrated* in vitro, *or alternatively the arterial blood (Hb = 15 g. per cent) equilibrated* in vivo *of a normal anaesthetized patient whose P_{CO_2} is acutely changed (Prys-Roberts, Kelman and Nunn, 1966). The uppermost curve is that of reduced but otherwise normal blood equilibrated* in vitro. *The lowermost curve is that of oxygenated blood with a metabolic acidosis (base deficit) of 5 mEq./l. equilibrated* in vitro

studied step changes of P_{CO_2} in anaesthetized patients and obtained *in vivo* dissociation curves of similar slope to those which would be obtained with the patient's blood *in vitro* if the haemoglobin concentration were reduced by a third (*Figures 97 and 98*). These curves permit calculation of the very small error in estimation of base excess in patients whose P_{CO_2} is far outside the normal range. The measured base excess will be about 2 mEq./l. low (apparent

metabolic acidosis) if blood is sampled when the P_{CO_2} is 80 mm Hg, and the measured base excess will be about 2 mEq./l. high (apparent metabolic alkalosis) if blood is sampled when the P_{CO_2} is 20 mm Hg. Values of P_{CO_2} outside these limits are comparatively rare and a correction factor can easily be applied if necessary.

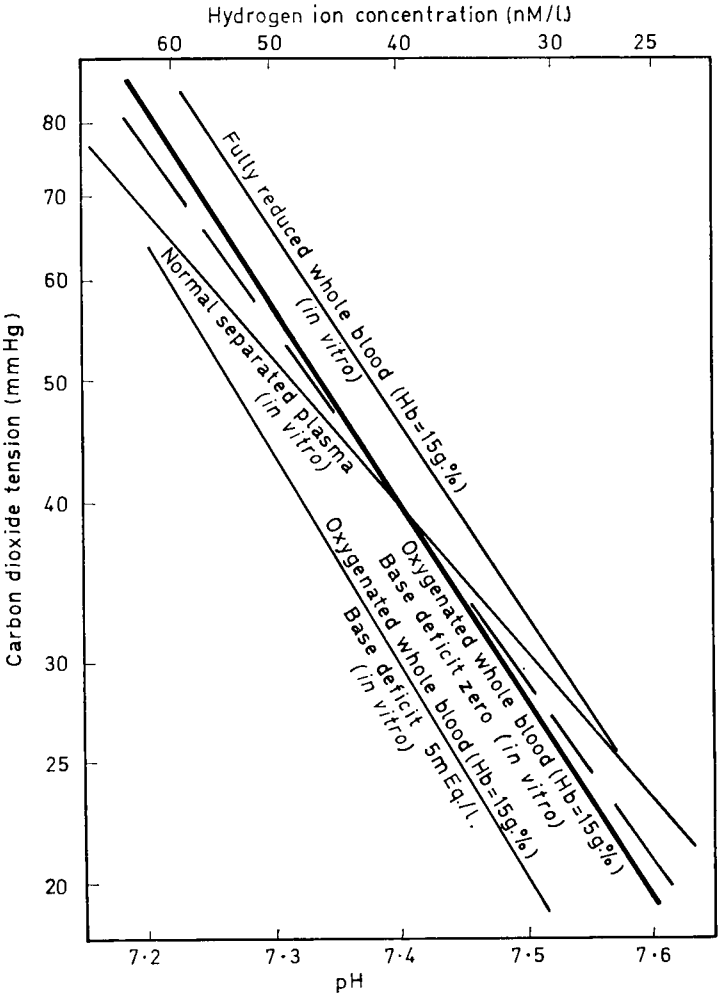


Figure 98. This graph shows a number of CO_2 equilibration curves plotted on the co-ordinates pH/log P_{CO_2}. For most biological fluids, the plot is linear over the physiological range. pH = 7·40 and P_{CO_2} = 40 mm Hg is the accepted normal value through which all curves for normal oxygenated blood or plasma pass. The steepest curve passing through this point is that of normal oxygenated blood; the flattest is that of plasma, both curves being obtained in vitro. *The broken curve describes blood of haemoglobin 10 g. per cent, equilibrated* in vitro, *or alternatively the arterial blood, equilibrated* in vivo (*Hb = 15 g. per cent*), *of a normal anaesthetized patient whose* P_{CO_2} *is acutely changed (Prys-Roberts, Kelman and Nunn, 1966). The uppermost curve is that of reduced but otherwise normal blood equilibrated* in vitro. *The lowermost curve is that of oxygenated blood with a metabolic acidosis (base deficit) of 5 mEq./l., equilibrated* in vitro

For further details of acid–base balance, the reader is referred to the monographs of Davenport (1958) and Siggaard-Andersen (1964). An excellent chapter has been contributed by Woodbury (1965), and Nunn (1962c) has reviewed the methods of presentation of acid–base data. Reference should also be made to Campbell (1962), Campbell and Dickinson (1960) and Huckabee (1961).

FACTORS INFLUENCING THE CARBON DIOXIDE TENSION IN THE STEADY STATE

In common with other catabolites, the level of carbon dioxide in the body fluids depends upon the balance between production and elimination. There is a continuous gradient of P_{CO_2} from the mitochondria (the site of production of

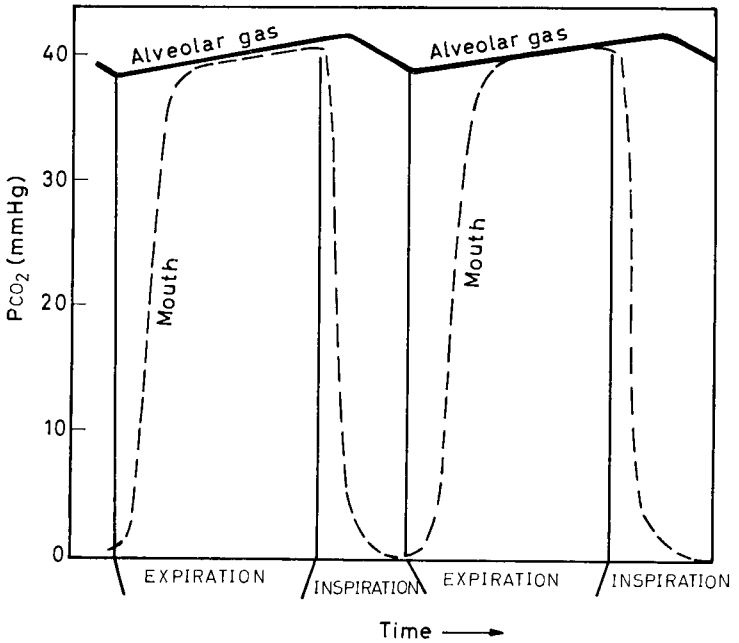


Figure 99. Changes in alveolar and mouth P_{CO_2} *during the respiratory cycle. The alveolar* P_{CO_2} *is shown by the continuous curve, and the mouth* P_{CO_2} *(as determined by a rapid analyser) by the broken curve. The mouth* P_{CO_2} *falls at the commencement of inspiration but does not rise during expiration until the anatomical dead space gas is washed out. The alveolar* P_{CO_2} *rises during expiration and also during the early part of inspiration until fresh gas penetrates the alveoli after the anatomical dead space is washed out. The alveolar* P_{CO_2} *then falls until expiration commences. This imparts a saw-tooth curve to the alveolar* P_{CO_2}

carbon dioxide) through the cytoplasm, the venous blood, the alveolar gas and thence by way of expired air to dispersal in the ambient air. The P_{CO_2} in all cells is not identical, but is lowest in tissues with the lowest metabolic activity and the highest perfusion (e.g. skin) and highest in tissues with the highest metabolic activity for their perfusion (e.g. the myocardium). Therefore the

P_{CO_2} of venous blood differs from one tissue to another, and the mixed venous P_{CO_2} is the integrated mean for the body as a whole.

In the pulmonary capillaries, carbon dioxide passes into the alveolar gas and this causes the alveolar P_{CO_2} to rise steadily during expiration. During inspiration, the inspired gas dilutes the alveolar gas and the P_{CO_2} falls by a few millimetres of mercury. This imparts a saw-tooth curve to the alveolar P_{CO_2} when it is plotted against time. One section of this curve may be determined from the carbon dioxide concentration determined at the mouth with a rapid analyser (*Figure 99*).

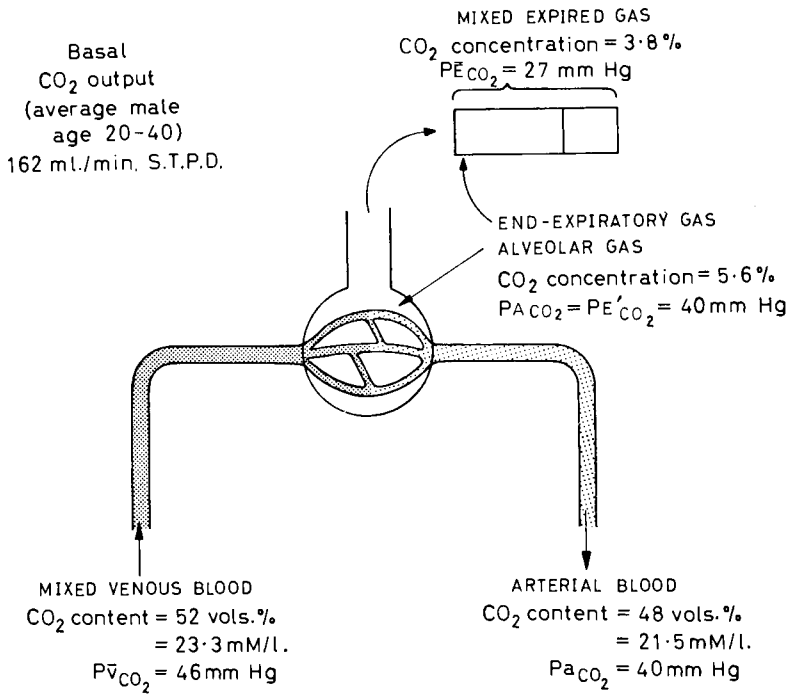


Figure 100. Normal values for CO_2 levels in the healthy unanaesthetized subject. These normal values are rounded off and ignore the small difference in P_{CO_2} between end-expiratory gas, alveolar gas and arterial blood. Actual values of P_{CO_2} depend mainly on alveolar ventilation but the differences depend upon maldistribution; the alveolar/end-expiratory P_{CO_2} difference depends on alveolar dead space and the very small arterial/alveolar P_{CO_2} difference on shunts. Scatter of V/Q ratios makes a small contribution to both alveolar/end-expiratory and arterial/alveolar P_{CO_2} gradients. The arterial/mixed venous CO_2 content difference is directly proportional to CO_2 output and inversely proportional to cardiac output. Secondary symbols: $\bar{E}$, mixed expired; E', end-expiratory; A, alveolar; a, arterial; $\bar{v}$, mixed venous

On the arterial side, the blood leaving the pulmonary capillary has a P_{CO_2} which is very close to that of the alveolar gas and, therefore, varies with *time* in the same manner as the alveolar P_{CO_2}. There is also a *regional* variation depending upon the ventilation/perfusion ratio of different parts of the lung. This exerts a marked effect upon regional P_{CO_2}, which is inversely related to the ventilation/perfusion ratio (*Figure 86*). The mixed arterial P_{CO_2} is the

integrated mean of blood from different parts of the lung, and a sample drawn over several seconds will average out the cyclical variations resulting from respiration.

When discussing factors influencing the level of carbon dioxide, it is more convenient to consider tension than content. This is because carbon dioxide always moves in accord with tension gradients even if they are in the opposite direction to concentration gradients. Also, the concept of tension may be applied with equal significance to gas and liquid phases: content has a rather different connotation in the two phases. Furthermore, it seems likely that the effects of carbon dioxide (e.g. upon respiration) are a function of tension rather than content. Normal values for tension and content are shown in *Figure 100.*

Each factor which influences the P_{CO_2} has already been mentioned in this book and it only remains in this chapter to draw them together, illustrating their relationship to one another. The following section may, therefore, be used either as an introduction to the subject or as a summary.

It is convenient first to summarize the factors influencing the alveolar P_{CO_2} and then to consider the factors which influence the relationship between the alveolar and the arterial P_{CO_2}.

The Alveolar P_{CO_2} ($P_{A_{CO_2}}$) (Figure 101)

Carbon dioxide is constantly being added to the alveolar gas from the pulmonary blood and removed from it by the alveolar ventilation. The concentration of carbon dioxide is simply equal to the ratio of the two, provided carbon dioxide is not inhaled.

$$\text{alveolar } CO_2 \text{ concentration} = \frac{\text{carbon dioxide output}}{\text{alveolar ventilation}}$$

This axiomatic relationship is the basis of all the methods of predicting the P_{CO_2} and is, in fact, a form of the Bohr equation. Derivations from this equation have been presented in Chapter 6 and we may note the following equation which describes the principal factors influencing the alveolar P_{CO_2}:

$$\begin{matrix}\text{alveolar} \\ P_{CO_2}\end{matrix} = \begin{matrix}\text{dry} \\ \text{barometric} \\ \text{pressure}\end{matrix} \left(\begin{matrix}\text{mean} \\ \text{inspired } CO_2 \\ \text{concentration}\end{matrix} + \frac{CO_2 \text{ output}}{\text{alveolar ventilation}} \right)$$

This equation is shown in graph form in *Figure 102.* Prediction of P_{CO_2} from ventilation has been discussed on page 153.

The dry barometric pressure is not a factor of much importance in the determination of alveolar P_{CO_2}, and normal variations of barometric pressure at sea level are unlikely to influence the P_{CO_2} by more than 1 or 2 mm Hg. At high altitude, the hypoxic drive to ventilation lowers the P_{CO_2}.

The mean inspired CO_2 concentration is a more difficult concept than it appears at first sight, and has been considered in relation to apparatus dead space on page 195. For the moment we may note that the effect of inspired carbon dioxide on the alveolar P_{CO_2} is additive. If, for example, a patient breathes gas with P_{CO_2} 28 mm Hg (about 4 per cent CO_2), the alveolar P_{CO_2} will be raised 28 mm Hg above the level it would be if there were no carbon dioxide in the

inspired gas, other factors remaining the same. The barometric pressure is the only limit to the elevation of P_{CO_2} which may be obtained by the inhalation of carbon dioxide mixtures. Arterial tensions of over 200 mm Hg may be produced by a few breaths of 30 per cent carbon dioxide.

Carbon dioxide output is equal to carbon dioxide production in a steady state. However, during unsteady states, output may be quite different from production (Nunn and Matthews, 1959). For example, during acute hypoventilation, the output may temporarily fall to very low figures until the alveolar carbon

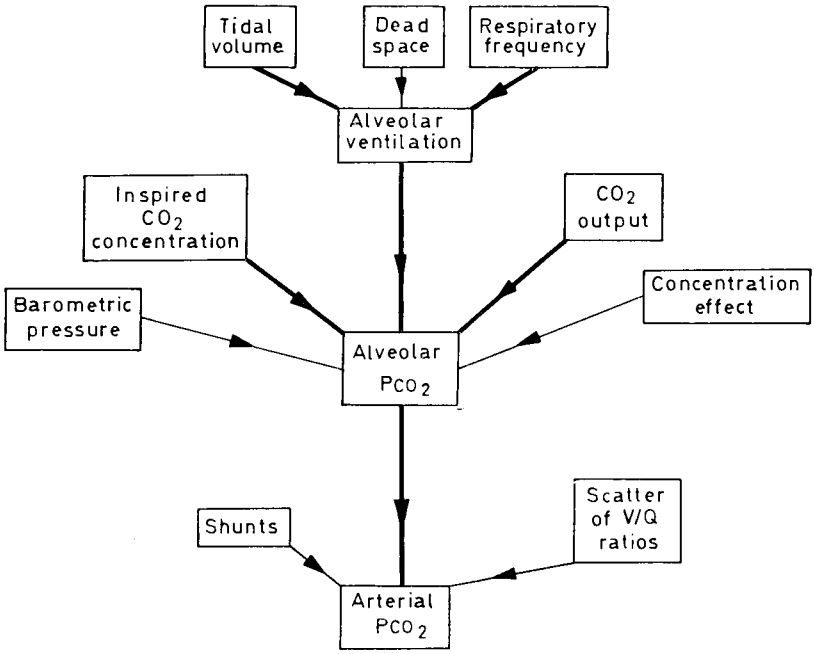


Figure 101. Summary of factors which influence P_{CO_2}*; the more important ones are indicated with the thicker arrows. In the steady state, the carbon dioxide output of an anaesthetized patient usually lies within the range 100–200 ml./min. and the alveolar* P_{CO_2} *is largely governed by the alveolar ventilation, provided that the inspired carbon dioxide concentration is zero. The barometric pressure is the only limit to the elevation of* P_{CO_2} *which may be brought about by the inhalation of gas mixtures containing* CO_2

dioxide concentration has risen. Conversely, acute hyperventilation results in a transient increase in carbon dioxide output. A sudden fall in cardiac output decreases the carbon dioxide output until the carbon dioxide concentration in the mixed venous blood rises. The unsteady state is considered in more detail later.

Alveolar ventilation, for the present purposes, means the product of the respiratory frequency and the difference between the tidal volume and the physiological dead space (page 178). It is subject to gross departures from normal during anaesthesia and in certain disease states. These changes are considered elsewhere in this book under the headings of ventilation (page 156) and dead space (page 191).

The concentration effect.—Apart from the factors shown in the equation above and in *Figure 102*, the alveolar P_{CO_2} is influenced by what is, for want of a better name, known as the concentration effect. This is caused by a sudden change in the net transfer of inert gases across the alveolar-capillary membrane. This is only likely to have an important effect on carbon dioxide at the end of an anaesthetic when large quantities of nitrous oxide are passing from the body stores into the alveolar gas, and a much smaller quantity of nitrogen is returning to its accustomed place in the body. This leads to a dilution of the alveolar carbon dioxide. The fall in P_{CO_2} is probably small but may be sufficient to

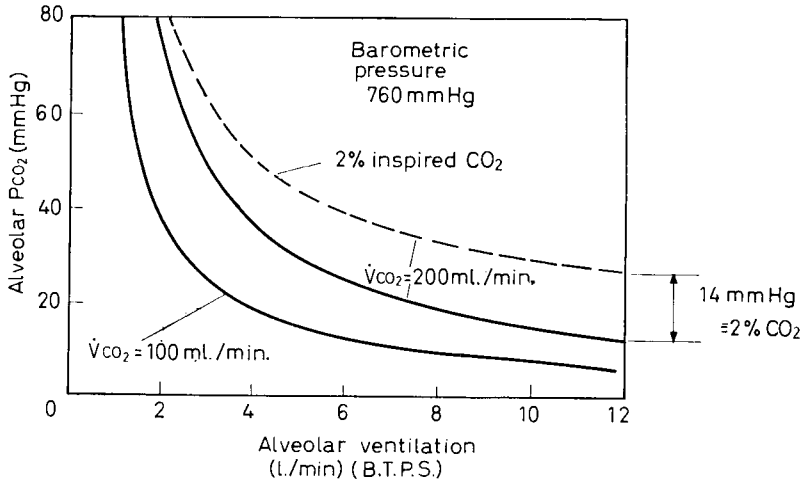


Figure 102. The effect of CO_2 output, alveolar ventilation and inspired CO_2 concentration on alveolar P_{CO_2}. The lower continuous curve shows the relationship between ventilation and alveolar P_{CO_2} for a carbon dioxide output of 100 ml./min. (S.T.P.D.). The upper continuous curve shows the relationship when the carbon dioxide output is 200 ml./min. (S.T.P.D.). The broken curve represents the relationship when the carbon dioxide output is 200 ml./min. and there is an inspired CO_2 concentration of 2 per cent. Two per cent CO_2 is equivalent to about 14 mm Hg and each point on the broken curve is 14 mm Hg above the upper of the two continuous curves. The continuous curves are rectangular hyperbolas with identical asymptotes (zero alveolar P_{CO_2} and zero alveolar ventilation). The broken curve is also a rectangular hyperbola but the horizontal asymptote is P_{CO_2} 14 mm Hg which is the tension in the inspired gas

cause a transient reduction in ventilation when nitrous oxide is withdrawn at the end of an operation. (*See also* page 336.)

The End-expiratory P_{CO_2}

In the normal, healthy, conscious subject, the end-expiratory gas consists almost entirely of alveolar gas. If, however, appreciable numbers of alveoli are ventilated but not perfused, they will contribute a significant quantity of CO_2-free gas from the alveolar dead space to the end-expiratory gas (*Figure 63*). As a result the end-expiratory P_{CO_2} (end-tidal or Haldane–Priestley sample) will have a lower P_{CO_2} than that of the alveoli which are perfused. Gas cannot be sampled selectively from the perfused alveoli, but Chapter 9 explains how the arterial P_{CO_2} usually approximates closely to the mean value for the perfused alveoli in spite of scatter of ventilation/perfusion ratios (*Figure 88*). It is, therefore, customary to compare the arterial P_{CO_2} with the end-expiratory

P_{CO_2} to demonstrate the existence of an appreciable proportion of unperfused alveoli. Studies during anaesthesia have shown an arterial/end-tidal P_{CO_2} gradient of about 5 (s.d. 2·5) mm Hg in patients without lung disease (Ramwell, 1958; Nunn and Hill, 1960).

The Alveolar/Arterial P_{CO_2} *Gradient* (Figure 101)

For reasons which have been discussed in Chapter 10, we may discount the possibility of any significant gradient between the P_{CO_2} of alveolar gas and pulmonary end-capillary blood. Arterial P_{CO_2} may, however, differ slightly from the mean alveolar P_{CO_2} as a result of shunting or scatter of ventilation/perfusion ratios. The magnitude of the gradient has been considered in Chapter 9 where it was shown that a shunt of 10 per cent will only cause an alveolar/arterial P_{CO_2} gradient of about 0·6 mm Hg. Since the normal degree of ventilation/perfusion ratio scatter causes a gradient of the same order, neither can be considered to cause a significant gradient and, for practical purposes, there is an established convention by which the arterial and alveolar P_{CO_2} values are taken to be identical. It is only in exceptional patients that the gradient is likely to exceed 2 mm Hg.

The table accompanying *Figure 88* shows the gradients in P_{CO_2} between air and arterial blood in imaginary but typical anaesthetized patients with 10 per cent alveolar dead space effect, 10 per cent shunt and the normal degree of scatter of ventilation/perfusion ratios. *Table 32* shows P_{CO_2} gradients measured in real anaesthetized patients. Much the largest part of the arterial/end-expiratory P_{CO_2} gradient is due to the component between the true mean alveolar gas and the end-expiratory gas, caused by alveolar dead space.

Table 32

Typical values for P_{CO_2} *in anaesthetized patients (from Nunn and Hill, 1960, and other unpublished data)*

	Spontaneous respiration	*Artificial ventilation*	
Minute volume (l./min., B.T.P.S.)	4·1	7·7	10·3
Arterial P_{CO_2} (mm Hg)	52	33	27
End-expiratory P_{CO_2} (mm Hg)	47	28	22
Mixed-expired P_{CO_2} (mm Hg)	30	19	16

Tissue P_{CO_2} Levels

There is very little information on the actual levels of P_{CO_2} in the tissues. Studies of cerebrospinal fluid and gas loculi in the tissues suggest that the 'mean' P_{CO_2} for the tissues studied is between 5 and 10 mm Hg higher than that of the arterial blood. The actual tensions are thus not much greater than in venous blood although it is likely that higher levels pertain within the mitochondria.

Carbon Dioxide Levels during Anaesthesia (Table 32)

From the above discussion of factors which influence carbon dioxide levels it will be clear that, during anaesthesia, the principal factors must be the

inspired carbon dioxide concentration, the carbon dioxide output and the alveolar ventilation, the last being a function of the total ventilation and the physiological dead space.

The concentration of carbon dioxide in the inspired gas is normally zero but may be raised accidentally or intentionally to any concentration. Accidental administration of about 30 per cent carbon dioxide has been described for endogenous carbon dioxide by Schultz and his colleagues (1960), and for exogenous carbon dioxide by Prys-Roberts, Smith and Nunn (1967). The only difference between the two conditions is that the increase of P_{CO_2} due to exogenous carbon dioxide may be very much more rapid than when the patient's own carbon dioxide is allowed to accumulate.

Carbon dioxide output in the anaesthetized patient is reasonably constant *during the steady state* and is likely to be within 50 ml./min. of the values shown in *Table 15.* Unsteady states are considered in the next section. They may cause wide temporary disparities between the carbon dioxide output and the carbon dioxide production which probably remains fairly constant.

The minute volume may vary widely during anaesthesia. The lower limits are reached during spontaneous respiration with either deep anaesthesia or partial neuromuscular blockade, when minute volumes as low as 1·95 l./min. have been recorded (Nunn, 1958a). On the other hand, during artificial ventilation, very high minute volumes may be attained and values in excess of 20 l./min. are common. Nunn (1958a) has demonstrated the effect of changes in ventilation on the P_{CO_2} of patients under routine anaesthesia and Figure 5 in that article may be compared with *Figure 102.*

The effects of anaesthesia upon the various subdivisions of the dead space have been discussed in Chapter 7. It is a reasonable working rule that the alveolar ventilation of a healthy, intubated anaesthetized patient is two-thirds of the total minute volume (excluding ventilation of the apparatus dead space; Nunn and Hill, 1960). *Including* apparatus dead space, alveolar ventilation approximates half the minute volume of intubated patients but only a third of the minute volume of patients breathing from a mask (Kain, Panday and Nunn, 1969).

It will be apparent from the paragraphs above that, during anaesthesia, the arterial P_{CO_2} may lie anywhere between 10 and, say, 250 mm Hg, largely according to the whim of the anaesthetist. In fact, it generally lies between 20 and 35 mm Hg during anaesthesia with artificial ventilation, and between 40 and 65 mm Hg during anaesthesia with spontaneous respiration.

During thoracotomy, values as high as 236 mm Hg were recorded by some anaesthetists in the days before general appreciation of the value of artificial ventilation in patients with an open thorax (Ellison, Ellison and Hamilton, 1955). With artificial ventilation, normal or subnormal values for arterial P_{CO_2} may be attained during thoracic surgery without excessively large minute volumes, 7 l./min. being sufficient in most cases (Nunn, 1961a).

CARBON DIOXIDE STORES AND THE UNSTEADY STATE

The quantity of carbon dioxide in the body is very large (about 120 litres), much of it being in the form of carbonates in bone or dissolved in lipids. Even the aqueous body fluids contain about 500 ml. of carbon dioxide per litre. In

contrast, all body fluids (except blood) contain considerably less oxygen than 2 ml./l., and even arterial blood contains only about 200 ml. of oxygen per litre.

Because of the vast amount of carbon dioxide in the body, the total quantity can only be changed very slowly when ventilation is altered out of accord with metabolic requirements. However, the body is not a single compartment but consists of an infinite number of compartments, each of which has its own time course of change of P_{CO_2} in response to a change in ventilation. As a simplification, it is reasonably satisfactory to represent the body as though it consisted of three compartments. *Figure 103* shows a hydrostatic analogy in which the depth of water represents P_{CO_2}, and the volume of water corresponds to volume of carbon dioxide. The production of CO_2 in the tissues is represented by the variable flow of water from the supply tank into the three lower tanks which represent the body compartments.

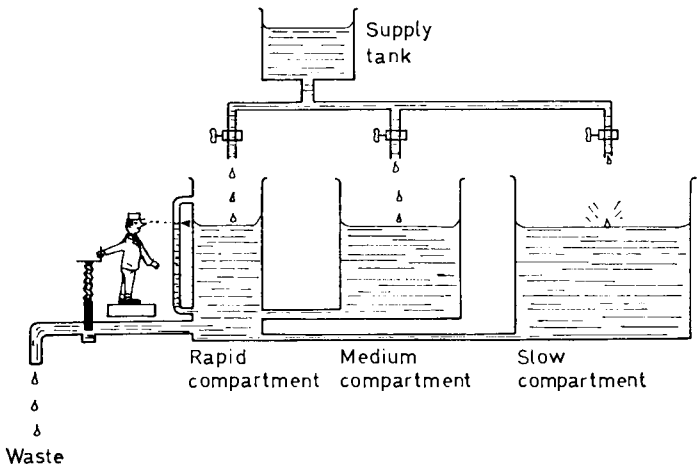


Figure 103. A hydrostatic analogy of the elimination of carbon dioxide. See text for full discussion

The rapid compartment represents circulating blood, brain, kidneys and other well-perfused tissues which are at a P_{CO_2} a few mm Hg higher than that of alveolar gas and tend to follow a similar time course during changes of P_{CO_2}. The medium compartment represents skeletal muscle (in the resting state) and other parts of the body with a moderate blood flow. This tank is quite large and is connected to the rapid compartment by a relatively narrow pipe; therefore, sudden changes in the level of water in the rapid tank will produce only gradual changes in the water level in the medium tank. (For example, during acute hyperventilation, the muscle P_{CO_2} falls more slowly than that of alveolar gas.) The slow compartment represents fat and bone and other tissues with a very large capacity for carbon dioxide, but which are only able to change their carbon dioxide level slowly. In the case of fat, this is because of poor blood supply while, in the case of bone, it is because of the slow process by which carbon dioxide is released from carbonates. It will be clear from the diagram that the level of water can change only very slowly in the slow compartment.

The elimination of carbon dioxide by alveolar ventilation is represented by the outflow pipe which is controlled by a tap operated by a man observing the level in the rapid compartment. He represents the 'respiratory centre', which controls alveolar ventilation in accord with the P_{CO_2} of the arterial blood (*inter alia*). If the outlet valve is suddenly opened widely (hyperventilation) while the inflow is unchanged, the levels will all fall to a new equilibrium level. That in the rapid compartment will start to fall rapidly as soon as the valve is opened, with those in the other tanks lagging behind. As the level in the 'fast' tank falls, the outflow rate slackens and the transfer of water from the medium and slow compartments to the rapid compartment then becomes appreciable in relation to the outflow. The final approach to the equilibrium level in the rapid compartment is then very slow.

If we plot the level of water in the rapid tank against time, during a sudden opening of the outlet valve, the graph will be analogous to the change in arterial P_{CO_2} produced by a sudden increase in ventilation (not associated with an increase in metabolism). The wash-out curve in each case is rather complex, being a compound of a number of exponential functions each with its own time constant (Appendix D). In fact, the changes can usually be adequately expressed as though there were only two compartments and two exponentials. As a further simplification we may sometimes consider the situation as though it were a single-compartment system represented by a single exponential. In fact such a simplified plot would not be so very different from the more accurate three-compartment model, and a practised eye and very careful measurements are needed to demonstrate the wash-out of multi-compartment systems.

If we may be permitted to talk of the human body as though it were a single-compartment system, we might go so far as to talk about the half-time of the system, which is the time required for the P_{CO_2} to fall half-way to its final value after a step increase in ventilation (*Figure 125*). This has been studied by Fahri and Rahn (1955a), and Nunn and Matthews (1959), and is of the order of 3–4 minutes in man. *Figure 104* (solid circles) shows a typical example of the time course of the fall of P_{CO_2}, in this case following a step increase of ventilation from 3·3 to 14 l./min. in an anaesthetized paralysed patient. The slow component of change cannot be detected against the background scatter of the experimental observations after 20 minutes.

It has been realized only comparatively recently that the time course of the increase of P_{CO_2} following a step decrease of ventilation does not necessarily follow the mirror image of the time course of decrease of P_{CO_2} when ventilation is increased. In fact, the rate of rise is much slower than the rate of fall, which is fortunate for anaesthetized patients in asphyxial situations. In the event of total respiratory arrest, the rate of rise of arterial P_{CO_2} is of the order of 3–6 mm Hg/min., which is the resultant of the rate of production of carbon dioxide and the capacity of the body stores to accommodate the carbon dioxide which is produced. Returning to the hydrostatic analogy in *Figure 103*, it will be clear that, if the outflow pipe is totally obstructed, the rate of rise of water will be the resultant of the inflow from the supply tank and the capacity of the tanks. The most important factor is the capacity of the rapid compartment because the changes in the other tanks are too slow to influence matters in an acute asphyxial situation. It happens that the maximal rate of rise is much slower than the rate of fall which can occur when the outflow valve is opened widely.

During acute hypoventilation in the anaesthetized patient, the rate of rise of arterial P_{CO_2} will always be less than the maximal rate in apnoea, and the study of Nunn (1964) suggested that the measurable rate of rise of P_{CO_2} during hypoventilation was unlikely to be complete in an hour. Sullivan, Patterson and Papper (1966) showed that the time course of rise was indeed very much slower than the known rate of fall of P_{CO_2} when ventilation was increased, and half-changes required about 15–20 minutes (open circles in *Figure 104*). The time course of rise of P_{CO_2} after a step reduction of ventilation is faster when the previous level of ventilation has been of short duration (Ivanov and Nunn, 1968).

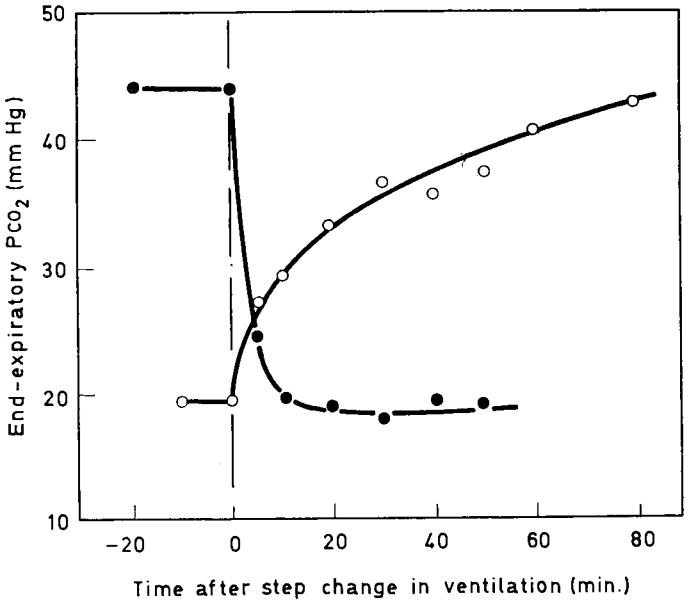


Figure 104 Time course of changes in end-expiratory P_{CO_2} *following step changes in ventilation. The solid circles indicate the changes in end-expiratory* P_{CO_2} *which followed a step change in ventilation from 3·3 to 14 l./min. The open circles show the change following a step change in ventilation from 14 to 3·3 l./min. in the same patient. During the fall of* P_{CO_2}, *half the total change is completed in about 3 minutes. During the rise of* P_{CO_2}, *half-change takes approximately 16 minutes*

The practical significance of the difference in time courses shown in *Figure 104* is that hyperventilation of an anaesthetized patient causes a rapid fall in P_{CO_2}, with the new low level attained, for all practical purposes, within about ten minutes. On the other hand, if a patient is permitted to hypoventilate, the P_{CO_2} will rise to a new high level but the change will not be precipitate. For example, if a patient hypoventilates at 3 litres per minute during an operation lasting one hour, we may expect the P_{CO_2} to rise towards a level of about 70 mm Hg, which is the predicted steady-state level of P_{CO_2} (page 149), appropriate allowance being made for apparatus dead space. However, the P_{CO_2} will only have risen from 40 to about 55 mm Hg by the end of the first 15 minutes, and is probably only about 63 mm Hg at the end of the operation.

Clearly, prediction of P_{CO_2} will be of very limited value after acute reductions in ventilation, and it must be remembered that prediction does not claim to indicate the actual P_{CO_2}, but the P_{CO_2} which will be attained if the level of ventilation is maintained (Nunn, 1960a).

It will be seen in Chapter 12 that, unlike the P_{CO_2}, the P_{O_2} changes very quickly after changes in ventilation. Consequently, changes in ventilation are followed by temporary changes in the respiratory exchange ratio although, if the ventilation is held constant, the respiratory exchange ratio must eventually return to the level determined by the metabolic processes of the body. Carbon dioxide stores have been reviewed by Farhi (1964).

APNOEIC MASS-MOVEMENT OXYGENATION (formerly known as DIFFUSION RESPIRATION)

When a patient becomes apnoeic, the alveolar gas tends to come into equilibrium with the mixed venous blood which continues to perfuse the lungs. Assuming normal initial values for the composition of the alveolar gas and mixed venous gas tensions, this would entail a rise of P_{CO_2} from 40 to 46 mm Hg and a fall of P_{O_2} from 105 to 40 mm Hg. The *volume* of gas which would require to cross the alveolar-capillary membrane is directly proportional to the gas tension change. Ignoring changes in the composition of the mixed venous blood and assuming an average F.R.C., equilibration of alveolar gas with mixed venous blood would require the output of 21 ml. of carbon dioxide and the uptake of 230 ml. of oxygen at normal lung volume. The small quantity of carbon dioxide could be transferred in a few seconds, but 230 ml. of oxygen would require more than a minute under basal conditions. Therefore, carbon dioxide would come into equilibrium within one circulation time while oxygen would take much longer. Thus for practical purposes, carbon dioxide does reach equilibrium while oxygen is always *tending towards* equilibrium but never reaching it, since the mixed venous P_{O_2} is always lower than the arterial P_{O_2} after the blood has passed through the systemic circulation. There are no appreciable body stores of oxygen, and therefore the arterial/mixed venous oxygen content difference must remain fairly constant.

What actually happens in apnoea depends upon the patency of the airway and the composition of the ambient gas if the airway is patent.

With airway occlusion the pattern of change is close to that described above. There is a rapid attainment of equilibrium between alveolar and mixed venous P_{CO_2}. The arterial, alveolar and mixed venous P_{CO_2} values remain close together and rise gradually at the rate of about 3–6 mm Hg/min., with more than 90 per cent of the metabolically produced carbon dioxide passing into the body stores. Alveolar P_{O_2} falls rapidly towards the mixed venous P_{O_2} which itself falls continuously as the arterial P_{O_2} decreases. The lung volume falls by the difference between the oxygen uptake and the carbon dioxide output. Initially the rate would be $230 - 21 = 209$ ml./min. The change in alveolar P_{O_2} may be calculated, and gross hypoxia supervenes after about 90 seconds if the experiment follows air breathing and starts at the functional residual capacity.

With patent airway and air as ambient gas the oxygen is initially taken up and the carbon dioxide rises as described above. However, instead of the lung volume

falling by the net gas exchange rate (initially 209 ml./min.), this amount of ambient gas is drawn in by mass movement down the trachea. If the ambient gas is air, the oxygen in it will be removed but the nitrogen will accumulate and rise above its normal concentration until gross hypoxia supervenes after about two minutes. This is likely to occur when the accumulated nitrogen has reached 90 per cent since the alveolar carbon dioxide concentration will then have reached about 8 per cent. Carbon dioxide elimination cannot occur as the mass movement of gas is down the trachea and this prevents the loss of carbon dioxide by diffusion. Measured at the mouth there is oxygen uptake but no carbon dioxide output; the respiratory exchange ratio is thus zero.

With patent airway and oxygen as the ambient gas the situation is quite different. Oxygen is drawn in by mass-movement and replaces the oxygen which crosses the alveolar-capillary membrane. No nitrogen is added to the alveolar gas, and the alveolar P_{O_2} only falls as fast as the P_{CO_2} rises (about 3–6 mm Hg/min.). Therefore the patient will not become seriously hypoxic for several minutes. If the patient has been breathing oxygen prior to the respiratory arrest, the starting alveolar P_{O_2} will be of the order of 660 mm Hg and therefore the patient can theoretically survive about 100 minutes of apnoea provided he is connected to a supply of 100 per cent oxygen. This, in fact, is true and has been demonstrated in both animals and man (Draper and Whitehead, 1944; Enghoff, Holmdahl and Risholm, 1951; Holmdahl, 1956; Frumin, Epstein and Cohen, 1959). The phenomenon has moved out of the laboratory into clinical anaesthesia (Holmdahl, 1953) and has been used as a practical anaesthetic technique, particularly for bronchoscopy when artificial ventilation may be difficult (Barth, 1954; Payne, 1962).

With preliminary inhalation of oxygen and an unobstructed supply of oxygen, there is no difficulty in maintaining an adequate arterial P_{O_2} during at least 20 minutes of apnoeic mass-movement oxygenation. However, the technique causes total retention of carbon dioxide and the arterial P_{CO_2} rises within the range 3–6 mm Hg/min. Hypercapnia is thus an inevitable feature of the technique. Arterial P_{CO_2} as high as 140 mm Hg has been reported by Payne (1962) after 11 minutes (with an initial P_{CO_2} of 83 mm Hg).

The technique has been modified by numerous workers in an attempt to prevent the rise of P_{CO_2}. Generally they suggest insufflation of oxygen into one or both bronchi in order to remove the carbon dioxide which is displaced from the subcarinal parts of the lung by the contraction of the heart (*see* page 183). These techniques are successful provided a fairly high gas flow is used.

Draper and Whitehead (1944) originally described the phenomenon as 'diffusion respiration' to stress that gas exchange occurred without overt tidal movement. However, it is now clear that there is a continuous mass-movement of ambient gas down the trachea and diffusion is no more involved than it is in normal tidal respiration. 'Diffusion respiration' is therefore now regarded as a misnomer and the recommended term is 'apnoeic mass-movement oxygenation' which is descriptive though not euphonious.

THE EFFECTS OF CHANGES IN THE CARBON DIOXIDE TENSION

Few subjects in the field of physiology are as complicated as the effects of

changes in the carbon dioxide tension. A whole book would be required to do justice to this topic alone, and therefore only a brief outline will be presented at this time. Previous reviews include Brown (1953), the special issue of *Anaesthesiology* of December 1960, Nunn (1962d), Robinson (1962) and Tenney and Lamb (1965).

A number of special difficulties encompass an understanding of the effects of changes in P_{CO_2}. Firstly, there is the problem of species difference, which is a formidable obstacle to the understanding of animal studies. The second

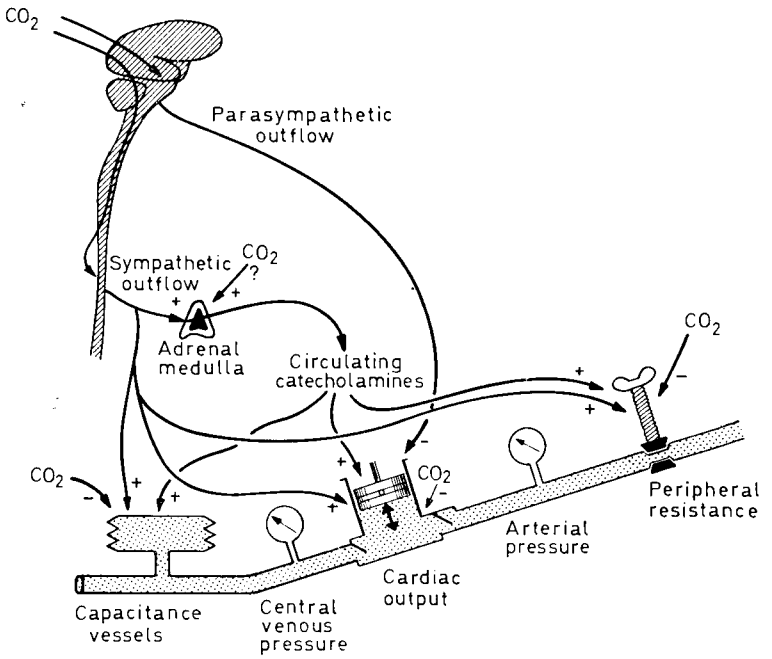


Figure 105. This diagram shows the complexity of the mechanisms by which carbon dioxide may influence the circulatory system. The over-all effect in the anaesthetized patient is an increase in cardiac output which is roughly proportional to the arterial P_{CO_2}. *The rise in cardiac output exceeds the rise in blood pressure and this may be described as a fall in peripheral resistance (total). In spite of the rise of cardiac output, there is an increase in central venous pressure. This implies that capacitance vessels are contracted to cause a rise in filling pressure with which the increased cardiac output does not keep pace. In the absence of sympathetic nervous system activity, the direct effect of carbon dioxide upon the myocardium causes a fall of cardiac output and a profound fall in peripheral resistance is also seen. A fall in arterial blood pressure is then inevitable*

difficulty arises from the fact that carbon dioxide can exert its effect in a number of ways. For example, the so-called 'inert gas' narcotic effect would presumably be produced by carbon dioxide in accord with its physical properties, although it is more likely to exert its effects upon the central nervous system by means of its unique ability to alter the intracellular pH (*see* above). This is quite apart from the fact that a change in P_{CO_2} usually alters the pH of the circulating blood. In addition, it remains possible that carbon dioxide

can exert specific effects unrelated to the mechanisms listed above, although this would be difficult to prove. The third difficulty in the understanding of the effects of carbon dioxide arises from the fact that the gas seems to act at many different sites. Sometimes the action of carbon dioxide at different sites produces opposite effects upon a particular function, and the action of carbon dioxide upon blood pressure (*Figure 105*) is an example of the complexity of the manner in which its effects may be produced.

Normal Range and Definitions

The normal range of arterial P_{CO_2} is 36–44 mm Hg.

*Hypocapnia** (synonymous with respiratory alkalosis and hypocarbia) describes a state in which the P_{CO_2} is reduced below the normal range. Values down to 20 mm Hg are commonplace during anaesthesia with artificial ventilation, and may be attained in the normal subject by voluntary hyperventilation. Lower values may be obtained by more vigorous artificial ventilation although, during spontaneous hyperventilation, the increased production of carbon dioxide by the respiratory muscles tends to prevent the attainment of very low levels of P_{CO_2}.

Hypercapnia (synonymous with respiratory acidosis and hypercarbia) describes a state in which the P_{CO_2} is elevated above the normal range. Values up to 50 mm Hg may be attained by breath holding but, by breathing mixtures of carbon dioxide in oxygen, the normal subject may attain a P_{CO_2} of about 80 mm Hg without serious ill effect. Higher values result in confusion and loss of consciousness. While breathing air, it is not possible for a hypoventilating patient to attain a P_{CO_2} in excess of about 100 mm Hg because at that level the attendant hypoxia will become critical. Patients under the care of anaesthetists frequently inhale oxygen concentrations in excess of 21 per cent and this permits much greater degrees of hypoventilation without the concomitant hypoxia which would develop if the patient were breathing air. In this respect severe hypercapnia may be considered an iatrogenic disorder. Many anaesthetists show considerable tolerance of the hypercapnia which they allow their patients to develop, and P_{CO_2} within the range 44–75 mm Hg is commonplace during anaesthesia with spontaneous respiration. Levels within the range 100–150 mm Hg have sometimes been permitted in the course of research projects, while levels as high as 160 mm Hg are apparently tolerated by some anaesthetists in the course of routine anaesthesia (Birt and Cole, 1965). Levels over 200 mm Hg have been reported during routine thoracic anaesthesia without artificial ventilation (Ellison, Ellison and Hamilton, 1955). It is against this background that we must review the much-discussed 'dangers of CO_2 retention'.

Difference between Hypercapnia of Endogenous and Exogenous Origin

The actual effects of carbon dioxide are identical whether the patient accumulates his own carbon dioxide, or whether he inhales carbon dioxide produced outside his body. The only difference is in the rate of rise of P_{CO_2} which is possible.

* Etymologically hypocapnia seems preferable to hypocarbia, both roots being of Greek origin; carbia is derived from the Latin.

If a resting or anaesthetized patient retains his own carbon dioxide (either by rebreathing or by hypoventilation) the rate of rise cannot exceed about 3–6 mm Hg/min., which is the rate determined by the ratio of his metabolism to his storage capacity for carbon dioxide. Except in total apnoea or total rebreathing, the rate of rise will be less than this and the case of acute hypoventilation in *Figure 104* shows a typical maximum rate of rise of P_{CO_2} of less than 2 mm Hg/min. In contrast, there is almost no limit to the rate of rise of P_{CO_2} which may be attained by the inhalation of high concentrations of carbon dioxide. During the administration of carbon dioxide for the purpose of abreaction, Meduna (1958) recorded falls of arterial pH to less than 7·0 within 40 seconds of the inhalation of 30 per cent carbon dioxide. This corresponds to a rise of more than 200 mm Hg/min., which is 100 times the rate of change likely to result from acute hypoventilation.

Effects upon the Nervous System

Carbon dioxide has at least five major effects upon the brain.

(1) It is the major factor governing the cerebral blood flow.

(2) It may be presumed to exert the inert gas narcotic effect in accord with its physical properties which are similar to those of nitrous oxide.

(3) It influences the excitability of the neurones, particularly relevant in the case of the reticulo-activating system.

(4) It is the main factor influencing the intracellular pH, which is known to have important effects upon the metabolism of the cell.

(5) It influences the C.S.F. pressure through changes in cerebral blood flow.

The interplay of these effects is difficult to understand, although the gross changes produced are well established. A reduction in P_{CO_2} causes a feeling of intoxication and enhances the actions of agents used to produce general anaesthesia (Gray and Rees, 1952). An increase in pain threshold (tibial pressure) has been reported by Clutton-Brock (1957) and this may be related to the effect of hypocapnia in potentiating anaesthesia. Nevertheless, there remains some doubt as to the mechanism by which this effect is produced. There has been no convincing demonstration that the effect is due to cerebral hypoxia caused by reduction of cerebral blood flow and it seems more likely to be caused by a decrease in excitability of neurones, or to altered distribution of certain drugs (page 320).

Elevation of P_{CO_2} produces unconsciousness at P_{CO_2} within the range 90–120 mm Hg (Westlake, Simpson and Kaye, 1955; Refsum, 1963), although this may be due to the associated change in arterial pH rather than to any specific effect of carbon dioxide. Carbon dioxide was used as an anaesthetic by Henry Hill Hickman in 1824, later by Ozanam (1862), and finally by Leake and Waters (1928). Thirty per cent carbon dioxide is sufficient for the production of anaesthesia, and this concentration causes total but reversible flattening of the electroencephalogram (Clowes, Hopkins and Simeone, 1955). Unfortunately, the use of carbon dioxide as an anaesthetic is impaired by the frequent production of convulsions at about the concentration required for anaesthesia (Leake and Waters, 1928). Higher concentrations have been shown to be tolerated by dogs, in whom the tendency to convulsions disappears when the P_{CO_2} rises above about 250 mm Hg.

Effects upon the Autonomic and Endocrine Systems

Survival in severe hypercapnia is, to a large extent, dependent on the autonomic response which is therefore one of the most important effects of carbon dioxide. A great many of the effects of carbon dioxide on other systems are, in fact, either due to or influenced by the autonomic response to carbon dioxide. Examples of this multiplicity of mechanisms of action are shown in *Figure 105.*

Nahas, Ligou and Mehlman (1960) and Millar (1960) have clearly shown the increase in plasma levels of both adrenaline and noradrenaline caused by an elevation of P_{CO_2} during apnoeic mass-movement oxygenation (*Figure 106*).

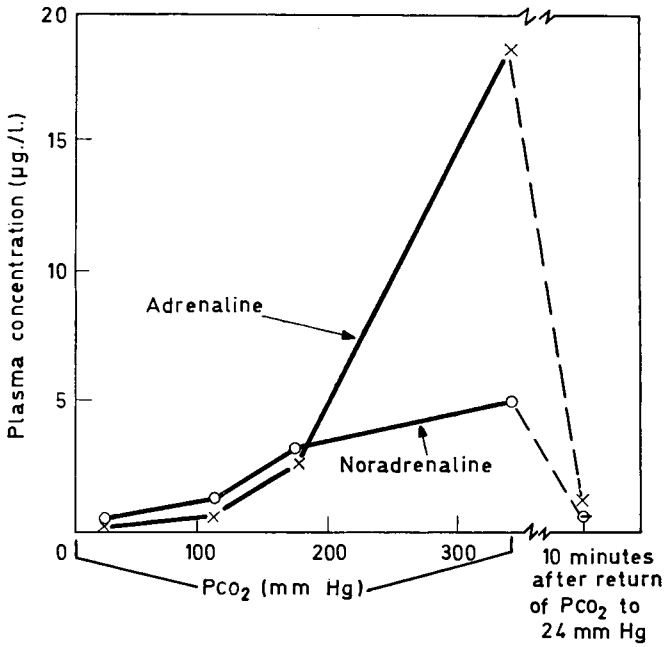


Figure 106. This graph shows the changes in plasma catecholamine levels in the dog during the rise of P_{CO_2} *from 22 to 338 mm Hg in the course of one hour of apnoeic oxygenation. After 10 minutes of ventilation with oxygen,* P_{CO_2} *returned to 24 mm Hg. Catecholamines were almost back to control values but the adrenaline remained higher than the noradrenaline. (Prepared from Table 4 of Millar, 1960)*

In moderate hypercapnia, there is a proportionate rise of adrenaline and noradrenaline, but, in gross hypercapnia (P_{CO_2} more than 200 mm Hg), there is an abrupt rise of adrenaline. Similar, though very variable, changes have been obtained over a lower range of P_{CO_2} in human volunteers inhaling carbon dioxide mixtures (Sechzer and his colleagues, 1960).

The relationship between P_{CO_2} and plasma catecholamine levels is considerably influenced by the administration of inhalational anaesthetic agents. Higher levels of adrenaline and noradrenaline are obtained during cyclopropane anaesthesia than in the unanaesthetized subject. Price and his colleagues (1960) reported levels of 10 µg./l. with a P_{CO_2} increase of only 80 mm Hg

during cyclopropane administration. However, the same group found that plasma catecholamine levels of patients under halothane anaesthesia rose in much the same way as in conscious subjects.

The effect of an increased level of circulating catecholamines is, to a certain extent, offset by a decreased sensitivity of target organs when the pH is reduced (Tenney, 1956). This is additional to the general depressant direct effect of carbon dioxide on target organs. There is also evidence that the anterior pituitary gland is stimulated by carbon dioxide resulting in increased secretion of ACTH (Tenney, 1960). Acetylcholine hydrolysis is reduced at low pH and therefore certain parasympathetic effects may be enhanced during hypercapnia.

It is generally believed that reduction of P_{CO_2} after a period of hypercapnia results in a further elevation of the plasma catecholamine level (*see* review by Tenney and Lamb, 1965). However, it is difficult to find experimental evidence for this statement and there is, in fact, quite a lot of evidence to suggest the contrary. Millar (1960) showed a rapid fall of both adrenaline and noradrenaline within minutes of reduction of a gross elevation of P_{CO_2} (*Figure 106*).

The principal evidence for post-hypercapnic elevation of catecholamine level seems to be the study of Tenney (1956), in which an auto-bio-assay was carried out using the denervated nictitating membrane of cats which were subjected to change of P_{CO_2}. The plasma level of catecholamine was derived from the degree of contraction of the membrane with reference to a single calibrating injection of a known amount of adrenaline: the accuracy of the procedure could thus be influenced by change in the sensitivity of the nictitating membrane which is known to be reduced by the direct action of carbon dioxide, as demonstrated in the same publication. It is therefore possible that the further contraction of the nictitating membrane during fall of P_{CO_2} was due, not to a further increase in catecholamine level, but to the fall of P_{CO_2} raising the sensitivity to the circulating catecholamines, which fell more slowly than the P_{CO_2}.

Some support for the theory of post-hypercapnic elevation of plasma catecholamine levels has been derived from the cardiovascular response to reduction of an elevated P_{CO_2}. This is considered below.

Effects upon the Respiratory System

Chapter 2 discusses in some detail the role of carbon dioxide in the control of ventilation. It is sufficient here to note that the P_{CO_2}/ventilation response curve is generally displaced to the right and its slope reduced by the action of anaesthetic agents and other depressant drugs (Severinghaus and Larson, 1965). In profound anaesthesia the response curve may be flat, or even sloping downwards, and carbon dioxide then acts as a respiratory depressant. In general the maximal stimulant effect is attained within the P_{CO_2} range 100–150 mm Hg (Graham, Hill and Nunn, 1960). At higher levels of P_{CO_2} the stimulation is reduced, while at very high levels respiration is depressed and later ceases altogether. Graham, Hill and Nunn (1960) made the curious observation that dogs maintained at a very high tension of carbon dioxide (above 350 mm Hg) eventually started breathing again. The breathing was of a gasping character but was sufficient to maintain life for at least an hour without any

artificial assistance to ventilation. The breathing in this state (termed 'supercarbia') is uninfluenced by changes in P_{CO_2} or by vagal section.

Reduction of P_{CO_2} does not always lead to apnoea in the naïve subject, who is unaware of the classical work. However, during anaesthesia, reduction of P_{CO_2} below the threshold value usually does result in apnoea (Fink, 1961). Therefore, to restore spontaneous respiration at the end of an operation in which artificial hyperventilation has been employed, it is necessary either to raise the P_{CO_2} above the apnoeic threshold value or to awaken the patient (Ivanov and Nunn, 1969). References to the respiratory effects of carbon dioxide are given in Chapter 2.

Effects upon Oxygenation of the Blood

Quite apart from the effect of carbon dioxide upon ventilation, it exerts two other important effects which influence the oxygenation of the blood. Firstly, if the concentration of nitrogen (or other 'inert' gas) remains constant, the concentration of carbon dioxide in the alveolar gas can only increase at the expense of oxygen which must be displaced. Secondly, an increase in P_{CO_2} causes a displacement of the oxygen dissociation curve to the right (page 354); in a patient with gross hypercapnia, Prys-Roberts, Smith and Nunn (1967) reported visibly desaturated arterial blood although the P_{O_2} was 104 mm Hg. Unfortunately, the saturation was not measured but subsequent studies suggested that a value of the order of 90 per cent would be expected.

Effects upon the Circulatory System

The effects of carbon dioxide upon the circulation are extraordinarily complicated due to the alternative modes of action upon the different components of the system (*Figure 105*). Many actions are in opposition to each other and, under different circumstances, the over-all effect of carbon dioxide upon certain circulatory functions can be entirely reversed. Special reference should be made to the review by Price (1960).

Myocardial contractility and heart rate are diminished by elevated P_{CO_2} in the isolated preparation (Jerusalem and Starling, 1910). However, in the intact subject, the depressant direct action of carbon dioxide is overshadowed by the stimulant effect mediated through the sympathetic system, and both cardiac output and heart rate are increased in linear relation to the P_{CO_2}, within the range of P_{CO_2} 20–80 mm Hg. This has been clearly shown in the anaesthetized patient, and is independent of changes in intrathoracic pressure (Prys-Roberts and his colleagues, 1967a). The rise in cardiac output is accompanied by a marked rise in cardiac filling pressure, suggesting that contraction of capacitance vessels occurs to a greater extent than cardiac output increases. It thus seems likely that the increase in cardiac output is driven mainly by increased filling pressure.

It is to be expected that an elevated P_{CO_2} will reduce the cardiac output when the sympathetic outflow is blocked either by ganglioplegic agents or by spinal block. Elevation of P_{CO_2} fails to increase cardiac output in the upright position and this is likely to be due to pooling of blood in the lower limbs (Asmussen, 1943).

At very high levels of P_{CO_2} it is likely that cardiac output falls. Study of a

single dog by Severinghaus, Mitchell and Nunn (unpublished) showed a progressive decline of cardiac output with increasing P_{CO_2} in supercarbia (*Table 33*).

Table 33

Circulatory changes at very high P_{CO_2}
(Observed in a single dog by Severinghaus, Mitchell and Nunn, unpublished)

Time	*Arterial blood*			*Cardiac output (l./min.)*	*Blood pressure syst./ diast. (mm Hg)*
	Pa_{CO_2} *(mm Hg)*	*pH*	P_{O_2} *(mm Hg)*		
11.51	51	7·32	294	3·14	165/115
12.35	393	6·50	204	2·34	165/110
13.00	468	6·42	152	0·98	90/60
13.15	540	6·41	120	0·64	85/45
14.33	48	7·28	293	1·29	115/95

The dog breathed spontaneously in the state of 'supercarbia' above a P_{CO_2} of 337 mm Hg which was attained at 12.25.
P_{CO_2} was gradually reduced from 13.16 until 14.33.
Cyclopropane anaesthesia was used when the P_{CO_2} was low.
Anaesthesia was terminated at 14.40 and the dog regained consciousness at 14.55. Recovery was uneventful.

Arrhythmias have been reported in unanaesthetized man during acute hypercapnia but have seldom been of serious import (cases reviewed by Nunn, 1962d, table I). The position is, however, more dangerous under anaesthesia with cyclopropane (Lurie and his colleagues, 1958), halothane (Black and his colleagues, 1959), and possibly with other agents which have not yet been adequately studied in man. With these anaesthetic agents it appears that arrythmias will always occur above a 'P_{CO_2} arrhythmic threshold' which is reported to be surprisingly constant for a particular patient under particular conditions. The mean value is 74 mm Hg for cyclopropane and 92 mm Hg for halothane. Multifocal ventricular extrasystoles have been reported and the danger of ventricular fibrillation cannot be discounted. This has not deterred the anaesthetists studied by Birt and Cole (1965). In their series, values for arterial P_{CO_2} rose as high as 160 mm Hg, and 17 of the 22 patients developed arrythmias, 4 showing multifocal ventricular extrasystoles. Nevertheless, no one seems to have condemned the technique which is apparently widely used. However, there remains the possibility that cases of ventricular fibrillation have occurred but not been reported. Most investigators have found that arrhythmias (short of ventricular fibrillation) have little effect upon the blood pressure and appear to do the patient no obvious harm.

It should be noted that Graham, Hill and Nunn (1960) raised the P_{CO_2} of a series of dogs to 550 mm Hg and found no arrhythmias regardless of whether the dogs were receiving cyclopropane or halothane. This is a good example of the importance of species difference and shows the error which may arise from extrapolation of evidence from animal experiments to man.

Arrhythmias caused by elevated P_{CO_2} in anaesthetized patients occur at catecholamine levels which are above normal, but which are not *per se* high enough to cause arrhythmias. It therefore seems that arrhythmias are caused

by increased sensitivity of the heart to carbon dioxide in addition to or instead of elevation of plasma catecholamine levels (Price and his colleagues, 1958).

There is widespread acceptance of the work of Brown and Miller (1952) that ventricular fibrillation may follow the sudden reduction of a high P_{CO_2} in dogs. Graham, Hill and Nunn (1960) and Millar (1960) were quite unable to confirm these observations after precipitous falls of P_{CO_2} caused by ventilation with oxygen. They suggest that in the study of Brown and Miller, the dogs may have suffered hypoxia caused by ventilation with air in the presence of a high P_{CO_2}. Extensive enquiries by the author over a period of ten years have only revealed one case of ventricular fibrillation which occurred in an anaesthetized patient during rapid reduction of an elevated P_{CO_2}. The subject has been further reviewed by Prys-Roberts, Smith and Nunn (1967). It is difficult, if not impossible to disprove a dangerous causal relationship of this type and the reader must draw his own conclusions.

Blood pressure is generally raised as P_{CO_2} increases in both conscious and anaesthetized patients (Price and his colleagues, 1960). However, the response is variable and certainly cannot be relied upon as an infallible diagnostic sign of hypercapnia. At very high levels of P_{CO_2} the blood pressure declines (*Table 33*) and appears to be the cause of death if the condition of supercarbia persists for much more than an hour (Graham, Hill and Nunn, 1960). Hypotension accompanies an elevation of P_{CO_2} if there is blockade of the sympathetic system by ganglioplegic drugs or spinal blockade (Payne, 1958b).

There is general agreement that hypotension follows a sudden fall of an elevated P_{CO_2}. Together with the fall of plasma catecholamine level, this is believed to account for the hypotension which follows cyclopropane anaesthesia (which is frequently accompanied by hypercapnia if respiration is spontaneous). Hypercapnia causes a rise in pulmonary arterial pressure and pulmonary vascular resistance (Barer, Howard and McCurrie, 1967).

Regional blood flow appears to be influenced by the P_{CO_2} in different ways for different organs (Tenney and Lamb, 1965). Brain (Kety and Schmidt, 1948; Lassen, 1959), heart and skin blood flow increases with rising P_{CO_2}, while skeletal muscle blood flow is reduced by hypercapnia although this effect is much diminished by general anaesthesia (McArdle and Roddie, 1958).

Effect upon the Kidney

Renal blood flow and glomerular filtration rate are little influenced by minor changes of P_{CO_2}. However, at high levels of P_{CO_2} there is constriction of the glomerular afferent arterioles leading to anuria. This effect is abolished in the denervated kidney (Irwin, Draper and Whitehead, 1957).

Chronic hypercapnia results in increased resorption of bicarbonate by the kidneys, further raising the plasma bicarbonate level, and constituting a secondary or compensatory 'metabolic alkalosis'. Chronic hypocapnia decreases renal bicarbonate resorption, resulting in a further fall of plasma bicarbonate and producing a secondary or compensatory 'metabolic acidosis'. In each case the arterial pH returns towards the normal value but the bicarbonate ion concentration departs even further from normality.

Although acute changes of P_{CO_2} do not produce a true metabolic acid–base

change, conventional techniques of acid–base measurement indicate an apparent base deficit of about 2 mEq./l. when the P_{CO_2} of a normal patient is acutely raised from 40 to 80 mm Hg. Similarly, a base excess of about 2 mEq./l. appears when the P_{CO_2} is acutely lowered to 20 mm Hg. Both abnormalities disappear immediately when the P_{CO_2} is restored to normal. These changes arise from the fact that the *in vivo* CO_2 equilibration curve of a patient is flatter than the *in vitro* curve of sampled blood (*Figures 97 and 98*). This interesting artefact is too small to be of practical consequence unless the P_{CO_2} is outside the limits 20–80 mm Hg. Such cases are comparatively rare and correction can be applied if this is required (Prys-Roberts, Kelman and Nunn, 1966).

Effect on Blood Electrolyte Levels

Hypercapnia is accompanied by a leakage of potassium from the cells into the plasma (Clowes, Hopkins and Simeone, 1955). Hepatectomy has demonstrated that most of the potassium comes from the liver, probably in association with glucose which is mobilized in response to the rise in plasma catecholamine levels (Fenn and Asano, 1956). Since the plasma potassium level takes an appreciable time to return to normal, repeated bouts of hypercapnia at short intervals result in a stepwise rise in plasma potassium.

A reduction in the ionized fraction of the total calcium has, in the past, been thought to be the cause of the tetany which accompanies severe hypocapnia. However, the changes which occur are too small to account for tetany, which only occurs in parathyroid disease when there has been a fairly gross reduction of ionized calcium (Tenney and Lamb, 1965). Hyperexcitability affects all nerves and spontaneous activity ultimately occurs. The spasms probably result from activity in proprioceptive fibres causing reflex muscle contraction.

Effect upon Drug Action

Changes in P_{CO_2} may affect drug action as a result of a great number of different mechanisms. Firstly, the distribution of the drug may be influenced by changes in perfusion of organs. Secondly, the ionization of drugs may be altered by the change in blood pH. Thirdly, the solubility of the drug in body fluids and the protein binding may be influenced. Payne (1958a) and Baraka (1964) have investigated the effects of P_{CO_2} on the action of relaxants. Wyke (1957) has reviewed the effect of changes in pH on the action of barbiturates.

Therapeutic Uses of Carbon Dioxide

The varied and powerful effects of increased P_{CO_2} suggest that the inhalation of carbon dioxide gas mixtures would have a clear place in therapy. In fact, this is not so and some believe that carbon dioxide has no place in the fields of anaesthesia, resuscitation and intensive therapy. Fear of accidental administration of high concentrations of carbon dioxide has caused many to omit cylinders of the gas from anaesthetic and other inhalational apparatus.

The main therapeutic indication for the administration of carbon dioxide is to stimulate respiration. This is useful to expedite the uptake and elimination of inhalational anaesthetic agents, and reference has already been made to the administration of carbon dioxide to raise the arterial P_{CO_2} above the apnoeic

threshold in order to encourage the resumption of spontaneous breathing after passive hyperventilation of unconscious patients (page 317). Although carbon dioxide may be used to stimulate breathing in these situations, its use in the treatment of ventilatory failure is very limited. Many patients in respiratory failure have a diminished or absent response to exogenous carbon dioxide and in such patients carbon dioxide will be ineffective in raising the minute volume, and may actually cause a decrease, possibly leading to carbon dioxide narcosis. Carbon dioxide is also likely to be ineffective or harmful if ventilation is limited by malfunction of the efferent motor pathway, the respiratory muscles or by raised airway resistance. Such patients will already have a raised P_{CO_2} and show a flattened P_{CO_2}/ventilation response curve which is very similar to that produced by depression of the central chemoreceptors (*Figure 9*). Scarcely any of the causes of ventilatory failure listed in *Figure 52* can be expected to be alleviated by the administration of carbon dioxide. Inhalation of 5 per cent carbon dioxide may be useful in the treatment of hiccup.

Carbon monoxide poisoning remains one of the clearest indications for the administration of carbon dioxide gas mixtures. Not only will stimulation of respiration hasten the elimination of carbon monoxide, but the venous P_{O_2} will be substantially increased by the shift of the dissociation curve of the remaining normal haemoglobin (*Figure 119*). Elevation of venous (and tissue) P_{O_2} by displacement of the dissociation curve of normal haemoglobin seems to be a rational therapeutic use for carbon dioxide but its clinical role for this purpose has not been fully explored. There is also clear evidence that elevation of P_{CO_2} would improve regional perfusion of certain organs, particularly the brain. However, there has been surprisingly little interest in this potentially important therapeutic use for carbon dioxide.

If carbon dioxide is used clinically, careful attention must be paid to dosimetry. Thus, maximal effectiveness in its use as a respiratory stimulant requires control of the concentration in the inspired gas. Therapy based on an elevation of arterial P_{CO_2} would clearly be ineffective if the patient's ventilatory response prevented any appreciable rise in P_{CO_2}. Ivanov and Nunn (1969) have examined quantitative aspects of some of the simpler methods of administration of exogenous and endogenous carbon dioxide.

CLINICAL RECOGNITION OF HYPERCAPNIA

The History

Severe hypercapnia is not common in anaesthetic practice and most cases fall into the following categories.

(1) Patients with obstructive airway disease. An acute-on-chronic rise of P_{CO_2} may result from pulmonary infection, or follow surgical operations, particularly thoracotomy.

(2) Retention of endogenous carbon dioxide due to faulty breathing apparatus such as leaking valves or exhausted soda-lime.

(3) Accidental administration of exogenous carbon dioxide.

Very rarely, acute hypoventilation arises from central causes, and may be overlooked by the nursing staff. Severe hypercapnia due to hypoventilation

cannot occur without concomitant hypoxia if a patient is breathing air. Therefore, gross hypercapnia (P_{CO_2} more than 90 mm Hg) can only occur when a patient is receiving oxygen (McNicol and Campbell, 1965).

Clinical Appearance

There are no infallible diagnostic signs of hypercapnia. The patient's skin is usually flushed and the pulse is generally full and bounding, with occasional extra systoles and possibly other forms of arrhythmia. The blood pressure is often raised but this is not always the case. However, hypercapnia should always be considered when there is an unexplained hypertension during anaesthesia. Hyperventilation will obviously be absent if hypercapnia is caused by hypoventilation. However, it may be noticed during accidental elevation of the concentration of carbon dioxide in the inspired gas. Muscle twitchings and a characteristic flap of the hands are seen when the P_{CO_2} approaches the level at which coma occurs. Convulsions occur at higher levels. It must be stressed that coma and depressed breathing may be the only signs of severe hypercapnia and the diagnosis may not be at all obvious. Respiratory depression occurs at high levels of P_{CO_2} and the mortality of the condition is very high unless the attendants are aware of the importance of prompt and vigorous treatment.

Tests for Hypercapnia

In all cases of undiagnosed coma, the arterial P_{CO_2} should be measured. If this is not practicable, the mixed venous P_{CO_2} may be measured by the rebreathing technique (*see* later). If it is found that the minute volume is substantially below the normal value (particularly if there is likely to be an increase in physiological dead space), hypercapnia is inevitable unless there is a reduction in metabolic rate (e.g. in hypothermia). A useful therapeutic test for hypercapnia is to ventilate the patient vigorously with a CO_2-free gas. In true cases of hypercapnia, there is a dramatic return of consciousness (Scurr, 1954). This may result in hypotension.

OUTLINE OF METHODS OF MEASUREMENT OF CARBON DIOXIDE

(review Severinghaus, 1960)

Fractional Concentration in Gas Mixtures

The reference method is chemical absorption. In medical circles the most accurate method usually employed is Lloyd's modification of the Haldane apparatus (Lloyd, 1958). A simpler version of Haldane's apparatus which is sufficiently accurate for clinical work has been described by Campbell (1960). The popularity of the Scholander apparatus has declined in Great Britain in recent years, but it may still be required for the analysis of very small samples (Scholander, 1947). All these methods are markedly influenced by the presence of nitrous oxide in gas samples and modifications of technique are required (Nunn, 1958b; Glossop, 1963).

Infra-red absorption can be used to compare the concentration of carbon dioxide in an unknown sample with the concentration in a known sample (DuBois and his colleagues, 1952). Unfortunately, the presence of other gases

has an appreciable effect upon the response of the instrument to a particular concentration of carbon dioxide (Cooper, 1957). This effect, known as collision broadening, is best overcome by calibrating with a known concentration of carbon dioxide in a diluent gas mixture which is similar to the gas sample for analysis. The particular virtue of infra-red analysers is that they can be made to respond within less than a quarter of a second and will thus show the changes in carbon dioxide concentration during a single respiratory cycle. *Figure 99* shows a typical capnogram from which the following information may be derived.

(1) The end-expiratory carbon dioxide concentration.
(2) The inspiratory carbon dioxide concentration.
(3) In conjunction with a record of the patient's tidal exchange, it is possible to see how much gas is exhaled before the carbon dioxide concentration at the lips rises to the alveolar plateau. This is the anatomical dead space.
(4) The slope of the alveolar P_{CO_2} plateau indicates the rate of rise of the alveolar P_{CO_2} during the course of expiration. This is increased by maldistribution of inspired gas or by an increase in the mixed venous/arterial P_{CO_2} difference.

Rapid analysis of gas mixtures for carbon dioxide can also be carried out with a sonic analyser or a mass spectrometer (Hill, 1965). Gas chromatography is a feasible method of analysing small samples of gas.

Blood Carbon Dioxide Concentration

For many years the concentration of carbon dioxide in blood or plasma has been measured by vacuum extraction followed by chemical absorption in the manometric apparatus of Van Slyke and Neill (1924). The micro-apparatus of Natelson (1951) is considerably easier to handle. A convenient alternative technique is dissociation of bicarbonate by adding a large volume of acid to the blood followed by measurement of P_{CO_2} of the blood-plus-acid (Linden, Ledsome and Norman, 1965). By suitable calibration with solutions of known concentrations of sodium bicarbonate, the method is capable of satisfactory accuracy. P_{CO_2} is measured by means of the P_{CO_2}-sensitive electrode (*see* below).

Blood P_{CO_2}

Four methods of measurement are available.

(1) A tiny bubble of gas may be equilibrated with blood at the patient's body temperature and then analysed quantitatively for carbon dioxide (Riley, Campbell and Shephard, 1957). P_{CO_2} is derived from the carbon dioxide concentration of the bubble and is close to that of the blood. The technique is difficult, and unsuitable for use in the presence of nitrous oxide.
(2) For many years P_{CO_2} was derived from the form of the Henderson–Hasselbalch equation given earlier in this Chapter (equation 10, page 291). This method is no longer popular since measurements of pH and CO_2 content are required and there is always uncertainty of the value which should be taken for pK'. Nevertheless, tolerable accuracy is attainable (Thornton and Nunn, 1960).
(3) P_{CO_2} of blood may be conveniently measured by interpolating the actual

pH in a plot of P_{CO_2} against pH derived from aliquots of the same blood sample. The plot is linear (*Figure 98*) and the whole operation has been greatly simplified by the use of the elegant micro-apparatus described by Siggaard-Andersen and his colleagues (1960). A small error is introduced if the sample is desaturated. Minor refinements of technique and the level of accuracy have been described by Kelman, Coleman and Nunn (1966). Accuracy is uninfluenced by the presence of anaesthetic gases.

(4) P_{CO_2} of any gas or liquid may be determined directly by use of the P_{CO_2}-sensitive electrode (Severinghaus and Bradley, 1958; Severinghaus, 1965). The P_{CO_2} of a film of bicarbonate solution is allowed to come into equilibrium with the P_{CO_2} of a sample across a membrane permeable to carbon dioxide. The pH of the bicarbonate solution is constantly monitored with a glass electrode and the log of the P_{CO_2} is inversely proportional to the recorded pH. The pH scale may therefore be engraved to read P_{CO_2} directly. The accuracy obtainable is comparable to that of other techniques and is uninfluenced by the presence of anaesthetic gases.

Indirect Measurement of Arterial P_{CO_2}

Measurement of end-expiratory P_{CO_2} is of limited value due to the variable arterial/end-expiratory P_{CO_2} gradient caused by anaesthesia or lung disease (page 189). However, the method is useful for recording changes. If a rapid carbon dioxide analyser is not available, end-expiratory samples may be collected (Rahn and his colleagues, 1946a; Nunn and Pincock, 1957).

Measurement of mixed venous P_{CO_2} is of greater value than measurement of end-expiratory P_{CO_2} since the mixed venous/arterial P_{CO_2} difference is fairly constant and seldom outside the range 4–9 mm Hg in the resting patient. The mixed venous P_{CO_2} may be estimated indirectly with very simple apparatus, using the rebreathing technique of Campbell and Howell (1960). Its modified use in children has been described by Sykes (1960). The collection of the gas sample which has been equilibrated with mixed venous blood is perfectly feasible in the unconscious patient and the technique should be available in every hospital, especially those where there are no facilities for measurement of P_{CO_2} of blood samples.

Measurement of P_{CO_2} *of venous blood draining from skin* has been advanced as an alternative, to avoid arterial puncture. The results are quite acceptable provided that skin blood flow is good (Brookes and Wynn, 1959). However, it is surprisingly difficult to collect a good sample of blood anaerobically from the veins on the back of the hand. As a rough rule, if the sample is very difficult to collect, the circulation is unlikely to be good enough for the arterial and venous P_{CO_2} to be acceptably close. Cooper and Smith (1961) found that agreement between arterial and cutaneous venous P_{CO_2} was good in the majority of a series of anaesthetized patients, but considerable discrepancies appeared in a minority of patients, thought to have circulatory disturbances. Blood from veins draining muscles (e.g. the median cubital vein) has a P_{CO_2} much higher than the arterial level.

Measurement of capillary P_{CO_2} on blood obtained from a skin prick suffers from the same uncertainties which surround cutaneous venous P_{CO_2}. However, the

technique is clearly useful in neonates. It is perhaps important to remember that an error of 5 mm Hg is seldom of much consequence in the management of a patient.

Handling of Blood Samples

It is important that samples be preserved from contact with air or oil, to which they may lose carbon dioxide. Analysis should be undertaken quickly as the P_{CO_2} of blood *in vitro* rises by about 0·1 mm Hg/min. at 37°C. If analysis is not carried out at the patient's body temperature, a correction factor should be applied, as the P_{CO_2} of an anaerobic blood sample falls by about 4 per cent for each degree centigrade cooling. Nomograms for correction for both these errors have been presented by Kelman and Nunn (1966b).

CHAPTER 12

OXYGEN

THE ROLE OF OXYGEN IN THE CELL

Most of the energy deployed in the mammalian body is derived from the oxidation of food-fuels, of which the most important is glucose:

$$C_6H_{12}O_6 + 6\ O_2 = 6\ CO_2 + 6\ H_2O + \text{energy}$$

The equation accurately describes the combustion of glucose in a test tube, but is only a crude, over-all representation of the oxidation of glucose in the body. The direct reaction does not produce energy in a form in which it can be utilized for the various activities of the living body. The biological oxidation proceeds by a large number of stages, with phased production of energy. This energy is not immediately released but is stored by means of the reaction of adenosine diphosphate (ADP) with inorganic phosphate ion to form adenosine triphosphate (ATP):

$$\text{ADP} + \text{inorganic phosphate ion} + \text{energy} \rightleftharpoons \text{ATP}$$

The third phosphate radical in ATP is held by a high energy bond which releases its energy when ATP is split back into ADP and inorganic phosphate ion. ADP is thus recycled indefinitely with ATP acting as a short-term store of energy available in a form which may be used directly for work such as muscle contraction, ion pumping, protein synthesis and secretion. ATP is commonly transported short distances between the sites of synthesis and utilization. For example, in voluntary muscles, it is formed in the mitochondria and used in the myofibrils.

There is no large store of ATP in the body and it must be synthesized continuously as it is being used. The ATP/ADP ratio is an indication of the level of energy which is currently carried in the ADP/ATP system and the ratio is normally related to the state of oxidation of the cell. The ADP/ATP system is not the only short-term energy store in the body but it is the most important.

The uses of ATP in the body lie outside the scope of this book, but its production from ADP is highly relevant to this chapter since the most efficient methods of production of ATP require the consumption of oxygen. However, the anaerobic methods are of great biological importance and were universal in the Pre-Cambrian era before the atmospheric Po_2 was sufficiently high for aerobic pathways of metabolism. Anaerobic metabolism is still the rule in certain organisms and in the mammalian body when energy requirements outstrip oxygen supply as, for example, during severe exercise.

The aerobic pathway permits the release of far greater quantities of energy

from the same amount of substrate and is therefore used whenever possible. In simplified form, the contrasting pathways can be shown as follows.

ANAEROBIC PATHWAY	AEROBIC PATHWAY
Glucose	Glucose
↓	↓
Pyruvic acid	Pyruvic acid
↓	↓
Lactic acid + 2 mol. of ATP	$CO_2 + H_2O$ + 38 mol. of ATP
(16 Calories of available energy)	(304 Calories of available energy)

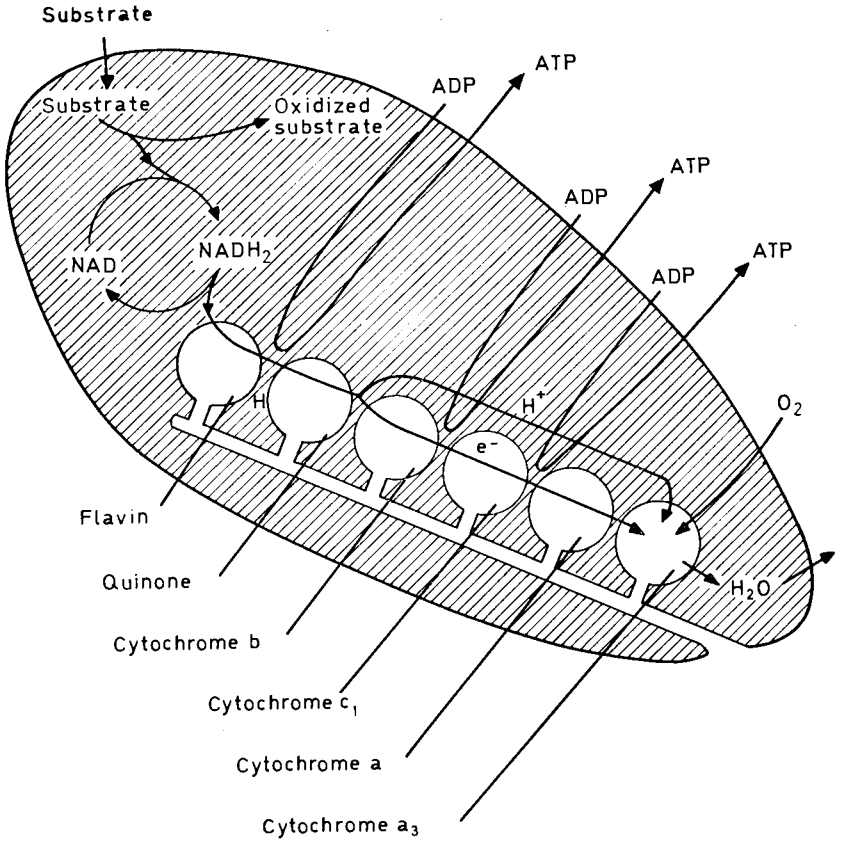


Figure 107. Diagrammatic representation of oxidation within the mitochondrion. The substrate diffuses from the cytoplasm into the mitochondrion where hydrogen is removed under the influence of the appropriate dehydrogenase enzyme. The hydrogen is carried by intramitochondrial NAD to the first of the chain of hydrogen carriers which are attached to the cristae of the mitochondria. When the hydrogen reaches the cytochromes, ionization occurs: the proton passes into the lumen of the mitochondrion while the electron is passed along the cytochromes where it converts ferrous iron to the ferric form. The final stage is at cytochrome a_3 where the proton and the electron combine with oxygen to form water. Three molecules of ADP are converted to ATP at the stages shown in the diagram. ADP and ATP can cross the mitochondrial membrane freely while there are separate pools of intra- and extramitochondrial NAD which cannot interchange

Burning glucose in a test tube liberates 673 Calories/mol. Thus, under conditions of oxidative metabolism, 45 per cent of the total energy is made available for biological work and this compares favourably with most man-made machines.

Localization of Oxygen Consumption in the Cell

Most of the oxygen consumption occurs in the mitochondria, where it combines

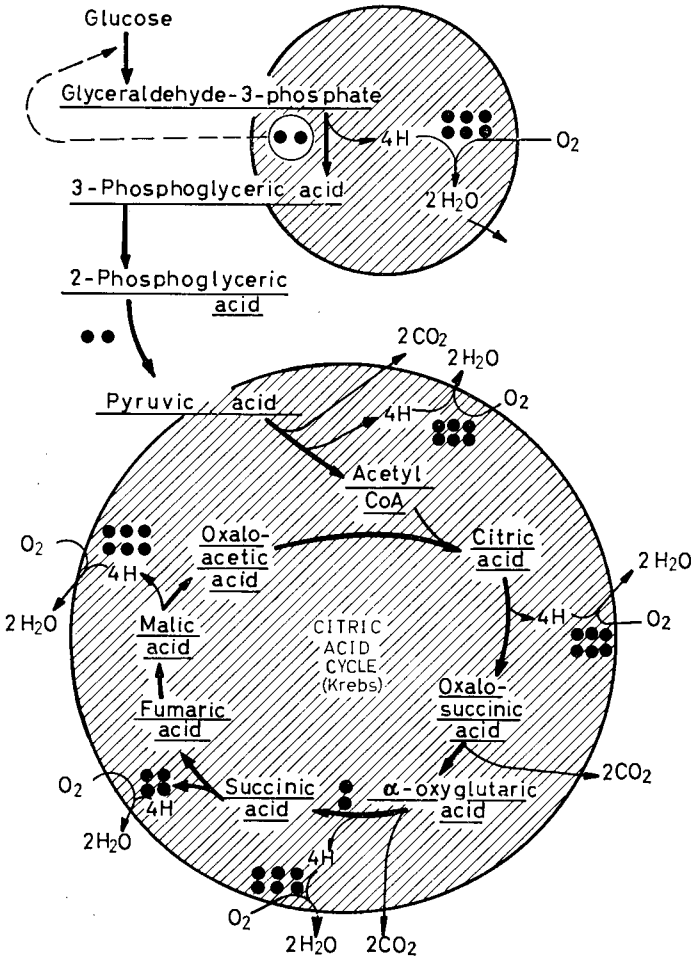


Figure 108. Successive stages in the principal oxidative metabolic pathway of glucose by the citric acid cycle. Many stages have been omitted for clarity. The two shaded circles represent mitochondria and indicate the reactions which can only take place within them. The names of substances which cross the membranes show those which are capable of diffusion into and out of the mitochondria. Underlining indicates that two molecules are formed from one of glucose. Black dots show where ATP is formed (the first two to be produced are offset by two which are required for the conversion of glucose to glyceraldehyde-3-phosphate). Note the dissociation between O_2 consumption and CO_2 production. The conversion of glyceraldehyde-3-phosphate to 3-phosphoglyceric acid can also take place in the cytoplasm as shown in Figure 109 but, in that case, it is not possible for the liberated hydrogen to be oxidized to water, since the $NADH_2$ cannot diffuse into the mitochondria

with hydrogen to form water. The hydrogen has previously been removed from a variety of substrates by nicotinamide adenine dinucleotide (NAD), and then passed along a chain of hydrogen carriers to combine with oxygen at cytochrome a_3 which is the end of the chain. *Figure 107* shows the transport of hydrogen along the chain, which consists of structural entities just visible under the electron microscope and arranged in a row along the cristae of the mitochondria. Three molecules of ATP are formed at various stages of the chain during the transfer of two atoms of hydrogen. The process, which is known as oxidative phosphorylation, is not associated directly with the production of carbon dioxide which is formed elsewhere in the metabolic pathways. Oxidative phosphorylation can only take place when the Po_2 within the mitochondrion is above a critical level, thought to be only a few millimetres of mercury (Chance, Schoener and Schindler, 1964). When the Po_2 falls below this level, metabolism reverts to anaerobic pathways.

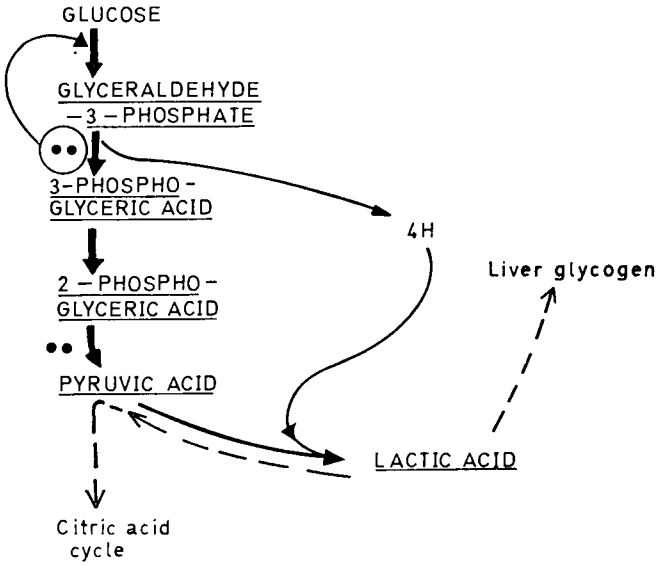


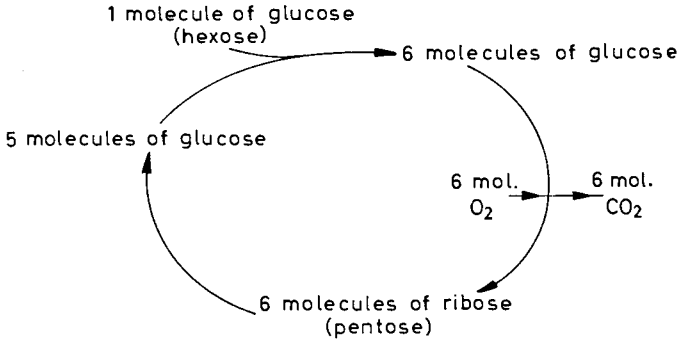
Figure 109. The Embden–Meyerhof pathway for anaerobic metabolism of glucose. Underlining indicates that two molecules are formed from one molecule of glucose. ATP production is shown by black dots, those produced in the second reaction being set against the two which are required to energize the first reaction. There is thus a net production of only two molecules of ATP per molecule of glucose. The hydrogen released at the second reaction is carried by extramitochondrial NAD and used in the reduction of pyruvic acid to lactic acid. No mitochondrial enzymes are used and no oxygen is required. The pathway has been greatly simplified in this diagram and many intermediate compounds have been omitted for clarity

The role of oxidative phosphorylation in the aerobic degradation of glucose is illustrated in *Figure 108*. One molecule of glucose is converted into two molecules of glyceraldehyde-3-phosphate in the cytoplasm of the cell. The latter substance then diffuses into the mitochondria where it is converted into 3-phosphoglyceric acid when hydrogen is removed by NAD and oxidized after transport along the chain shown in *Figure 107*. The next reactions can take

place in the cytoplasm down to the point where pyruvic acid is formed. The oxidation of pyruvic acid, however, can only take place in the mitochondria where hydrogen is removed and oxidized at successive stages of the familiar citric acid cycle. It will be seen that the production of carbon dioxide also occurs within the mitochondria but that it is not directly associated with oxygen consumption. The scheme shown in *Figure 108* also accounts for the consumption of oxygen in the metabolism of fat. After hydrolysis, glycerol is converted into pyruvic acid while the fatty acids shed a series of 2-carbon molecules in the form of acetyl CoA. Pyruvic acid and acetyl CoA enter the citric acid cycle and are then degraded in the same manner as though they were derived from glucose. Amino acids are dealt with in similar manner after deamination.

Figure 109 illustrates the anaerobic metabolism of glucose, a pathway which is followed either when there is a shortage of oxygen or, in the case of erythrocytes, when there is an absence of the respiratory enzymes located in the mitochondria. The conversion of glyceraldehyde-3-phosphate to 3-phosphoglyceric acid can take place in the plasma with hydrogen released as in the aerobic pathway but, in this case, to extramitochondrial NAD. This hydrogen cannot be oxidized but it is taken up lower down the pathway by the reduction of pyruvic acid to lactic acid. This series of changes is associated with the formation of only two molecules of ATP in contrast to the 38 produced in the course of aerobic metabolism. However, considerable chemical energy remains in the lactic acid which, in the presence of oxygen, can be reconverted to pyruvic acid and then oxidized in the citric acid cycle, producing the balance of 36 molecules of ATP. Alternatively, lactic acid may be converted into liver glycogen to await more favourable conditions for oxidation.

Some 10–20 per cent of total oxygen consumption may occur in the cytoplasm by way of the Warburg–Dickens pathway which is independent of the mitochondrial enzymes. In this process one of the carbon atoms of a molecule of glucose is oxidized to carbon dioxide leaving a 5-carbon residue which is the pentose ribose. The respiratory quotient of the change is unity. Subsequently the ribose is reconverted to glucose by the combination of 6 molecules of the pentose to form 5 molecules of the hexose. This pathway, which is also known as the hexose (or pentose) phosphate shunt, is almost as efficient as the intramitochondrial oxidation and produces 36 molecules of ATP from the oxidation of 1 molecule of glucose.



The hexose phosphate shunt

These descriptions of metabolic pathways have been simplified as far as is compatible with explanation of the role of oxygen in the cell. Greater detail is to be found in many standard texts, but perhaps the most readable are those of Loewy and Siekevitz (1963) and Rose (1966), both of which discuss the relation of structure to function. Carbohydrate metabolism during anaesthesia has been reviewed by Greene (1963).

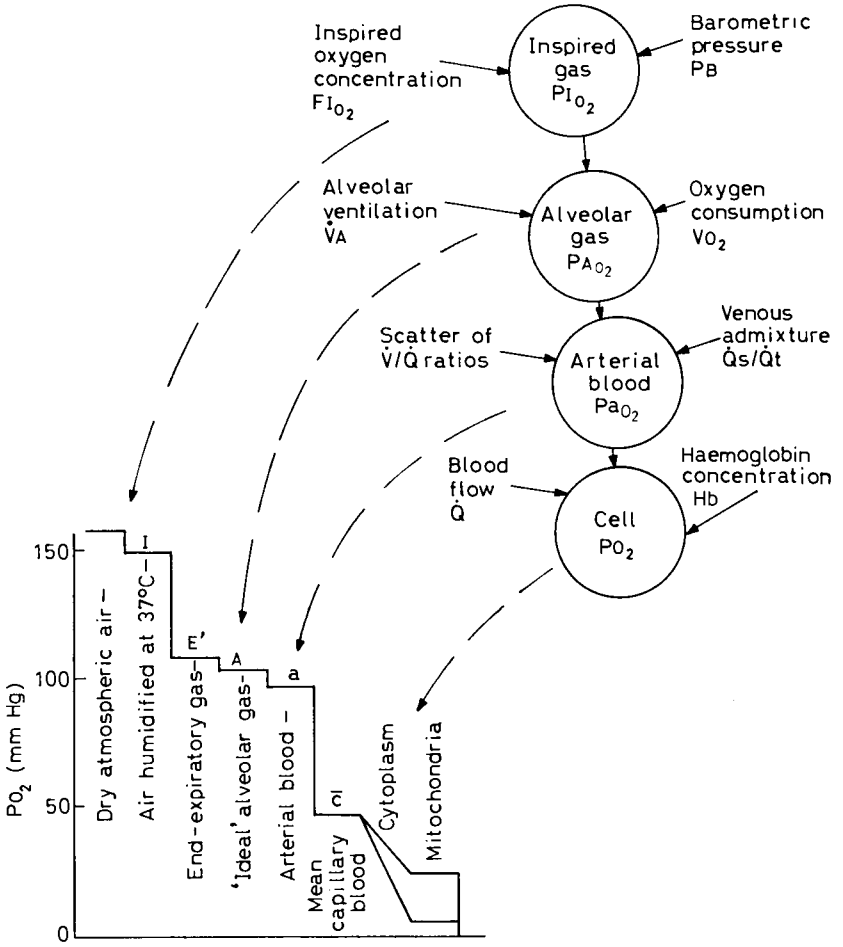


Figure 110. On the left is shown the oxygen cascade with P_{O_2} *falling from the level in the ambient air down to the level in mitochondria, which is the site of utilization. On the right is shown a summary of the factors influencing oxygenation at different levels in the cascade*

Significance of Oxygen

The production of large quantities of ATP from glucose requires oxygen. Anaerobic metabolism produces much smaller quantities of ATP which may permit satisfactory function of certain organs, notably voluntary muscle. The central nervous system, however, is quite unable to function on anaerobic

metabolism since this cannot provide the very large quantity of ATP which is needed for maintenance of the ion concentration gradients that are essential for function and survival of neurones. Anaerobic metabolism may occur in the central nervous system, but alone it can maintain neither function nor structural integrity (*see also* page 364).

The remainder of this chapter (and, to a certain extent, the whole of this book) is concerned with the problem of maintaining the cellular oxygen tension at a level which permits the production of ATP by aerobic metabolism. The actual tension required in the mitochondria is in excess of about 1·5 mm Hg (the Pasteur point). The Po_2 of dry atmospheric air is about 160 mm Hg but this falls progressively during the transport of oxygen to the mitochondria, the whole process being conveniently described as the oxygen cascade (*Figure 110*). Factors influencing the height of the various steps of the cascade are also shown in *Figure 110*.

DILUTION OF INSPIRED OXYGEN BY WATER VAPOUR

Analysis with the Haldane apparatus indicates the true fractional concentration of oxygen in a dry gas mixture. If the gas sample is humidified, the added water vapour is ignored and the indicated fractional concentration of oxygen is still that of the dry part of the gas mixture. Thus the normal value for atmospheric oxygen (20·93 per cent) indicates the concentration of oxygen in the dry gas phase regardless of whether the gas is humidified or not. However, humidification such as occurs when dry air is inhaled through the upper respiratory tract, dilutes air with water vapour and so reduces the Po_2. The process is similar to the reduction in Po_2 which occurs when ether vapour is added to air (Scott, 1847).

When dry gas kept at normal barometric pressure is humidified with water vaporized at 37°C, 100 volumes of the dry gas take up about 6 volumes of water vapour, giving a total gas volume of 106 units but containing the same number of molecules of oxygen. The Po_2 is thus reduced by the fraction $\frac{6}{106}$. It follows from Boyle's law that Po_2 after humidification is indicated by the following expression:

$$\begin{pmatrix}\text{fractional concentration of oxygen}\\ \text{in the dry gas phase}\\ \text{(Haldane value)}\end{pmatrix} \times \left(\begin{matrix}\text{barometric}\\ \text{pressure}\end{matrix} - \begin{matrix}\text{saturated water}\\ \text{vapour pressure}\end{matrix}\right)^{*}$$

Therefore the effective Po_2 of inspired air at a body temperature of 37°C is:

$$\frac{20{\cdot}93}{100} \times (760 - 47)^{*} = \frac{20{\cdot}93}{100} \times 713$$
$$= 149 \text{ mm Hg}$$

It will be noted that, as a rough approximation, the percentage concentration of a gas can be converted to a tension by multiplying by 7; e.g. Po_2 of air is approximately $21 \times 7 = 147$ mm Hg, tension of 2 per cent halothane is approximately $2 \times 7 = 14$ mm Hg, and the tension of 5 per cent carbon dioxide is approximately $5 \times 7 = 35$ mm Hg.

* The quantity in parentheses is known as the 'dry barometric pressure'.

In respiratory physiology, gas tensions are almost always considered as being exerted by gas humidified at body temperature. This applies to inspired gas because it cannot participate in gas exchange until after it has been humidified in the upper respiratory tract. Therefore calculations almost always employ the *dry* barometric pressure whether considering inspired, alveolar or expired gas.

FACTORS INFLUENCING ALVEOLAR TENSION OF OXYGEN

The general equation for the calculation of the alveolar tension of a gas has been stated on pages 153 et seq. In the case of oxygen:

$$\text{alveolar } P_{O_2} \fallingdotseq \begin{matrix}\text{dry}\\ \text{barometric}\\ \text{pressure}\end{matrix} \left(\begin{matrix}\text{inspired}\\ \text{oxygen}\\ \text{concentration}\end{matrix} - \frac{\text{oxygen uptake}}{\text{alveolar ventilation}} \right) \quad \ldots(1)$$

This equation is only approximate and does not include the second order correction factor due to the small difference in volume between the inspired and expired gas. Normally this factor is small but, during the exchange of a soluble gas such as nitrous oxide, the difference may be quite large.

Various forms of the alveolar air equation may be used to correct for this difference. The commonest forms assume that the number of molecules of nitrogen inhaled equals the number exhaled. This, of course, is very seldom true during and after anaesthesia, and in the intensive care ward. Therefore, the anaesthetist may require to use a special form of the equation introduced by Filley, MacIntosh and Wright (1954), which makes no assumptions of inert gas equilibrium and is appropriate to most of the varied conditions encountered by the anaesthetist:

$$P_{A_{O_2}} = P_{I_{O_2}} - P_{A_{CO_2}} \left(\frac{P_{I_{O_2}} - P\bar{E}_{O_2}}{P\bar{E}_{CO_2}} \right) \quad \ldots(2)$$

Applications of the equation have been discussed by Nunn (1963). A further modification has been described by Kelman and Prys-Roberts (1967) which allows for the addition of carbon dioxide to the inspired gas of the patient.

In its more accurate forms (e.g. equation 2), the equation is used principally for calculation of the 'ideal' alveolar P_{O_2}, a theoretical entity which was introduced on page 178 and explained in greater detail on pages 262 et seq. 'Ideal' alveolar gas approximates in composition to the mixed gas which is exhaled at the end of expiration from the perfused alveoli. In practice it is defined as having a P_{CO_2} equal to that of arterial blood, and a respiratory exchange ratio equal to that of mixed expired gas. Comparison of 'ideal' alveolar P_{O_2} with arterial P_{O_2} is the standard method of measurement of 'venous admixture' (pages 262 et seq.).

In its simplified form (equation 1), the alveolar air equation is useful for consideration of the important quantitative relationships between barometric pressure, inspired oxygen concentration, oxygen uptake and alveolar ventilation. *Figure 111* shows the relationship for normal barometric pressure and basal oxygen consumption. The quantitative basis of the relationship was considered on pages 153 et seq. It suffices here to stress the following points.

Dry barometric pressure.—Other factors remaining constant, the alveolar P_{O_2} will be directly proportional to the dry barometric pressure which falls with increasing altitude to become zero at 19 kilometres where the actual barometric pressure equals the saturated vapour pressure of water at body temperature. A pressure of two atmospheres (absolute) approximately doubles the alveolar P_{O_2} if other factors remain constant.

Ventilation.—There is a hyperbolic relationship between alveolar P_{O_2} and alveolar ventilation. As ventilation is increased, the alveolar P_{O_2} rises asymptotically towards (but never reaches) the P_{O_2} of the inspired gas (*Figure 111*). It will be seen from the shape of the curves that changes in ventilation *above* the normal level have comparatively little effect upon alveolar P_{O_2}. In contrast,

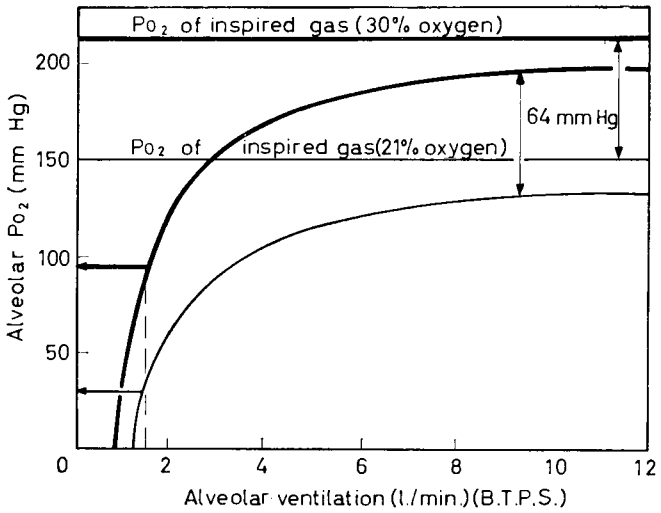


Figure 111. The effect on alveolar P_{O_2} *of increasing the inspired oxygen concentration from 21 per cent (thin curve) to 30 per cent (heavy curve). The patient is assumed to have an oxygen consumption of 200 ml./min. (S.T.P.D.). In this example, the alveolar* P_{O_2} *is reduced to a dangerously low level when breathing air at an alveolar ventilation of 1·5 l./min. At this point, oxygen-enrichment of the inspired gas to 30 per cent is sufficient to raise the alveolar* P_{O_2} *almost to within the normal range. All points on the heavy curve are 64 mm Hg above the corresponding points on the thin curve at the same ventilation*

changes in ventilation *below* the normal level may have a very marked effect on alveolar P_{O_2}. At very low levels of ventilation, the alveolar ventilation is quite critical and small changes may precipitate gross hypoxia. The critical zone may be deduced from a study of *Figure 111.*

Oxygen consumption.—The role of oxygen consumption has received insufficient attention and there is an unfortunate tendency to consider that all patients consume 250 ml. of oxygen per minute under all circumstances. However, it is true that during uncomplicated anaesthesia oxygen consumption does not

vary widely, mean values being rather less than basal and of the order of 200 ml./min. (*see Table 15*). Hypothermia causes substantial reductions in oxygen consumption, while pyrexia, shivering, struggling and restlessness may cause very large increases in oxygen consumption which are potentially important in the post-operative period and during intensive care (Bay, Nunn and Prys-Roberts, 1968). The influence of increased oxygen consumption on the alveolar P_{O_2} is quantitatively important. *Figure 112* shows curves relating ventilation to alveolar P_{O_2} for different values of oxygen consumption. It will be seen that increases in oxygen consumption will require corresponding increases in alveolar ventilation for the maintenance of normal alveolar P_{O_2}. For example, a patient who is shivering during recovery from halothane anaesthesia may

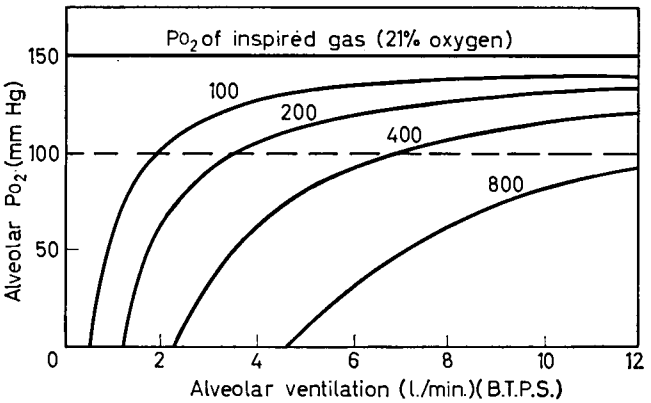


Figure 112. The relationship between alveolar ventilation and alveolar P_{O_2} *for different values of oxygen consumption for a patient breathing air at normal barometric pressure. The figures on the curves indicate the oxygen consumption in ml./min. (S.T.P.D.). Alveolar ventilation is in l./min. (B.T.P.S.). A typical value for oxygen consumption by an anaesthetized patient is 200 ml./min; 100 ml./min. would be an average figure during hypothermia at 30°C. Higher values may be brought about by restlessness, struggling, pyrexia or shivering. Note that the alveolar ventilation required to maintain any particular alveolar* P_{O_2} *is directly proportional to the oxygen consumption. (In calculations of this type it is important to make the correction required by the fact that oxygen consumption and alveolar ventilation values are commonly expressed at different temperatures and pressures—* see *Appendix B*)

have an oxygen consumption of 500 ml./min., and require a minute volume of 15 l./min. for maintenance of a normal alveolar P_{O_2}. Hypoxia will result if a patient cannot increase his ventilation to cover increased oxygen consumption as, for example, during a convulsion.

In the short term, cardiac output can influence the alveolar P_{O_2}. For example, if other factors remain constant, a sudden reduction in cardiac output will temporarily raise the alveolar P_{O_2} since less blood passes through the lungs to remove oxygen from the alveolar gas. However, the reduced cardiac output also causes increased oxygen extraction in the tissues supplied by the systemic circulation and before long the mixed venous oxygen level is decreased. When that has happened, the removal of oxygen from the alveolar gas returns to its original level as the reduction in blood flow rate is compensated by the greater

amount of oxygen which is taken up per unit volume of blood flowing through the lungs. Thus, in the long term cardiac output does not directly influence the alveolar P_{O_2} and only the oxygen consumption appears in equation (1).

Inspired oxygen concentration.—The alveolar P_{O_2} will be raised or lowered by an amount equal to the change in the inspired gas P_{O_2}, provided that other factors remain constant. Since the concentration of oxygen in the inspired gas should always be under the control of the anaesthetist, it is a most important therapeutic tool which may be used to counteract a number of different factors which may impair oxygenation.

The effect of an increase in the inspired oxygen concentration from 21 to 30 per cent is shown in *Figure 111.* For any alveolar ventilation, the improvement of alveolar P_{O_2} will be $(760 - 47)\ (30/100 - 21/100) = 64$ mm Hg. This will be of great importance if hypoventilation while breathing air has reduced the alveolar P_{O_2} to 30 mm Hg, a value which is close to the lowest level compatible with life. Oxygen enrichment of inspired gas to 30 per cent will then increase the alveolar P_{O_2} to 94 mm Hg, which is almost within the normal range. Thus 30 per cent is the maximum concentration of oxygen in the inspired gas which will be required to correct the alveolar P_{O_2} of a patient breathing air, who has become hypoxaemic as a result of hypoventilation. If higher concentrations are required, the patient could not survive while breathing air and the elevation of P_{CO_2} (uninfluenced directly by changes in inspired oxygen) will be dangerously high. Such cases require treatment by increase of alveolar ventilation such as, for example, by artificial ventilation or tracheostomy. In *Figure 51,* ventilation/alveolar P_{O_2} curves were constructed for a wide range of inspired oxygen concentrations. This figure indicates the protection against hypoxaemia (due to hypoventilation) which is afforded by different concentrations of oxygen in the inspired gas.

An entirely different problem is hypoxaemia due to venous admixture, which can be alleviated partially or fully by increasing the oxygen concentration in the pulmonary end-capillary blood as much as possible. This may require the inhalation of 100 per cent oxygen (page 346).

The 'concentration', third gas or Fink effect.—The above diagrams and equations have ignored a factor which influences alveolar P_{O_2} during exchange of large quantities of soluble gases such as nitrous oxide. This effect was mentioned briefly in connection with carbon dioxide on page 304. Its effect on oxygen is probably more important.

During the administration of nitrous oxide, large quantities of the more soluble gas replace smaller quantities of the less soluble nitrogen previously dissolved in body fluids. There is thus a net uptake of 'inert' gas into the body from the alveoli, causing a *temporary* increase in the concentration of both oxygen and carbon dioxide, which will thus *temporarily* exert a higher tension than would otherwise be expected. Conversely, during recovery from nitrous oxide anaesthesia, large quantities of nitrous oxide leave the body to be replaced with smaller quantities of nitrogen. There is thus a net loss of 'inert' gas from the body into the alveoli causing dilution of oxygen and carbon dioxide, both of which will *temporarily* exert a lower tension than would otherwise be expected.

The magnitude of the effect and its clinical significance are still uncertain. It is possible to calculate the extent of the alveolar gas tension changes by a method described by Nunn (1963). During the inhalation of 100 per cent nitrous oxide there is a delay in the expected fall of alveolar P_{O_2} (first noticed indirectly by Rottenstein in 1880), and furthermore the P_{CO_2} is raised, tending to cause hyperventilation. Both effects combine to reduce the hypoxaemia which would otherwise be expected to follow. During recovery from nitrous oxide anaesthesia, on the other hand, there is a transient fall of alveolar P_{O_2} combined with a fall of P_{CO_2} which is probably sufficient to depress the breathing and result in a further fall of P_{O_2}. This phenomenon, under the name of 'diffusion anoxia' has been described by Fink, Carpenter and Holaday (1954) and Rackow, Salanitre and Frumin (1961), and considered as a cause of post-operative hypoxaemia by Marshall and Millar (1965).

THE ALVEOLAR/ARTERIAL P_{O_2} DIFFERENCE

Significance of the Alveolar/Arterial P_{O_2} Difference

In the normal healthy subject, breathing air, the arterial and alveolar P_{O_2} do not differ by more than a few millimetres of mercury. However, during anaesthesia and in many patients undergoing intensive care, the alveolar/arterial P_{O_2} difference is increased and may be very large indeed. If such patients breathe 21 per cent oxygen, the alveolar/arterial P_{O_2} difference may be sufficient to cause serious arterial hypoxaemia. An increase of the alveolar/arterial P_{O_2} difference is, in fact, the commonest cause of hypoxia and is the most important consideration in controlling the arterial oxygenation in the clinical environment.

Unlike the alveolar P_{O_2}, the alveolar/arterial P_{O_2} difference cannot be predicted from easily measured quantities, and the anaesthetist has no simple means of knowing the magnitude of the alveolar/arterial P_{O_2} difference in a particular patient under his care. It is, therefore, important for him to understand the factors which influence the difference and thus to have some idea of the probable limits. In particular, he should understand the principles of restoration of arterial P_{O_2} by increasing the inspired oxygen concentration, since this measure is taken in almost every patient under his care.

Factors Influencing the Magnitude of the Alveolar/Arterial P_{O_2} Difference

Chapter 9 explains in some detail the components of the alveolar/arterial P_{O_2} difference and it now remains to consider the actual magnitude of the difference and the influence of various factors upon it. So many factors must be considered that the subject is not easy to understand. Nevertheless, the matter is of clinical importance and quantitative consideration appears essential for an understanding of oxygen homeostasis.

The calculations are unfortunately laborious though not fundamentally difficult. Nomograms and special purpose slide rules (Severinghaus, 1966) are useful but the calculations are sufficiently complex to merit the use of a

digital computer, and Kelman's program (1966b) has proved of great value, not only for study of individual patients but also for exploring the quantitative aspects of the subject in general (Kelman and his colleagues, 1967). The usefulness of the computer program has been extended to those without ready access to a computer by the preparation of a book of tables printed directly from the computer and used after the manner of log tables (Kelman and Nunn, 1968).

It will be recalled that the alveolar/arterial Po_2 difference results from venous admixture (or physiological shunt) which consists of two components: (*a*) shunted venous blood which mingles with the oxygenated blood leaving the pulmonary capillaries; (*b*) a component due to scatter of ventilation/perfusion ratios in different parts of the lungs.

Figure 85 shows the derivation of the following axiomatic relationship for the first component:

$$\frac{\dot{Q}s}{\dot{Q}t} = \frac{Cc'_{O_2} - Ca_{O_2}}{Cc'_{O} - C\bar{v}_{O_2}}$$

Two points should be noted.

(1) The equation gives a slightly false impression of precision since it assumes that all the shunted blood is *mixed* venous. This is not the case, Thebesian and bronchial venous blood being obvious exceptions.

(2) Oxygen content of pulmonary end-capillary blood (Cc'_{O_2}) is, in practice, calculated on the basis of the end-capillary oxygen tension (Pc'_{O_2}) being equal to the 'ideal' alveolar Po_2 (*see* page 262).

The equation may be cleared and solved for the pulmonary end-capillary/arterial oxygen content difference as follows:

$$Cc'_{O_2} - Ca_{O_2} = \frac{\frac{\dot{Q}s}{\dot{Q}t}(Ca_{O_2} - C\bar{v}_{O_2})^*}{1 - \frac{\dot{Q}s}{\dot{Q}t}} \qquad ...(3)$$

$Ca_{O_2} - C\bar{v}_{O_2}$ is the arterial/mixed venous oxygen content difference and is a function of the oxygen consumption and the cardiac output thus:

$$\dot{Q}t\,(Ca_{O_2} - C\bar{v}_{O_2}) = \dot{V}o_2 \quad \text{(Fick equation)}^* \qquad ...(4)$$

Substituting for $(Ca_{O_2} - C\bar{v}_{O_2})$ in equation (3), we have:

$$Cc'_{O_2} - Ca_{O_2} = \frac{\dot{V}o_2 \frac{\dot{Q}s}{\dot{Q}t}}{\dot{Q}t\left(1 - \frac{\dot{Q}s}{\dot{Q}t}\right)}^* \qquad ...(5)$$

This equation shows the content difference in terms of oxygen consumption ($\dot{V}o_2$), the venous admixture ($\dot{Q}s/\dot{Q}t$) and the cardiac output ($\dot{Q}t$).

* Scaling factors are required to correct for the inconsistency of the units which are customarily used for the quantities in this equation.

The significance of cardiac output has not received due attention until recent years. However, it will be clear that this factor must be of considerable importance, since a reduced cardiac output results in an increased arterial/mixed venous oxygen content difference. This means that the shunted blood will be more desaturated and will therefore cause a greater fall of the arterial oxygen level than would less desaturated blood flowing through a shunt of the same magnitude.

The final stage in the calculation is to convert the end-capillary/arterial oxygen *content* difference to the *tension* difference. The oxygen content of blood is the sum of the oxygen in physical solution and that which is combined with haemoglobin:

$$\text{oxygen content of blood} = \alpha\, P_{O_2} + S_{O_2} \times \text{Hb} \times 1{\cdot}39$$

where: α is the solubility coefficient of oxygen in blood (not plasma!); S_{O_2} is the saturation, and varies with P_{O_2} according to the oxygen dissociation curve, which itself is influenced by temperature, pH and base excess (Bohr effect); Hb is the haemoglobin concentration (g./100 ml.); 1·39 is the volume of oxygen (ml.) which can combine with 1 g. of haemoglobin.

Carriage of oxygen in the blood is discussed in detail on pages 348 et seq.

Derivation of the oxygen content from the P_{O_2} is excessively laborious if due account is taken of pH, base excess, temperature and haemoglobin concentration. Derivation of P_{O_2} from content is even more laborious as an iterative approach is required. Tables of tension/content relationships are particularly useful, and *Table 34* is an extract from Kelman and Nunn (1968) to show the format and general influence of the several variables.

Table 34

Oxygen content of human blood (ml./100 ml.) as a function of P_{O_2} *and other variables (values from the computer-written tables of Kelman and Nunn, 1968)*

	Haemoglobin concentration (g./100 ml.)		
	10	14	18
P_{O_2} at pH 7·4, 37°C, base excess zero			
50	11·99	16·72	21·45
70	13·29	18·53	23·76
100	13·85	19·27	24·69
150	14·20	19·70	25·20
200	14·41	19·94	25·47
P_{O_2} at pH 7·2, 37°C, base excess zero			
50	10·45	14·57	18·69
70	12·60	17·56	22·52
100	13·62	18·94	24·27
150	14·11	19·58	25·04
200	14·37	19·87	25·38
P_{O_2} at pH 7·4, 34°C, base excess zero			
50	12·81	17·87	22·93
70	13·59	18·94	24·30
100	13·96	19·43	24·89
150	14·24	19·76	25·28
200	14·44	19·98	25·51

The fourth significant figure is not of clinical importance but is useful for interpolation.

The principal factors influencing the magnitude of the alveolar/arterial Po_2 difference caused by venous admixture may be summarized as follows.

The magnitude of the venous admixture increases the alveolar/arterial Po_2 difference with direct proportionality for small shunts, although this is lost with larger shunts (*Figure 113*).

The actual alveolar Po_2 has a profound but non-linear effect on the alveolar/arterial Po_2 gradient (*Figure 113*). The alveolar/arterial oxygen *content* difference

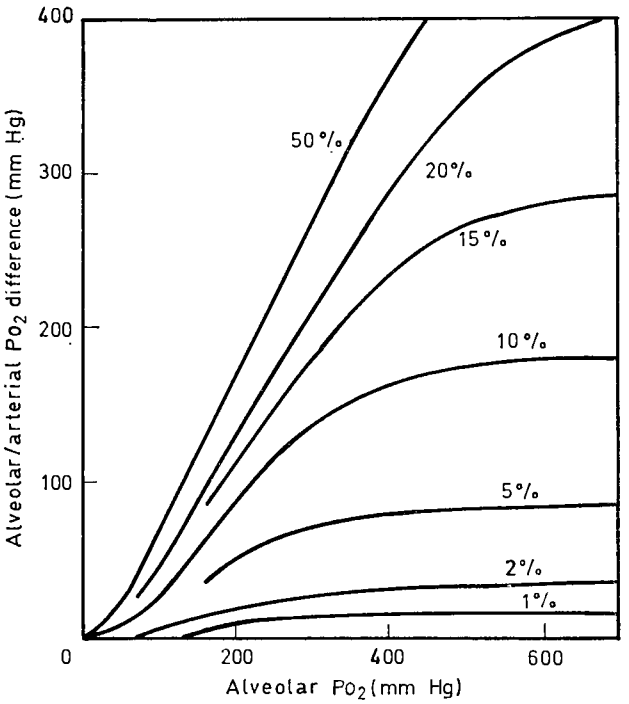


Figure 113. Influence of shunt on alveolar/arterial Po_2 *difference at different levels of alveolar* Po_2. *For small shunts, the difference (at constant alveolar* Po_2*) is roughly proportional to the magnitude of the shunt. For a given shunt, the alveolar/arterial* Po_2 *difference increases with alveolar* Po_2 *in non-linear manner governed by the oxygen dissociation curve. At high alveolar* Po_2*, a plateau of alveolar/arterial* Po_2 *difference is reached but the alveolar* Po_2 *at which the plateau is reached is higher with larger shunts. Note that, with a 50 per cent shunt, an increase in alveolar* Po_2 *produces an equal increase in alveolar/arterial* Po_2 *difference. Therefore, the arterial* Po_2 *is independent of changes in alveolar* Po_2*, if other factors remain constant. Constants incorporated in this diagram: arterial/venous oxygen content difference, 5 ml./100 ml.; Hb concentration, 14 g./100 ml.; temperature of blood, 37°C; pH of blood, 7·40; base excess, zero. Figures in the graph indicate shunt as percentage of total pulmonary blood flow*

is uninfluenced by the alveolar Po_2 (equation 5), and the effect on the *tension* difference arises entirely in conversion of *content* to *tension*: it is thus a function of the slope of the dissociation curve at the Po_2 of the alveolar gas. For example,

a loss of 1 vol. per cent of oxygen from blood with a Po_2 of 700 mm Hg causes a fall of Po_2 of about 325 mm Hg, most of the oxygen being lost from physical solution. However, if the initial Po_2 were 100 mm Hg, a loss of 1 vol. per cent would only cause a fall of Po_2 of 35 mm Hg, most of the oxygen being lost from combination with haemoglobin. Should the initial Po_2 be only 50 mm Hg, a loss of 1 vol. per cent would cause a very small change in Po_2 of the order of 5 mm Hg, drawn almost entirely from combination with haemoglobin at a point where the dissociation curve is steep.* This effect is clearly shown in *Figure 113.* The clinical implication of this is that the alveolar/arterial Po_2 difference will be greatest when the alveolar Po_2 is highest (other factors being the same). Thus the really high alveolar/arterial Po_2 differences tend to occur in those patients whose alveolar Po_2 is high enough to withstand them. If the alveolar Po_2 be reduced (e.g. by underventilation), then the alveolar/arterial Po_2 gradient will be diminished if other factors remain the same. The arterial Po_2 thus falls less than the alveolar Po_2. This is fortunate and may be considered as one of the many benefits deriving from the shape of the oxygen dissociation curve. With a 50 per cent venous admixture, the arterial Po_2 is almost independent of changes in alveolar Po_2.

Cardiac output changes produce inverse changes of the arterial/mixed venous oxygen content difference if the patient's oxygen consumption remains the same (Fick equation 4). Equation (5) shows that there is also an inverse relationship between the cardiac output and the alveolar/arterial oxygen *content* difference if the venous admixture is constant (*Figure 114b*). However, when the *content* difference is converted to *tension* difference, the relationship to cardiac output is no longer truly inverse, but assumes a complex non-linear form in consequence of the shape of the oxygen dissociation curve. The relationship between cardiac output and alveolar/arterial Po_2 difference shown in *Figure 114a* applies only to the conditions specified, particularly the alveolar Po_2, which was assumed to be 180 mm Hg in the preparation of this diagram.

The temperature, pH and base excess of the patient's blood influence the dissociation curve (page 355). In addition, temperature affects the solubility coefficient of oxygen in blood. All three factors influence the relationship between tension and content (*see Table 34*).

Therefore, the effect of venous admixture on the alveolar/arterial Po_2 difference is influenced by all these factors although the effect is not usually important except in extreme deviations from normal.

The haemoglobin concentration influences the partition of oxygen between physical solution and chemical combination. While the haemoglobin concentration does not influence the pulmonary end-capillary/arterial oxygen *content* difference (equation 5), it exerts an effect on the *tension* difference. For example, at a cardiac output of 5 l./min. and oxygen consumption of 200 ml./min., venous admixture of 20 per cent results in a pulmonary end-capillary/arterial oxygen content difference of 0·5 vols. per cent. Assuming an alveolar Po_2 of 180 mm

* These figures only apply to certain specified conditions—haemoglobin concentration 14 g./100 ml., 37°C, pH 7·40, base excess zero. A change in any of these factors will alter the figures.

Hg, the alveolar/arterial P_{O_2} difference is influenced by haemoglobin concentration as follows.

Haemoglobin concentration (g./100 ml.	*Alveolar/arterial* P_{O_2} *difference (mm Hg)*	*Arterial* P_{O_2} *(mm Hg)*
8	113	67
10	109	71
12	105	75
14	101	79
16	98	82

(Different figures would be obtained by selection of a different value for alveolar P_{O_2}.)

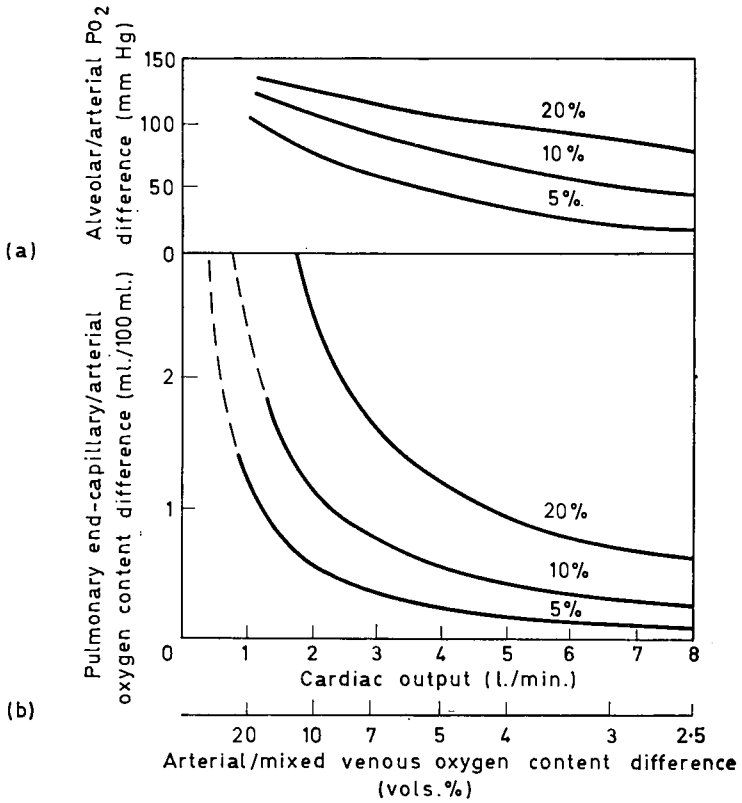


Figure 114. Influence of cardiac output on the alveolar/arterial P_{O_2} *difference. In this example it is assumed that the patient has an oxygen consumption of 200 ml./min. and an alveolar* P_{O_2} *of 180 mm Hg. Changes in cardiac output produce an inverse change in the pulmonary end-capillary/arterial oxygen content difference (graph b). When converted to tension differences, the inverse relationship is distorted by the effect of the oxygen dissociation curve in a manner which is applicable only to the particular alveolar* P_{O_2} *of the patient (graph a). (Alveolar* P_{O_2} *is assumed equal to pulmonary end-capillary* P_{O_2}*)*

Alveolar ventilation.—The over-all effect of changes in alveolar ventilation on the arterial P_{O_2} presents an interesting problem, and serves to illustrate the integration of the separate aspects of the factors discussed above. An increase in the alveolar ventilation may be expected to have the following results.

(1) *The alveolar* P_{O_2} must be raised provided the barometric pressure, inspired oxygen concentration and oxygen consumption remain the same (equation 1 and *Figure 111*).

(2) *The alveolar/arterial* P_{O_2} *difference* is increased for the following reasons.

(*a*) The increase in the alveolar P_{O_2} will increase the alveolar/arterial P_{O_2} difference if other factors remain the same (*Figure 113*).

(*b*) Under many conditions which apply during anaesthesia, a fall of P_{CO_2} (resulting from an increase in alveolar ventilation) reduces the cardiac output, which will increase the alveolar/arterial P_{O_2} difference if other factors remain the same (equation 5 and *Figure 114*).

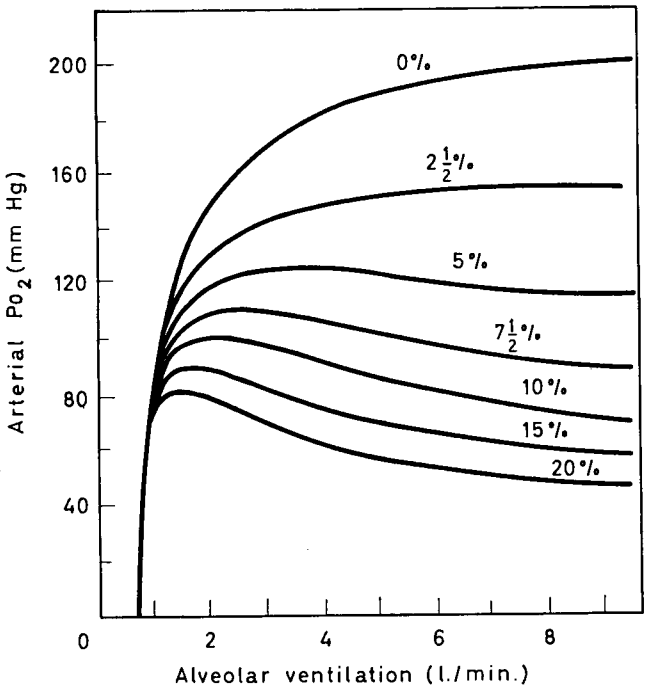


Figure 115. The effect of alveolar ventilation on arterial P_{O_2} *is the algebraic sum of the effect upon the alveolar* P_{O_2} (*Figure 111*) *and the alveolar/arterial* P_{O_2} *difference. When the increase in the latter exceeds the increase in the former, the arterial* P_{O_2} *will be diminished. The figures in the diagram indicate the percentage venous admixture. The curve corresponding to zero per cent venous admixture will indicate the alveolar* P_{O_2}. *Constants incorporated in the design of this figure: inspired* O_2 *concentration, 30 per cent;* O_2 *consumption, 200 ml./min.; respiratory exchange ratio, 0·8. It has been assumed that the cardiac output is influenced by the* P_{CO_2} *according to the equation:* $\dot{Q} = 0{\cdot}039 \times P_{CO_2} + 2{\cdot}23$. (*Reproduced from Kelman and his colleagues, 1967, by courtesy of the Editor of the* British Journal of Anaesthesia)

(*c*) The change in arterial pH resulting from the reduction in P_{CO_2} causes a small, unimportant increase in alveolar/arterial P_{O_2} difference.

Thus an increase in alveolar ventilation may be expected to raise the alveolar P_{O_2} *and* the alveolar/arterial P_{O_2} difference. The resultant change in arterial P_{O_2} will depend upon the relative magnitude of the two changes. *Figure 115* shows the changes in arterial P_{O_2} caused by variations of alveolar ventilation at an inspired oxygen concentration of 30 per cent in the presence of varying degrees of venous admixture, assuming that cardiac output is influenced by P_{CO_2} as described in the legend. Up to an alveolar ventilation of 1·5 l./min., an increase in ventilation will always raise the arterial P_{O_2}. Beyond that, in the example cited, further increases in alveolar ventilation will only increase the arterial P_{O_2} if the venous admixture is less than 3 per cent. For larger values of venous admixture, the increase in the alveolar/arterial P_{O_2} difference exceeds the increase in the alveolar P_{O_2} and the arterial P_{O_2} is thus decreased.

$\dot{V}/\dot{Q}$ Scatter

It was explained in Chapter 9 that scatter in ventilation/perfusion ratios produces an alveolar/arterial P_{O_2} difference for the following reasons.

(1) More blood flows through the underventilated overperfused alveoli, and the mixed arterial blood is therefore heavily weighted in the direction of the suboxygenated blood from areas of low $\dot{V}/\dot{Q}$ ratio. The smaller amount of blood flowing through areas of high $\dot{V}/\dot{Q}$ ratio cannot compensate for this (*Figure 86*).

(2) Due to the bend in the upper part of the dissociation curve, the fall in saturation in blood from areas of low $\dot{V}/\dot{Q}$ ratio tends to be greater than the rise in saturation in blood from areas of high $\dot{V}/\dot{Q}$ (*Figure 87*). This provides a second reason why blood from alveoli with a high $\dot{V}/\dot{Q}$ cannot compensate for blood from alveoli with a high $\dot{V}/\dot{Q}$ ratio.

Considered from the quantitative point of view, the second effect will clearly be less important at higher levels of alveolar P_{O_2} since in that region the dissociation curve will be flatter. In fact, if the alveolar P_{O_2} is in excess of about 400 mm Hg, it is generally considered that the effect of $\dot{V}/\dot{Q}$ scatter is negligible since blood from all alveoli will be 100 per cent saturated regardless of the $\dot{V}/\dot{Q}$ ratio. However, this view overlooks the first consideration (1, above), and even when inhaling 100 per cent oxygen, the excess flow from regions of low $\dot{V}/\dot{Q}$ will reduce the mean arterial P_{O_2} below the mean alveolar P_{O_2}.

Having said this much, it is difficult to be any more precise because we have, at the time of writing, no definite information on the degree of scatter of $\dot{V}/\dot{Q}$ ratios during anaesthesia. If the scatter were the same in the supine anaesthetized patient as in the upright conscious subject, the effect of changes in alveolar P_{O_2} would be as follows.

Alveolar P_{O_2} (*mm Hg*)	*Alveolar/arterial* P_{O_2} *difference caused by 'normal'* $\dot{V}/\dot{Q}$ *scatter* (*mm Hg*)
50	6
105	5
500	3

If the $\dot{V}/\dot{Q}$ scatter is increased, the resultant effect on the alveolar/arterial P_{O_2} difference will be greater. *Figure 116b* shows an example worked out for a hypothetical patient with the gross scatter of $\dot{V}/\dot{Q}$ ratios depicted in the graph. It will be seen that the alveolar/arterial P_{O_2} difference due to the $\dot{V}/\dot{Q}$ scatter does not entirely disappear at high levels of alveolar P_{O_2}, although it is reduced.

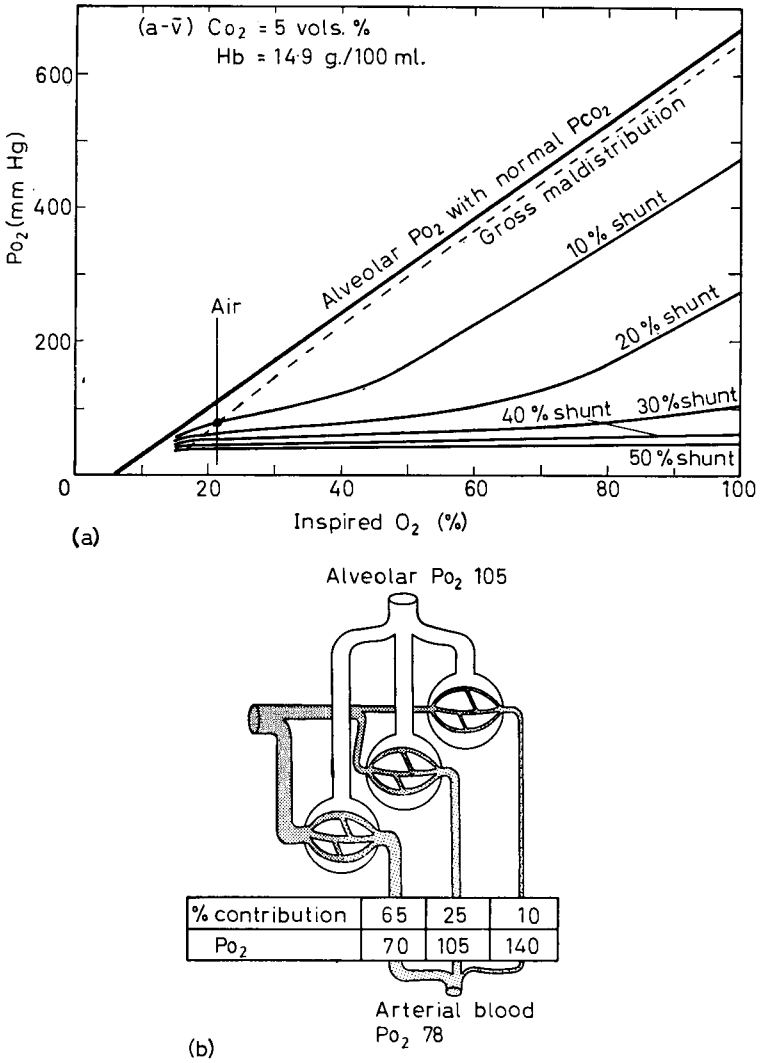


Figure 116. Effect of changes in inspired oxygen concentration on P_{O_2} *in the presence of abnormalities of distribution. (a) The upper line shows the alveolar* P_{O_2} *as a function of the inspired oxygen concentration. The continuous curves indicate the arterial* P_{O_2} *with shunts of different magnitudes. The broken curve indicates the arterial* P_{O_2} *in the presence of* $\dot{V}/\dot{Q}$ *ratios illustrated in (b). In all cases it is assumed that the alveolar ventilation remains normal (alveolar* P_{CO_2} *= 40 mm Hg). (Reproduced from Nunn (1966) by courtesy of the Editor of the* Canadian Anaesthetists' Society Journal)

Compensation for Increased Alveolar/Arterial P_{O_2} Difference by Raising the Inspired Oxygen Concentration

Despite the difficulty and complex nature of the concepts presented in the last few pages, their practical importance is great. If all anaesthetized patients and those undergoing intensive care were to breathe 21 per cent oxygen, most would be hypoxaemic and many would be seriously hypoxic. In some, the principal cause of hypoxaemia would be hypoventilation. However, in most the reason would be the increased alveolar/arterial P_{O_2} difference, due to venous admixture, the effect of which would often be magnified by increased arterial/mixed venous oxygen content difference owing to the cardiac output being disproportionately low for the oxygen consumption.

In most cases, the anaesthetist is unable to correct the factors which increase the alveolar/arterial P_{O_2} difference and the patient is treated empirically by elevation of the inspired oxygen concentration to a level which is known to result in a satisfactory arterial oxygen level in a particular patient or in patients in general. Thus, in difficult cases undergoing intensive care, it is advisable to measure the arterial P_{O_2} at intervals to ensure that the inspired oxygen concentration is adequate. This is not practicable during routine anaesthesia and most anaesthetists simply raise the inspired oxygen concentration to 30 per cent or above, knowing that such a level is generally satisfactory in the great majority of patients.

We have seen above that, when underventilation is not sufficiently severe to cause dangerous elevation of P_{CO_2}, an increase of inspired oxygen concentration to about 30 per cent should be sufficient to restore the alveolar P_{O_2} to normal. Similarly, if the alveolar/arterial P_{O_2} difference is enlarged because of excessive $\dot{V}/\dot{Q}$ scatter, a moderate elevation of inspired P_{O_2} may be sufficient to cause satisfactory saturation of the blood leaving even the worst-ventilated alveoli and this would restore the arterial P_{O_2} to a normal value. In the example of gross scatter for $\dot{V}/\dot{Q}$ ratios shown in *Figure 116b*, it can be shown that the inhalation of 25 per cent oxygen is sufficient to restore the arterial P_{O_2} to 100 mm Hg.

If an increase in the alveolar/arterial P_{O_2} difference is due to shunt, the required augmentation of the inspired oxygen concentration becomes a matter for calculation. In general, much higher concentrations are required than for compensation for underventilation or $\dot{V}/\dot{Q}$ scatter. *Figure 116a* permits calculation of the required concentration in the examples shown. Reading from the graph, the following conclusions may be drawn:

10 per cent shunt	30 per cent inspired oxygen should restore normal arterial P_{O_2}.
20 per cent shunt	57 per cent inspired oxygen should restore normal arterial P_{O_2}.
30 per cent shunt	97 per cent inspired oxygen should restore normal arterial P_{O_2}.
40 per cent shunt	normal arterial P_{O_2} cannot be restored by increasing the inspired oxygen concentration.
50 per cent shunt	changes in inspired oxygen concentration have almost no effect upon arterial P_{O_2} (*Figure 113*).

It is often said that oxygen is ineffective for correction of the arterial hypoxaemia caused by shunt because the unshunted blood cannot hold much additional oxygen, being already 95 per cent saturated. This is only relatively true, and the additional oxygen which can be carried (partly in solution) is able to compensate entirely for shunts up to about 30 per cent.

Shunts in excess of 30 per cent are by no means rare in anaesthetic practice and, apart from congenital cardiac disease, may be caused by lung trauma, fat embolus, massive lung collapse, pneumonia, etc. Such patients may require an inspired oxygen concentration close to 100 per cent, and this cannot be attained with oxygen tents, venturi systems, nasal catheters, or the various types of disposable masks which are so useful for the administration of the lower concentrations of oxygen required by patients with underventilation, $\dot{V}/\dot{Q}$ scatter and smaller shunts. One hundred per cent oxygen must be administered by apparatus which has an airtight seal with the patients' respiratory tract. This may be attained either with a cuffed endotracheal tube, a cuffed tracheostomy tube or a perfectly fitting face-mask. In an emergency, the best method of giving 100 per cent oxygen is an anaesthetic gas circuit with the mask held on the face by a trained person. Long-term administration of 100 per cent oxygen may require tracheostomy or intubation in order to ensure continuity of the airtight seal.

TRANSPORT OF OXYGEN FROM THE LUNGS TO THE CELL

We may regard the most important function of the respiratory and circulatory systems to be the supply of oxygen to the cells of the body. The quantity of oxygen transferred in one minute has been termed the 'oxygen flux' (Nunn and Freeman, 1964), and is equal to the following:

$$\begin{array}{l}\text{cardiac output} \times \text{arterial oxygen content} \\ = \quad 5{,}000 \quad \times \quad \dfrac{20}{100} \quad = 1{,}000 \text{ ml./min.} \\ \quad \text{ml./min.} \qquad \text{ml. } O_2\text{/ml. blood}\end{array}$$

Of this 1,000 ml./min., approximately 250 is utilized by the conscious resting subject. The circulating blood thus loses 25 per cent of its oxygen and the mixed venous blood is approximately 75 per cent saturated. The 75 per cent of unextracted oxygen forms an important reserve which may be drawn upon under the stress of such conditions as exercise, to which additional extraction forms one of the integrated adaptations (Barcroft, 1934).

The arterial oxygen content consists predominantly of oxygen in combination with haemoglobin and this fraction is given by the following expression:

$$\text{saturation} \times \text{haemoglobin concentration} \times 1{\cdot}39^*$$

Ignoring the oxygen in physical solution, the full expression for the oxygen flux is as follows:

$$\begin{array}{l}\text{cardiac output} \times \text{arterial } O_2 \text{ saturation} \times \text{haemoglobin concentration} \times 1{\cdot}39 = \text{oxygen flux} \\ 5{,}000 \times \dfrac{95}{100} \times \dfrac{15}{100} \times 1{\cdot}39 = 1{,}000 \\ \text{ml./min.} \qquad\qquad \text{g./ml.} \qquad\qquad \text{ml./min.}\end{array}$$

* 1·39 is the volume of oxygen (ml.) which will combine with 1 g. of haemoglobin.

Note that three variable factors determine the oxygen flux.

(1) *Cardiac output* or, for a particular organ, the regional blood flow. Failure of this factor has been termed 'stagnant anoxia' (Barcroft, 1920).

(2) *Arterial oxygen saturation.* Failure of this (for whatever reason) has been termed 'anoxic anoxia'.

(3) *Haemoglobin concentration* deficiency, as a cause of tissue hypoxia, has been termed 'anaemic anoxia'.

It is important to note that the oxygen flux equals the product of the three variables and one constant. If one variable is halved, the oxygen flux is halved, but if all three variables are halved, the oxygen flux is reduced to one-eighth of the original value. One-eighth of 1,000 is 125 ml./min., and this is a value which, if maintained for any length of time, is incompatible with life, although the reductions of the individual variables are not in themselves lethal.

The quantitative implications of the oxygen flux have been explored by Nunn and Freeman (1964) who stressed the conclusion that criteria for the adequacy of each variable must be considered in relation to the other variables. Thus a degree of arterial hypoxaemia which may be tolerated in the otherwise healthy patient may be dangerous in patients with impaired circulation or anaemia.

THE CARRIAGE OF OXYGEN IN THE BLOOD

Oxygen is carried in the blood in two forms. Much the greater part is in reversible chemical combination with haemoglobin, while a smaller part is in physical solution in plasma and intracellular fluid. The ability to carry large quantities of oxygen in the blood is of great importance to the organism, since without haemoglobin the amount carried would be so small that the cardiac output would need to be increased by a factor of about 20 to give an adequate oxygen flux. This would require a considerable increase in blood volume and, under such handicaps, animals could not have developed to their present extent. The biological significance of the haemoglobin-like compounds is thus immense and is probably exceeded only by chlorophyll, which closely resembles haemoglobin although containing magnesium in place of iron.

Haemoglobin

The haemoglobin molecule has been the subject of many years of detailed x-ray crystallographic analysis by the team led by Perutz in Cambridge. We now know a great deal about its structure and can postulate a structural basis for some of its remarkable properties (Roughton, 1964; Lehmann and Huntsman, 1966).

The haemoglobin molecule consists of four protein chains, each of which carries a haem group (*Figure 117*), the total molecular weight being 64,458. The amino acids comprising the chains have now been identified and it is known that, in the commonest type of adult human haemoglobin (Hb A), there are two types of chain, two of each occurring in each molecule. The two α chains each have 141 amino-acid residues, with the haem attached to a

histidine* residue occupying position 87. The two β chains each have 146 amino-acid residues, with the haem attached to a histidine residue occupying position 92. *Figure 117b* shows details of the point of attachment of the haem in the α chain. Similar information for the β chain is given on page 294.

The four chains of the haemoglobin molecule lie in a ball like a crumpled necklace. However, the form is not random and the actual shape is of critical importance and governs the reaction with oxygen. The shape is maintained by loose bonds between certain amino acids on different chains and also between some amino acids on the same chain. One consequence of these bonds is that the haem groups lie in crevices formed by weak bonds between the haem groups and histidine residues, other than those to which they are attached by normal valency linkages. For example, *Figure 117c* shows a section of an α chain with the haem group attached to the iron atom which is bound to the histidine residue in position 87. However, the haem group is also attached by a loose bond to the histidine residue in position 58. This forms a loop and places the haem group in a crevice which limits and controls the ease of access for oxygen molecules.

Structural Basis of the Bohr Effect

The precise shape of the haemoglobin molecule is altered by factors which influence the strength of the loose bonds and such factors include temperature, pH and salts. This alters the accessibility of the haem groups to oxygen and is believed to be the basis of the mechanism by which the affinity of haemoglobin for oxygen is altered by these factors, an effect which is generally considered in terms of its influence upon the dissociation curve (*Figure 120*).

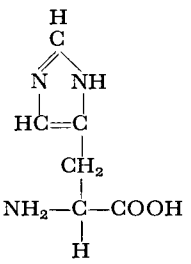
Structural Basis of the Haldane Effect (page 292)

It appears that the shape of the haemoglobin molecule is altered by the uptake of oxygen to form oxyhaemoglobin. It is believed that this increases the ionization of certain $—NH_2$ or $=NH$ groups and so reduces their ability to undertake carbamino carriage of carbon dioxide (*Figure 94*).

Abnormal Forms of Haemoglobin

There are a great number of abnormal forms of haemoglobin. Many changes in the molecule alter the reaction with oxygen, even though they concern a part of the amino-acid chain remote from the attachment of the haem group. Apart from the α and β chains already mentioned, γ and δ chains occur normally in combination with α chains. γ and δ chains have different

* Histidine is an amino acid with the following formula (*see* page 294).



amino-acid sequences. The combination of two γ chains with two α chains constitutes foetal haemoglobin (Hb F) and the combination of two δ chains with two α chains constitutes A_2 haemoglobin (Hb A_2) which forms 2 per cent of the

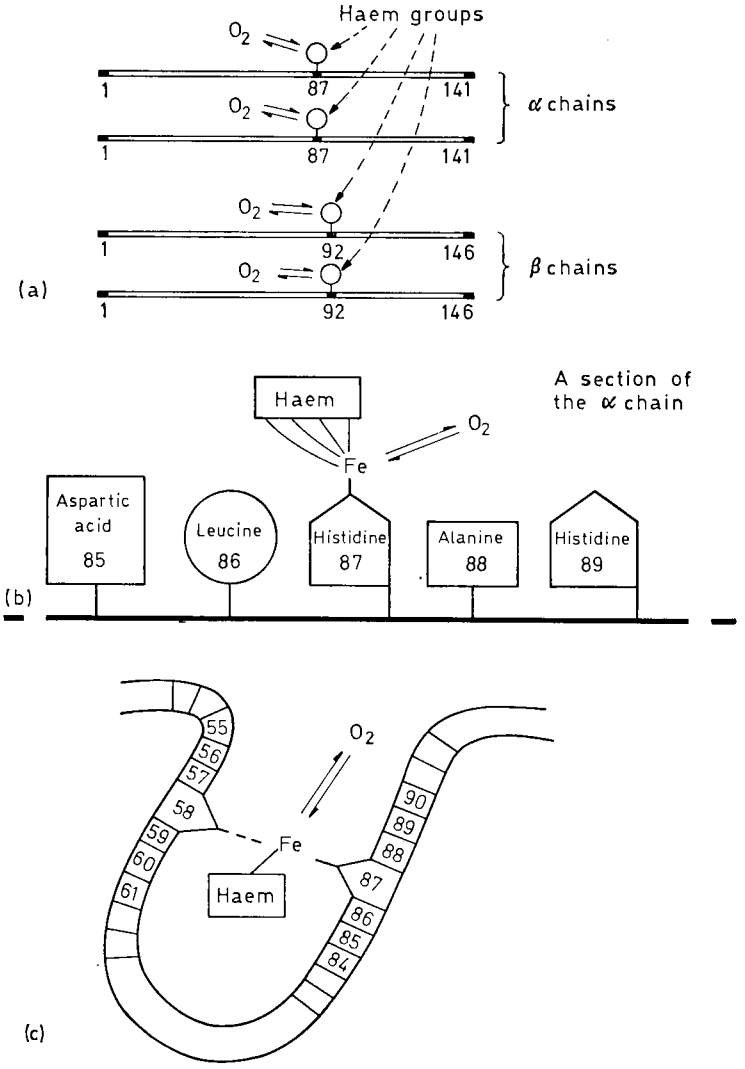


Figure 117. The haemoglobin molecule consists of four amino-acid chains, each carrying a haem group. (a) Two chains are identical, each with 141 amino-acid residues (α chains). The other two are also identical and have 146 amino-acid residues (β chains). (b) shows the attachment of the haem group to the α chain. (c) depicts the crevice (formed by bond between haem and second histidine residue (58)) which contains the haem group

total haemoglobin in normal adults. Other variations in the amino-acid chains can be considered abnormal, and many are associated with disordered oxygen carriage or impaired solubility.

Sickle cell anaemia is caused by the presence of Hb S in which glutamic acid replaces valine in position 6 on the two β chains. This apparently trivial substitution is sufficient to cause critical loss of solubility in the reduced state. It is a hereditary condition and in the homozygous state is a grave abnormality. The heterozygous form (sickle cell trait) is much less serious and there is no convincing evidence that it presents an increased hazard in anaesthesia (Gilbertson; Ball; and Watson-Williams, 1967).

Thalassaemia is another hereditary disorder of haemoglobin. It consists of a suppression of formation of Hb A with a compensatory production of foetal haemoglobin (Hb F) which persists throughout life instead of falling to low levels after birth. The functional disorder thus includes a shift of the dissociation curve to the left (*Figure 118*).

Abnormal ligands.—The iron in haemoglobin is able to combine with other inorganic molecules apart from oxygen. The compounds so formed are, in general, more stable than oxyhaemoglobin and therefore block the combination of haemoglobin with oxygen. The most important of these abnormal compounds is carboxyhaemoglobin but ligands may also be formed with nitric oxide, cyanide, ammonia and a number of other substances. Apart from the loss of oxygen-carrying power, there is often a shift of the dissociation curve to the left (*see* later), so that the remaining oxygen is only released at lower tensions of oxygen. This may cause tissue hypoxia when the arterial Po_2 and oxygen content would otherwise appear to be at a safe level.

Methaemoglobin consists of haemoglobin in which the iron has assumed the trivalent ferric form. Methaemoglobin is unable to combine with oxygen but is slowly reconverted to haemoglobin in the normal subject by the action of enzymes which are deficient in familial methaemoglobinaemia (Lehmann and Huntsman, 1966). Alternatively, conversion may be brought about by reducing agents such as ascorbic acid or methylene blue. The nitrite ion is a potent cause of methaemoglobin formation and is a major factor in poisoning by higher oxides of nitrogen (*see* symposium in May 1967 issue of *British Journal of Anaesthesia*). Methaemoglobin and sulphaemoglobin are a brownish colour and produce a slate-grey colouring of the patient which may be confused with cyanosis.

Kinetics of the Reaction of Oxygen with Haemoglobin

There is now ample experimental proof of Adair's intermediate compound hypothesis (1925) which proposed that the oxidation of haemoglobin proceeds in four separate stages. If the whole haemoglobin molecule, with its four haem groups, is designated as 'Hb_4', the reactions may be presented as follows:

$$Hb_4 + O_2 \underset{k_1}{\overset{k_1'}{\rightleftharpoons}} Hb_4O_2 \qquad K_1 = \frac{k_1'}{k_1}$$

$$Hb_4O_2 + O_2 \underset{k_2}{\overset{k_2'}{\rightleftharpoons}} Hb_4O_4 \qquad K_2 = \frac{k_2'}{k_2}$$

$$Hb_4O_4 + O_2 \underset{k_3}{\overset{k_3'}{\rightleftharpoons}} Hb_4O_6 \qquad K_3 = \frac{k_3'}{k_3}$$

$$Hb_4O_6 + O_2 \underset{k_4}{\overset{k_4'}{\rightleftharpoons}} Hb_4O_8 \qquad K_4 = \frac{k_4'}{k_4}$$

The velocity constant of each dissociation is indicated by a small k, while the addition of a prime (') indicates the velocity constant of the corresponding forward reaction. k'_3 is thus the velocity constant of the reaction of Hb_4O_4 with O_2 to yield Hb_4O_6. The ratio of the forward velocity constant to the reverse velocity constant equals the equilibrium constant of each reaction in the series (represented by capital K).

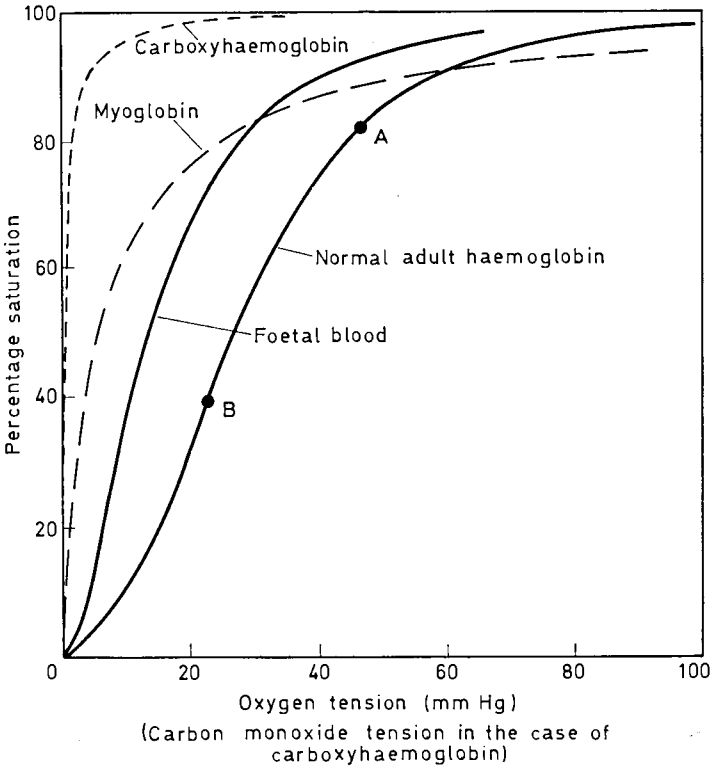


Figure 118. Dissociation curves of normal adult haemoglobin compared with foetal blood. Curves for myoglobin and carboxyhaemoglobin are shown for comparison. Note: (1) Foetal blood is adapted to operate at a lower P_{O_2} *than adult blood. (2) Myoglobin approaches full saturation at* P_{O_2} *levels pertaining in voluntary muscle (10–20 mm Hg); the bulk of its oxygen can only be released at very low oxygen tension. (3) Carboxyhaemoglobin can only be dissociated by the maintenance of very low levels of* Pco. *After birth, foetal haemoglobin is progressively replaced with adult haemoglobin and the dissociation curve gradually moves across to the position of the adult curve. In a patient with a normal circulation and haemoglobin concentration, point* A *represents the greatest deterioration of arterial oxygenation which should pass untreated. Arterial blood corresponding to point* B *is at the threshold of loss of consciousness from hypoxia*

The separate velocity constants have been measured and it is now known that the last reaction has a forward velocity constant (k'_4) which is much higher than that of the other reactions. During the saturation of the last 75 per cent of reduced haemoglobin, the last reaction will predominate and the high velocity counteracts the effect of the ever-diminishing number of oxygen-receptors which would otherwise slow the reaction rate by the law of mass

action (Staub, Bishop and Forster, 1961). In fact, the reaction proceeds at much the same rate until saturation is completed. The significance of this to oxygen transfer in the lung has been presented by Staub (1963a), and its importance in the matter of 'diffusing capacity' is discussed on page 272.

The velocity of the dissociation of oxyhaemoglobin is somewhat slower than its formation. The velocity constant of the combination of carbon monoxide

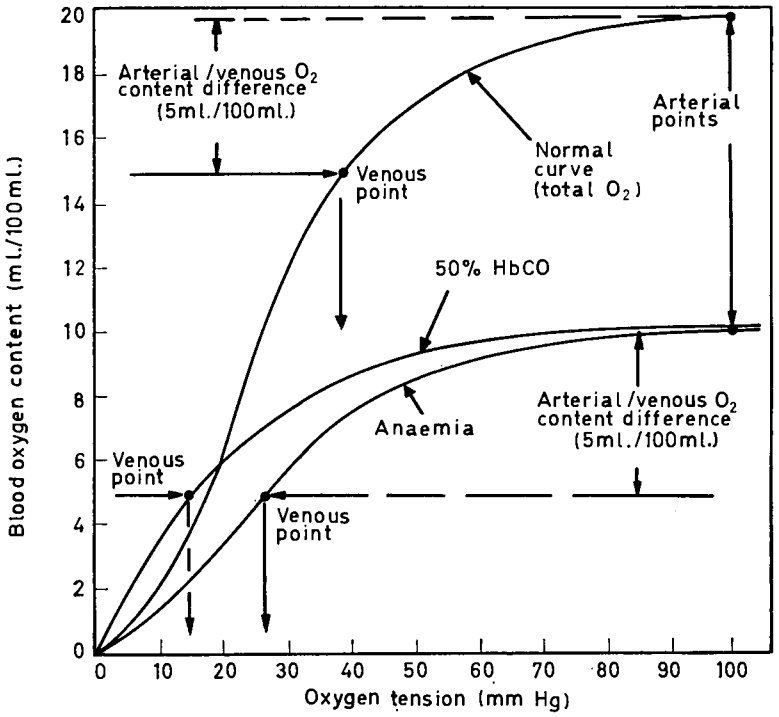


Figure 119. Influence of anaemia and carbon monoxide poisoning on the relationship between oxygen tension and content. The normal curve is constructed for a haemoglobin concentration of 14·4 g./100 ml. Assuming an arterial/venous oxygen content difference of 5 ml./100 ml., the venous P_{O_2} *is about 40 mm Hg. The curve of anaemic blood is constructed for a haemoglobin concentration of 7·2 g./100 ml. If the arterial/venous oxygen content difference remains unchanged, the venous* P_{O_2} *will fall to 27 mm Hg, a level which is low but not dangerously so. The curve of 50 per cent carboxyhaemoglobin is based on a total haemoglobin (incl. carboxyhaemoglobin) of 14·4 g./100 ml. The curve is interpolated from Roughton (1964). Assuming an arterial/venous oxygen content difference of 5 ml./100 ml., the venous* P_{O_2} *is only 14 mm Hg, a level which is dangerously low as it must be associated with a greatly reduced tissue* P_{O_2}. *Arterial* P_{O_2} *is assumed to be 100 mm Hg in all cases*

with haemoglobin is of the same order, but the rate of dissociation of carboxyhaemoglobin is extremely slow by comparison.

The Oxyhaemoglobin Dissociation Curve

Under specified conditions of temperature, pH and certain other factors, a certain P_{O_2} will always result in the same percentage saturation of haemoglobin. The relationship is constant for a particular type of haemoglobin but is

altered by changes in the sequence of amino acids in the protein part of the molecule (*Figure 118*). This diagram also shows the dissociation curve of myoglobin which differs from haemoglobin in having only one amino-acid chain and one haem group per molecule. It thus combines with only one molecule of oxygen. The familiar carboxyhaemoglobin dissociation curve is also shown but its precise form is greatly influenced by the Po_2.

Carbon monoxide is well known to displace oxygen from combination with haemoglobin, but it also displaces the dissociation curve of the remaining

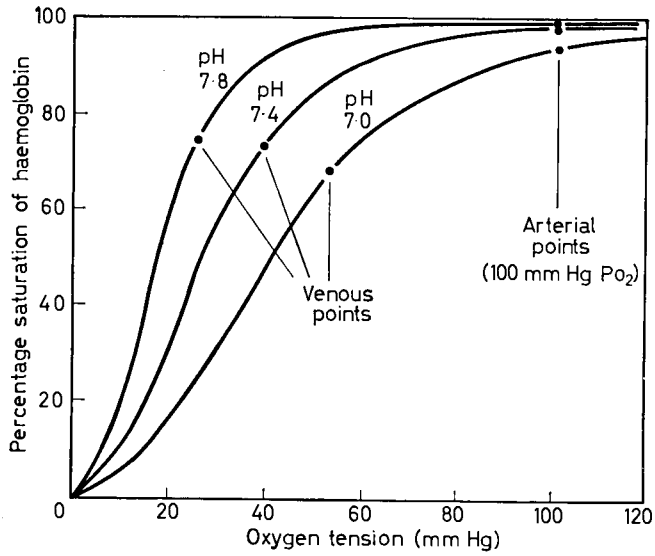


Figure 120. The Bohr effect and its effect upon oxygen tension. The centre curve is the normal curve under standard conditions; the other two curves show the displacement caused by the indicated changes in pH, other factors remaining constant. The venous points have been determined on the basis of a fixed arterial/venous oxygen saturation difference of 25 per cent in each case. They are thus 25 per cent saturation less than the corresponding arterial saturation which is equivalent to a Po_2 *of 100 mm Hg in each case. Under the conditions shown, alkalosis lowers venous* Po_2 *and acidosis raises venous* Po_2. *This effect is reversed in severe arterial hypoxaemia. Tissue* Po_2 *is related to venous* Po_2. *Temperature, 37°C; base excess, zero*

oxyhaemoglobin to the left. This is best shown in a plot of oxygen content against Po_2 (*Figure 119*), the values shown on the *Y* axis being the sum of dissolved and combined oxygen. The upper curve is for the normal concentration of haemoglobin. The lowest of the three curves applies to a patient with haemoglobin at half the normal concentration. At each Po_2, the oxygen content is approximately half that of the patient with a normal concentration of haemoglobin. The intermediate curve applies to blood with normal haemoglobin concentration but with half of the haemoglobin bound to carbon monoxide, resulting in a displacement of the dissociation curve of the remaining haemoglobin. It will be seen that, in comparison with the anaemic blood, this displacement has little effect on the volume of oxygen carried at the arterial point, provided that it is in excess of about 60 mm Hg. However, the effect on

the venous Po_2 after the unloading of oxygen in the tissues is very great. Assuming an arterial Po_2 of 100 mm Hg and an arterial/venous oxygen content

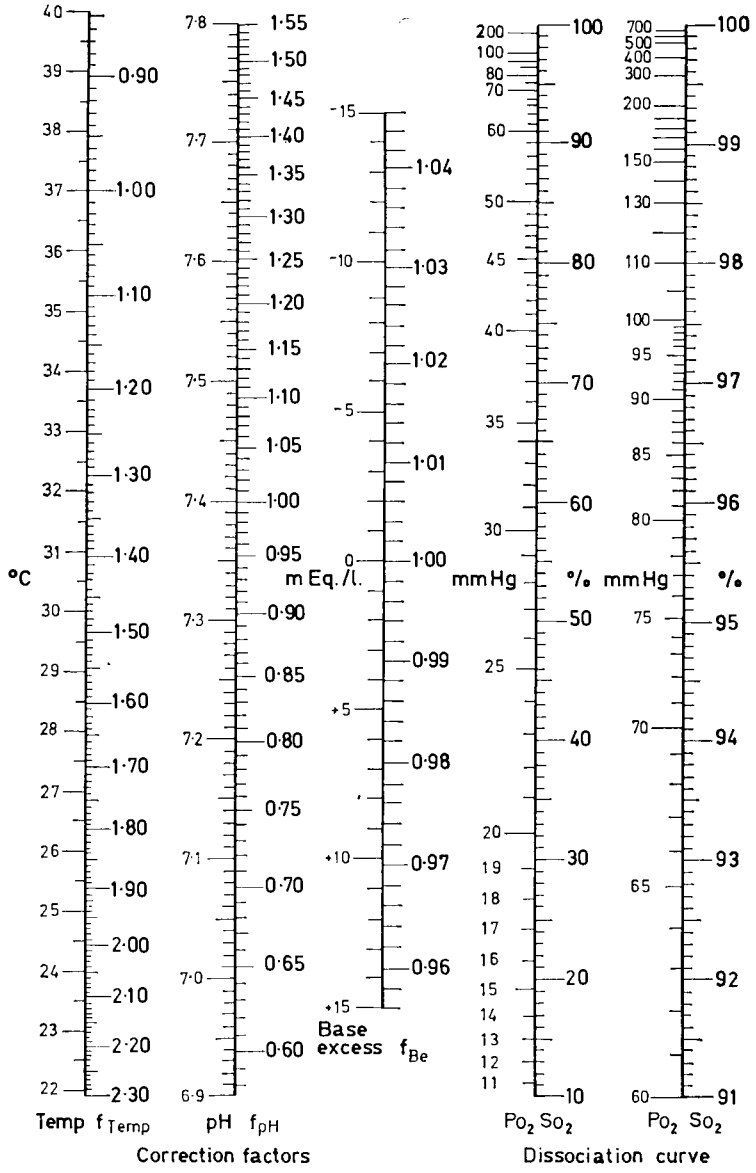


Figure 121. The standard oxyhaemoglobin dissociation curve with factors which displace it. The two right-hand line charts give corresponding values of Po_2 *and saturation for standard conditions (temperature, 37°C; pH, 7·40; base excess, zero). The remaining lines indicate the factors by which the actual measured* Po_2 *should be multiplied before entering the standard dissociation curve to determine the saturation. When more than one factor is required, they should be multiplied together as in the example given in the text. (Reproduced from Kelman and Nunn (1966b) by courtesy of the Editor of the* Journal of Applied Physiology)

difference of 5 vols. per cent, the venous point of the curve corresponds to a Po_2 of 14 mm Hg, a level which would be associated with an unacceptable reduction of tissue Po_2 (*see* page 360).

The Bohr effect.—Figure 120 shows the familiar Bohr effect which may be represented as the displacement of the dissociation curve by variations in pH. Respiratory acid–base changes have a somewhat greater effect upon the dissociation curve than do metabolic changes which result in the same change in pH. It is customary to calculate the effect due to a particular change of pH and then to apply a small correction for any metabolic acid–base disturbance which is present. Quantitatively, the displacement of the dissociation curve may be expressed as an 'apparent Po_2' which would produce the same saturation if pH were normal. For example, at pH 7·8, a Po_2 of 40 mm Hg produces the same saturation as a Po_2 of 62 mm Hg at 7·4. The 'apparent Po_2' is thus 62 mm Hg.

Since the effects of temperature, pH and the correction for acid–base disturbances are all similar, their influence on the dissociation curve may be considered simultaneously. The usual practice is to derive a factor for the influence of each and then to multiply them together. This combined factor is then multiplied by the observed Po_2 to give the apparent Po_2 which may be entered into the standard dissociation curve to indicate the saturation. The factors may be determined from the line charts in *Figure 121*; its use is illustrated by the following example.

	Factor
Blood temperature 33·7°C	1·20
Blood pH 7·08	0·70
Blood base excess −7 mEq./l.	1·02
Combined factor = 1·20 × 0·70 × 1·02 =	0·86
Observed Po_2 = 70 mm Hg;	
apparent Po_2 = 70 × 0·86 = 60 mm Hg	
Calculated saturation (from line chart) = 91 per cent	

This calculation may be expeditiously performed on the slide rule described by Severinghaus (1966). The factors are also incorporated in the digital computer subroutine described by Kelman (1966a) and feature in the tables produced by Kelman and Nunn (1968).

Clinical significance of the Bohr effect.—There is a good deal of confusion about the clinical significance of the Bohr effect. It is generally appreciated that a shift to the right (caused by low pH) impairs oxygenation in the lungs but aids release of oxygen in the tissue. However, there is often a failure to appreciate the over-all significance of these two effects in combination. It is essential to think in quantitative terms and an illustrative example is set out in *Figure 120*. The arterial Po_2 is assumed to be 100 mm Hg and arterial saturation is clearly decreased by a reduction of pH. However, the effect is small except when the arterial Po_2 is very low (less than about 60 mm Hg) or when the pH falls to extremely low values at normal Po_2 (Prys-Roberts, Smith and Nunn, 1967).

At the venous point the position is quite different, and the examples in *Figure 120* show the venous oxygen tensions to be very markedly affected. Assuming that the arterial/venous oxygen saturation difference is constant at

25 per cent, it will be seen that at low pH the venous Po_2 is raised to 52 mm Hg, while at high pH the venous Po_2 is reduced to 26 mm Hg. This is important as the tissue Po_2 is influenced directly by the venous Po_2. Over a wide range of conditions it will be found that a fall of pH will always raise the venous Po_2 provided other factors remain constant. In fact other factors are unlikely to remain constant, and both cerebral blood flow and cardiac output are likely to be increased by a moderate respiratory acidosis which would further tend to raise the venous and tissue Po_2. Thus, far from being universally harmful as is so often assumed, there seems no doubt that respiratory acidosis raises tissue Po_2, particularly in the brain. Of course, this is not the whole story and it would be equally wrong to believe that respiratory acidosis is universally beneficial. Considerable judgment and a good deal more research are necessary to indicate in what circumstances the condition of a patient may be improved by the deliberate induction of an acidosis or the avoidance of an alkalosis.

OXYGEN STORES AND THE STEADY STATE

It is a fact of the utmost importance that the body oxygen stores are meagre and, if replenishment ceases, are normally insufficient to sustain life for more than a few minutes. The principal stores are shown in *Table 35.*

Table 35

	While breathing air	*While breathing 100 % oxygen*
In the lungs (F.R.C.)	450 ml.	3,000 ml.
In the blood	850 ml.	950 ml.
Dissolved in tissue fluids	50 ml.	? 100 ml.
In combination with myoglobin	? 200 ml.	? 200 ml.
Total	1,550 ml.	4,250 ml.

While breathing air the total oxygen stores are small. To make matters worse, very little of this small store of oxygen can be released without an unacceptable reduction in Po_2. Reference to the dissociation curves in *Figure 118* shows that blood will not release substantial quantities of oxygen until the Po_2 falls below 40 mm Hg. Myoglobin is even more reluctant to part with its oxygen and very little can be released above a Po_2 of 20 mm Hg.

Breathing oxygen causes a substantial increase in total oxygen stores. Most of the additional oxygen is accommodated in the alveolar gas where 80 per cent of it may be withdrawn without causing the Po_2 to fall below the normal value. With 2,400 ml. of easily available oxygen, there is no difficulty in explaining why after breathing oxygen it is possible to hold one's breath for as long as eight minutes without becoming hypoxic.

The small size of the oxygen stores means that changes in factors affecting the alveolar or arterial Po_2 will produce their full effects very quickly after the change. This is in contrast to carbon dioxide where the size of the stores buffers the body against rapid changes. *Figure 122* shows the time course of changes in

P_{O_2} which may be expected to follow step changes in ventilation. These are rapid and may be contrasted with the gradual changes in P_{CO_2} produced by the same changes in ventilation. *Figure 104* showed how the time course of changes of P_{CO_2} was different for falling and rising P_{CO_2}.

Factors which reduce the P_{O_2} always act rapidly, but the following is the order of rapidity of changes which produce anoxia.

(1) *Circulatory arrest.* When the circulation is arrested, hypoxia supervenes as soon as the oxygen in the tissues and stagnant capillaries has been exhausted. In the case of the brain, with its high rate of oxygen consumption, there is a mere 10 seconds before consciousness is lost. If the eyeball is compressed to occlude its vessels, vision commences to be lost at the periphery within about six seconds (a convincing experiment which was suggested by Rahn, 1964).

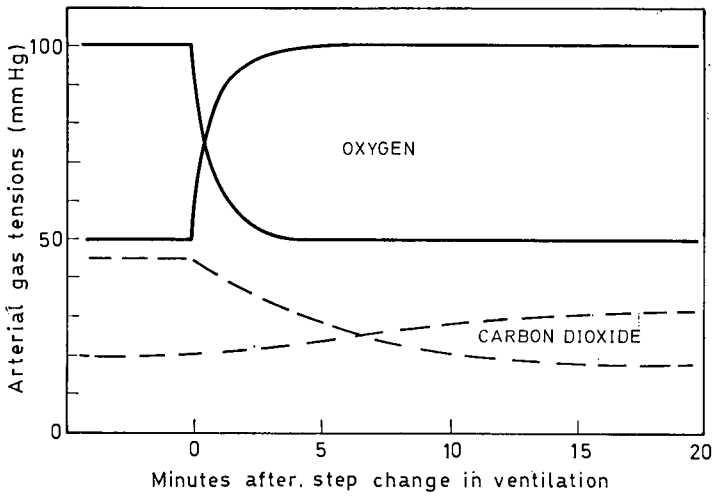


Figure 122. The upper pair of curves indicates the rate of change of arterial P_{O_2} *following step changes in ventilation. Half of the total change occurs in about 30 seconds. The rising curve could be produced by an increase of alveolar ventilation from 2 to 4 l./min. while breathing air* (see *Figure 111*). *The falling curve could result from the corresponding reduction of alveolar ventilation from 4 to 2 l./min. The lower pair of curves indicates the time course of changes in* P_{CO_2} *which are very much slower than for oxygen. These changes are shown in greater detail in Figure 104*

Circulatory arrest also differs from other forms of hypoxia in the failure of clearance of products of anaerobic metabolism (e.g. lactic acid) which is not a factor in simple arterial hypoxaemia. Resulting intracellular acidosis may well be an important factor in cerebral damage from stagnant hypoxia.

(2) *Exposure to a barometric pressure of less than 47 mm Hg.* At a pressure of less than 47 mm Hg, body fluids boil and alveolar gas is replaced with 100 per cent steam. The P_{O_2} rapidly falls to zero and consciousness is lost within one circulation time, which is of the order of 15 seconds (Ernsting and McHardy, 1960).

(3) *Inhalation of nitrogen.* Washing out the alveolar oxygen by hyperventilation with nitrogen results in a very rapid fall of arterial P_{O_2}, which reached

30 mm Hg in 30 seconds in a series of dogs (Cater and his colleagues, 1963). Even more rapid changes were obtained in human volunteers by Ernsting (1963).

(4) *Inhalation of nitrous oxide.* Alveolar wash-out with a soluble gas such as nitrous oxide would be expected to cause a slower fall of P_{O_2} because of the loss of the flushing gas into the tissues. This is, however, difficult to demonstrate as many variables are hard to control. Heller and Watson (1962) showed a precipitous descent of arterial P_{O_2} in one patient breathing 100 per cent nitrous oxide. A level of 24 mm Hg was reached after 30 seconds.

(5) *Apnoea.* The rate of onset of anoxia is dependent upon the initial alveolar P_{O_2} and the rate of oxygen consumption. It is, for example, more rapid while swimming underwater than while breath holding in the laboratory. Generally speaking, after breathing air, 90 seconds of apnoea results in a substantial fall of P_{O_2} to a level which threatens the subject with loss of consciousness. If a patient has previously inhaled oxygen, the arterial P_{O_2} should remain above 100 mm Hg for at least three minutes of apnoea (Heller and Watson, 1961), and this is the basis of the usual method of protection against hypoxia during the interference with ventilation which accompanies tracheal intubation. (If the patient is pre-oxygenated and then connected to a supply of oxygen while apnoeic, the arterial P_{O_2} is well maintained for a long time by the process of 'apnoeic mass-movement oxygenation'—*see* page 310.)

Since a steady state for oxygen is very rapidly attained, it follows that oxygen uptake is seldom appreciably different from oxygen consumption. Therefore measurement of oxygen uptake usually gives a satisfactory estimate of the oxygen consumption. In contrast, measured values of carbon dioxide output may be very different from the simultaneous level of carbon dioxide production if the ventilation is unsteady. During the irregular breathing of anaesthesia with spontaneous respiration, values for carbon dioxide output may range widely, while values for oxygen consumption are reasonably steady (Nunn and Matthews, 1959; Nunn, 1964).

For a fuller discussion of oxygen stores, the reader is referred to Farhi and Rahn (1955a), Farhi (1964) and Rahn (1964).

HYPOXIA

Definition of Hypoxia

In the case of hypercapnia, there is little difficulty in ascribing numerical values to the degree of hypercapnia. The arterial P_{CO_2} is normally considered to be an adequate index since the arterial/venous P_{CO_2} difference is seldom more than about 12 mm Hg and cellular, venous and arterial P_{CO_2} are thus close together, relative to the high values of arterial P_{CO_2} which occur in hypercapnia.

In the case of hypoxia, the position is different. Not only is the arterial/venous P_{O_2} difference much greater than the corresponding P_{CO_2} difference, but the absolute levels of P_{O_2} in hypoxia are lower than the corresponding levels of P_{CO_2} in hypercapnia. Therefore, differences in cellular, venous and arterial P_{O_2} are of great importance in any consideration of hypoxia. This is

particularly true in cases of pure 'stagnant hypoxia' where the arterial Po_2 may be normal.

An additional difficulty concerns the different measures of blood-oxygen level and there is some confusion as to whether tension, saturation or content is the most appropriate measure.

Hypoxia may be defined as a state in which aerobic metabolism is reduced by a fall of Po_2 within the mitochondria. There is a consequent reduction in available ATP and accumulation of products of anaerobic metabolism, both of which are detrimental to the function of the cell. The degree of hypoxia will vary from one organ to another so that the clinical diagnosis of hypoxia is usually related to the organ considered most vulnerable. This is usually the brain but in special circumstances may be heart, kidney, liver or a limb.

Cellular Po_2 is the starting point for quantitative consideration of hypoxia. Oxidative phosphorylation to form ATP occurs in the mitochondria and will continue down to a Po_2 of about 1 mm Hg (page 332). Po_2 gradients within the cell are considered on page 284, and there is reason to believe that neurones will no longer function when the Po_2 at their surface is reduced below about 20 mm Hg. Po_2 varies from one cell to another and is also different in different parts of the same cell. There are therefore insuperable difficulties in defining or measuring 'the tissue Po_2'.

Venous Po_2 is a more feasible measurement than cellular Po_2, and the venous Po_2 approximates to the mean Po_2 at the surface of the cells in the region drained by the venous blood.* Some cells close to the arterial end of the capillaries will have a higher Po_2 while others lying between the venous end of two or more capillaries will have a lower Po_2 (*Figure 93*). Nevertheless, the venous Po_2 is a useful practicable measure of the oxygenation of an organ, and consciousness is lost when the internal jugular venous Po_2 falls below about 20 mm Hg (McDowell, personal communication).

Lowest tolerable level of arterial Po_2.—It is now interesting to extend this argument and consider in what circumstances the venous Po_2 may fall below the critical level of 20 mm Hg, which in normal blood corresponds to 32 per cent saturation and about 6·4 ml./100 ml. oxygen content. If the brain has an oxygen consumption of 46 ml./min. and a blood flow of 620 ml./min., it follows that the arterial/venous oxygen content difference is about 7·4 ml./100 ml. We may then say that, *under these conditions and so far as the brain is concerned*, an arterial oxygen content of 13·8 ml./100 ml. is the minimum which will avoid cerebral hypoxia. It is a simple matter to show that with normal haemoglobin concentration, pH, etc., this would correspond to a saturation of 68 per cent and an arterial Po_2 of 36 mm Hg. This calculation and others under various different conditions are set out in *Table 36*.

The calculation which has just been made leads to the conclusion that an arterial Po_2 of less than 36 mm Hg would result in cerebral hypoxia, *if all other factors remained normal*. The major difficulties arise from the last clause.

* The significance of the venous Po_2 is lost when there are shunts which permit arterial blood to mix with blood draining the tissue. However, significant shunts do not occur in the organs which are most vulnerable to hypoxia.

Other factors may not be normal but may be unfavourable as a result of multiple disability in the patient (e.g. anaemia combined with a low cerebral blood flow). Alternatively, other factors may be favourably influenced by the powerful homeostatic mechanisms which exist to protect the brain from hypoxia. These include the polycythaemia of chronic arterial hypoxaemia, increased cerebral blood flow in anaemia and the vasopressor response to cerebral hypoxia. Cerebral vascular resistance is diminished by reduced arterial blood pressure and arterial hypoxaemia.

Table 36

Lowest arterial oxygen levels compatible with a cerebral venous Po_2 *of 20 mm Hg under various conditions*

	Blood O_2 *capacity (ml./100 ml.)*	*Brain* O_2 *consump. (ml./min.)*	*Cerebral blood flow (ml./min.)*	*Cerebral venous blood*			*Art./ven.* O_2 *content difference (ml./100 ml.)*	*Arterial blood*		
				Po_2 *(mm Hg)*	*Sat. (%)*	O_2 *content (ml./100 ml.)*		O_2 *content (ml./100 ml.)*	*Sat. (%)*	Po_2 *(mm Hg)*
Normal values	20	46	620	33	63	12·6	7·4	20·0	97·5	100
Uncompensated arterial hypoxaemia	20	46	620	20	32	6·4	7·4	13·8	68	36
Arterial hypoxaemia with increased cer. blood flow	20	46	1,240	20	32	6·4	3·7	10·1	50	27
Arterial hypoxaemia with polycythaemia	25	46	620	20	32	8·0	7·4	15·4	61	32
Arterial hypoxaemia with alkalosis*	20	46	620	20	46	9·2	7·4	16·6	82	37
Arterial hypoxaemia with hypothermia†	20	23	620	20	57	11·4	3·7	15·1	75	27
Uncompensated cerebral ischaemia	20	46	340	20	32	6·4	13·5	19·9	98	112
Uncompensated anaemia	12	46	620	20	32	3·8	7·4	11·2	93	67
Anaemia with increased cer. blood flow	12	46	870	20	32	3·8	5·3	9·1	75	40
Combined anaemia and ischaemia	15	46	460	20	32	4·8	10·0	14·8	97	92

* pH 7·6 † temp. 30° C; cerebral O_2 consumption reduced to half normal

The possible combinations of conditions are so great that it is not feasible to discuss every possible situation. Instead, certain important examples have been selected which illustrate the fundamentals of the problem, and these have been set out in *Table 36*. Further consideration of *arterial hypoxaemia* shows that a twofold increase of cerebral blood flow would permit a further fall of arterial Po_2 to 27 mm Hg before the cerebral venous Po_2 reached 20 mm Hg. This is important as an increase in cerebral blood flow may be expected to follow

severe hypoxia. Polycythaemia (haemoglobin concentration of about 18 g./100 ml.) does not confer the same degree of benefit and the lower limit of arterial Po_2 would then be 32 mm Hg. Alkalosis, which may be expected to result from the hypoxic drive to respiration, confers no advantage at all. Considerable advantage derives from hypothermia but this is all due to the reduction in cerebral metabolism, and not at all to the shift of the dissociation curve.

Uncompensated *ischaemia* is seen to be dangerous, and a 45 per cent reduction in cerebral blood flow means that the arterial Po_2 cannot fall below the normal value without exposing the brain to risk of hypoxia. Uncompensated *anaemia* is almost equally dangerous, although an increase in cerebral blood flow restores a satisfactory safety margin. In the example in *Table 36*, a 40 per cent reduction of blood oxygen capacity and a 40 per cent increase of cerebral blood flow permits the arterial Po_2 to fall to 40 mm Hg without the cerebral venous Po_2 falling below 20 mm Hg, a situation which is close to that which applies in uncomplicated arterial hypoxaemia. The last line in *Table 36* shows the very dangerous combination of anaemia and ischaemia. In this example the haemoglobin concentration is reduced to about 11 g./100 ml. and the cerebral blood flow to three-quarters of the normal value. Neither abnormality is very serious considered separately, but in combination the arterial Po_2 cannot be reduced below 92 mm Hg without the cerebral venous Po_2 falling below 20 mm Hg.

This table must not be taken too literally. There are many minor factors which have not been considered and it appears that maximal cerebral vasodilatation may be expected to occur in any condition which threatens cerebral oxygenation. We must also bear in mind that there may be circumstances in which the critical organ is not the brain but the heart, liver or kidney. However, the message of *Table 36* is that there is no simple answer to the question 'What is the safe lower limit of arterial Po_2?'. We may say that, in an otherwise normal patient who is able to respond with cerebral vasodilatation, the lowest tolerable arterial Po_2 would appear to be about 27 mm Hg. This figure accords with the fact that men have remained conscious while breathing air on the summit of Everest where the alveolar Po_2 may be calculated to be about 28 mm Hg with the arterial Po_2 a few millimetres of mercury lower. Patients presenting with severe respiratory disease who are still conscious while breathing air tend to have a lower limit of arterial Po_2 of about 20 mm Hg (Refsum, 1963; McNicol and Campbell, 1965). Such patients would have compensatory polycythaemia and maximal cerebral vasodilatation.

Questions of fitness for surgery and anaesthesia in the presence of disorders of factors influencing oxygen flux cannot be decided in isolation but must be answered after considering the patient as a whole, and in the light of the additional disturbances which may be expected to result from operation and anaesthesia.

Compensatory Mechanisms in Hypoxia

Hypoxia presents a serious threat to the body and vigorous compensatory mechanisms come into play. These mechanisms are usually robust and not easily impaired by drugs or disease. Where they conflict with other mechanisms acting in the opposite direction, the compensation for hypoxia is usually dominant. Thus, for example, in hypoxia with concomitant hypocapnia, hyperventilation and increase of cerebral blood flow occur in spite of the lowered

P_{CO_2} (Turner and his colleagues, 1957). Certain compensatory mechanisms will come into play whatever the reason for the hypoxia, although their effectiveness will depend to a large extent upon its actual cause. For example, hyperventilation will be largely ineffective in stagnant hypoxia since hyperventilation while breathing air can do little to increase the oxygen content of the arterial blood, and usually nothing to increase perfusion.

Hyperventilation results from a fall of arterial P_{O_2} but the response is non-linear (page 31). Moderate falls of arterial P_{O_2} below the normal level have little effect, but falls below 50 mm Hg cause a marked increase which becomes maximal at about 25 mm Hg. The inter-relationship between hypoxia and other factors in the control of breathing is discussed in Chapter 2.

Pulmonary distribution of blood flow is improved by hypoxia as a result of the increase in pulmonary artery pressure (page 216).

Cardiac output is increased by hypoxia together with the regional blood flow to almost every major organ, particularly the brain (Cohen and his colleagues, 1967).

Haemoglobin concentration is not increased by acute hypoxia in man, although it is elevated by chronic hypoxia due to residence at altitude, chronic respiratory disease, etc.

Autonomic system is concerned in many of the responses to hypoxia. The immediate response of cardiac output is reflex and is initiated by the chemoreceptors: it occurs before there has been any measurable rise in circulating catecholamines. The reduction of cerebral and probably the myocardial vascular resistance is not dependent upon circulating catecholamines or on autonomic innervation. The effect appears to be due to a local response within the vessels themselves. Nevertheless, catecholamine levels are raised in due course.

Anaerobic metabolism is increased in severe hypoxia in an attempt to maintain the production of ATP. This may be detected by an increase in arterial/venous excess lactate difference. Attempts have been made to use this as an index of hypoxia but results have been disappointing (Price and his colleagues, 1966). In the case of the brain, lactate may be retained within the neurones, causing a delay in the rise of the venous lactate level.

Organ Survival Times

Lack of oxygen stops the machine and, if prolonged, wrecks the machinery. The time of circulatory arrest up to the first event (the survival time) must be distinguished from the duration of anoxia which results in the second event (the revival time), the latter being defined as the time beyond which no recovery of function is possible. Anoxia lasting more than the survival time but less than the revival time may result in prolonged impairment of function during recovery (Graham, 1961).

Survival times depend upon many factors. There is a pronounced difference between different organs, ranging from less than a minute for the cerebral cortex to about two hours for skeletal muscle. Heart is intermediate with a survival time of about five minutes, liver and kidney probably being about ten

minutes. Revival times tend to be about four times as long as survival times but the ratio is greater in the case of the brain which has a revival time of the order of five minutes.

Apart from the inherent differences in sensitivity of organs, survival time is influenced by oxygen consumption and oxygen stores in the tissue. An inactive organ (such as a heart in asystole or an anaesthetized brain) has increased resistance to hypoxia (Wilhjelm, 1966) and there is a small but definite increase in survival time after hyperbaric oxygenation. Hypothermia decreases oxygen demand and increases oxygen storage in physical solution. Both factors, particularly the former, increase resistance to hypoxia.

Cerebral resistance to hypoxia is markedly influenced by the accumulation of metabolites such as lactic acid, produced by anaerobic metabolism under conditions of hypoxia. The fall in intracellular pH is probably no less important than the energy deprivation and seems to be associated with the tissue oedema which follows anoxia. When anoxia follows chronic hypoxia, there is, surprisingly, less evidence of cell damage than in acute anoxia. It is thought that this is due to the reduction in lactic acid formation, owing to glucose depletion during the period of chronic hypoxaemia (Lindenberg, 1963; Geddes, 1967). A comparison of available energy from anaerobic and aerobic metabolism (page 327) shows that a nineteenfold increase in glucose consumption is required in anoxia. This quantity of glucose cannot enter neurones, which therefore suffer energy depletion and reduction of intracellular glucose concentration during hypoxia.

Survival of an organ after anoxia depends on many secondary factors which influence oxygen transport during the recovery phase. If the heart has been severely affected in generalized hypoxaemia, there may be a depression of function during recovery which will diminish oxygen transport to other organs. Tissue oedema, particularly in the brain, may decrease the local perfusion and oxygen transport for a considerable time during recovery.

HYPEROXIA

Extreme hyperventilation, while breathing air, may raise the arterial Po_2 to about 120 mm Hg. Higher levels can only be obtained by oxygen-enrichment of the inspired gas, or by elevation of the ambient pressure. Although by this means, the arterial Po_2 can be raised to very high figures, the increase in arterial oxygen *content* is, in the normal subject, quite small being largely restricted to the fraction in physical solution (*Table 37*). Provided that the arterial/venous oxygen content difference remains constant, it follows that the increase in venous oxygen content is the same as that of the arterial blood. This means that, with a normal arterial/venous oxygen content difference, the venous blood will not become fully saturated during the inhalation of 100 per cent oxygen until the pressure is elevated to more than 2 atmospheres absolute. Unless the venous blood is more than about 97 per cent saturated, the rise in venous Po_2 is not at all spectacular (*Table 37*). Since the tissue Po_2 is related to the venous Po_2, it follows that the tissue Po_2 is not raised to anything like the extent of the arterial Po_2 during oxygen therapy at normal and raised barometric pressure.

It is convenient to consider two degrees of hyperoxia. The first ranges from

normal levels up to a Po_2 of inspired gas of one atmosphere. This may be attained either by the inhalation of 100 per cent oxygen at normal barometric pressure or by the inhalation of air at 5 atmospheres absolute pressure. The second degree ranges above an inspired gas Po_2 of one atmosphere and may be attained by the inhalation of 100 per cent oxygen at pressure in excess of one atmosphere. This is currently being evaluated for therapeutic purposes under the term 'hyperbaric oxygenation'. Comparable values of Po_2 may be obtained by breathing air at pressures in excess of 5 atmospheres absolute.

Table 37

Oxygen levels attained in the normal subject by changes in the oxygen tension of the inspired gas

	At normal barometric pressure		*At 2 atm. absolute*	*At 3 atm. absolute*
Inspired gas	Air	Oxygen	Oxygen	Oxygen
Inspired gas Po_2 (humidified) (mm Hg)	150	713	1,426	2,139
Arterial Po_2* (mm Hg)	100	600	1,313	2,026
Arterial oxygen content† (ml./100 ml.)	19·3	21·3	23·4	25·5
Arterial/venous oxygen content difference (ml./100 ml.)	5·0	5·0	5·0	5·0
Venous oxygen content (ml./100 ml.)	14·3	16·3	18·4	20·5
Venous Po_2 (mm Hg)	39	48	68	360

(Tissue perfusion may be reduced by elevation of Po_2. This tends to increase the arterial/venous oxygen content difference which will limit the rise in venous Po_2. The increases in venous Po_2 shown in this table will therefore be too great in certain circumstances.)

* Reasonable values have been assumed for Pco_2 and alveolar/arterial Po_2 difference.

† Normal values are assumed for Hb, pH, etc.

Hyperoxia produced by Oxygen-enrichment of Inspired Gas at Normal Barometric Pressure

Indications

The commonest indications for oxygen-enrichment of inspired gas are the prevention of arterial hypoxaemia caused either by hypoventilation or by venous admixture. However, oxygen-enrichment may also be used to mitigate the effects of ischaemia or anaemia (stagnant and anaemic hypoxia). Additional specific indications are clearance of gas loculi and the treatment of carbon monoxide poisoning.

Stagnant anoxia can be marginally relieved by the inhalation of oxygen, which will elevate the oxygen content of the arterial blood to the extent shown in *Table 37*. The Po_2 increase is impressive but the content change is small. However, before dismissing oxygen therapy for stagnant hypoxia, it should be remembered that the improvement in oxygen flux may be critical and may result in significant improvement of myocardial function. Freeman (1962) has demonstrated reduction of mortality in critically bled dogs following the administration of oxygen. Possible modes of action were explored by Freeman and Nunn (1963). Definitive treatment should, of course, be aimed at improving the circulation.

Anaemic hypoxia can be relieved by oxygen therapy for the reasons outlined above. However, since the combined oxygen is less than in the normal subject,

the effect of the additional oxygen carried in solution will be relatively more important.

Clearance of gas loculi in the body may be greatly accelerated by inhalation of 100 per cent oxygen which may also be considered as denitrogenation. The principle of this form of therapy depends upon the reduction of the total tension of the dissolved gases in the venous blood. This results in the blood draining the tissues having surplus capacity to carry away gas dissolved from the loculi within the area of venous drainage. In the normal subject breathing air, the total gas tensions in venous blood are always about 50 mm Hg less than in the arterial blood since the arterial/venous P_{O_2} fall is about ten times greater than the corresponding P_{CO_2} rise:

	Arterial blood	*Venous blood*
P_{O_2} (mm Hg)	100	40
P_{CO_2} (mm Hg)	40	46
P_{N_2} (mm Hg)	570	570
Total gas tensions	710	656

It is of the utmost importance that the venous blood should have a total gas tension which is subatmospheric. This means that there is always capacity to dissolve away a gas loculus and ensures that all potential spaces in the body remain empty and can even sustain a pressure below atmospheric. The importance of this in the pleural 'cavity' has already been stressed (page 46).

When a subject breathes 100 per cent oxygen, the difference between the total gas tensions of arterial and venous blood becomes even greater:

	Arterial blood	*Venous blood*
P_{O_2} (mm Hg)	600	50 (*see Table 37*)
P_{CO_2} (mm Hg)	40	46
P_{N_2} (mm Hg)	0	0
Total gas tensions	640	96

The total gas tension of the venous blood is now very markedly subatmospheric and the venous blood has a greatly increased capacity to dissolve gas which is lying in loculi.

The use of oxygen to remove gas is indicated after air embolus. It may also be used to ease intestinal gas pressure in patients with intestinal obstruction, to hasten recovery from pneumoencephalography and to aid absorption of pneumoperitoneum and pneumothorax.

Carbon monoxide poisoning has long been recognized as a most important indication for oxygen therapy. Not only is the oxygen content of the arterial blood improved, but the clearance rate of carboxyhaemoglobin is accelerated (Sharp, Ledingham and Norman, 1962).

Dangers Associated with the Inhalation of 100 per cent Oxygen

Ventilatory depression may occur in those patients who, by reason of drugs or disease, have been ventilating in response to hypoxic drive. Ventilatory depression resulting from removal of hypoxic drive cannot produce hypoxia,

but there is a danger of hypercapnia which may induce coma (Donald and Paton, 1955). Since this complication was first described there has been a certain tendency to avoid oxygen therapy for fear of hypercapnia. However, the dangers of hypoxia are much greater than the dangers of hypercapnia. Therefore, oxygen therapy should never be withheld because of the danger of causing ventilatory depression. The correct procedure is to give oxygen therapy and to treat any consequent ventilatory depression if and when it occurs.

It is important to remember that a patient inhaling a high concentration of oxygen may suffer a gross reduction of ventilation without becoming hypoxic, although the P_{CO_2} must inevitably rise. In the example shown in *Figure 51*, if the patient inhales 40 per cent oxygen, the alveolar P_{O_2} will still be 100 mm Hg when the alveolar ventilation has fallen to 800 ml./min. There will be no hypoxia and no cyanosis but, at that ventilation, the P_{CO_2} may be expected to rise to 150 mm Hg. Therefore, all patients breathing spontaneously during oxygen therapy must be watched carefully for signs of ventilatory depression: absence of cyanosis affords no guarantee that the ventilation is satisfactory.

Pulmonary collapse must result if a section of the lung is filled with oxygen and then subjected to airway obstruction. The pulmonary arterial blood, which is almost always less than 80 per cent saturated, removes oxygen from the sequestered section of lung in accord with a P_{O_2} gradient from alveolus to pulmonary arterial blood which may amount to many hundreds of millimetres of mercury. Such a pressure gradient is of the order of that required to inflate a bicycle tyre and the lung tissues cannot withstand the absorption of oxygen without collapse.

This phenomenon may be demonstrated in the normal subject by breathing at minimum lung volume after pre-oxygenation of the lungs. When the lung volume is close to residual volume there is widespread closure of airways (*Figure 13*) and extensive collapse occurs within ten minutes (Nunn and his colleagues, 1965b). The same changes occur when pilots breathing 100 per cent oxygen are exposed to high gravitational forces. The discovery of post-flight lung collapse by Ernsting (1960) led to the introduction of an appropriate amount of nitrogen in the oxygen mixtures breathed at high altitude. Collapse of this type would be expected in American astronauts who, in the early flights, inhaled 100 per cent oxygen at low pressures in the presence of exceptionally high gravitational forces. Surprisingly, their chest x-rays have been normal after landing and this is perhaps a testimony to the fitness of the astronauts.

There is still some uncertainty about the extent of the danger of absorption collapse while breathing oxygen at normal lung volumes. The calculated shunt does not appear to be markedly different for anaesthetized patients who breathe oxygen, oxygen/nitrous oxide, or oxygen/nitrogen mixtures (Nunn, 1964; Webb and Nunn, 1967). Furthermore, mice have lived for nearly two months in an atmosphere of pure oxygen, behaving normally and producing normal offspring (MacHattie and Rahn, 1960). However, in the present state of knowledge there would appear to be a risk of collapse for patients breathing oxygen if they should undergo an expiratory coughing spasm or else suffer a regional airway obstruction.

The Lorrain-Smith effect refers to pulmonary damage caused by exposure of the lung tissue to excessively high oxygen tensions. It has been shown above that venous blood and systemic tissues do not normally attain a high Po_2 during the inhalation of 100 per cent oxygen. However, pulmonary tissue differs from all others in being exposed to the full Po_2 of the inspired gas. Pulmonary damage can be produced in certain animals but clear evidence of the Lorrain-Smith effect in man is lacking. Some subjects report substernal pain but the absence of changes in astronauts is convincing evidence of the lack of serious effects in man. Reports of effects of oxygen upon the respiratory tract have been reviewed by Lambertsen (1965). It should perhaps be emphasized that considerable discomfort results from prolonged inhalation of dry gas and in many experiments there has been a failure to humidify oxygen supplied from a cylinder.

Retrolental fibroplasia consists of vascular obliteration and fibroblastic infiltration in the retina, and only occurs in neonates who have been hyperoxygenated (Patz, 1958). The condition does not contra-indicate the use of oxygen in the neonate but care must be exercised to prevent the Po_2 rising higher than is necessary.

Fire risk is enormously increased when inflammable material is exposed to an atmosphere of oxygen (Denison, Ernsting and Cresswell, 1966).

The dangers of oxygen which have been described above apply to patients who are anaesthetized with inhalational agents, such as halothane and/or cyclopropane, carried in very high concentrations of oxygen. An additional disadvantage of such techniques is that it excludes the use of nitrous oxide which many regard as a useful anaesthetic agent. These are the prices which must be paid for the virtual guarantee of oxygenation afforded by the use of near-100 per cent concentrations of oxygen.

Hyperoxia with Po_2 in Excess of One Atmosphere Absolute

Oxygen tensions in excess of 1 atmosphere may be obtained by the use of 100 per cent oxygen at pressures in excess of 1 atmosphere. Alternatively, lower concentrations of oxygen may be employed at proportionately higher pressures. The special features of hyperbaric oxygenation are as follows.

(1) Arterial Po_2 values reach very high values in excess of 1,000 mm Hg.
(2) Pulmonary tissue Po_2 presumably reaches levels of the same order as those of the alveolar gas.
(3) In contrast to the inhalation of oxygen at 1 atmosphere, hyperbaric oxygenation results in a steep rise of venous and tissue Po_2 (*Table 37*).

Biochemical Effects of Very High Tissue Po_2

Paul Bert (1878) first showed that oxygen was a toxic substance to 'every living thing', although the Po_2 at which toxic effects become manifest is now known to vary widely, being low in anaerobic bacteria and high in human lung tissue. The mode of action of toxicity of oxygen in tissues is complex and the interference with metabolism seems to be widespread. Firstly, there is undoubted inactivation of many enzymes, particularly those with sulphydryl

(—SH) groups. The effects of enzyme inactivation are probably associated with the decrease in oxygen consumption of tissue homogenates which can be shown when the Po_2 is raised (Davies and Davies, 1965).

It also appears that the brain content of gamma-aminobutyric acid is diminished in intact animals exposed to high pressures of oxygen. Furthermore, administration of gamma-aminobutyric acid was found to confer protection from oxygen convulsions (Haugaard, 1964).

Finally, there is a radiomimetic effect of oxygen which interferes with formation of deoxyribonucleic acid (DNA) and synthesis of protein (Gerschman, 1964). It has been postulated that both ionizing radiations and oxygen at high Po_2 have a common action in the formation of oxidizing free radicals which cause similar tissue damage regardless of their origin. Catalase plays an important part in decomposing these radicals. It is deficient in those organisms which are most sensitive to the toxic effects of oxygen. The effects of oxygen and radiation are additive and it is well known that the biological effects of radiation are increased at high Po_2. This is important in radiotherapy since cancer cells often outgrow their blood vessels and so become necrotic and attain a low Po_2. This confers considerable radioprotection in comparison with host cells which are at a higher Po_2 (Gray and his colleagues, 1953). It is believed that this effect is a major factor militating against the success of radiotherapy, and efforts to circumvent it include the use of hyperbaric oxygenation (*see* below), attempts to reduce the Po_2 of the host (Cater and his colleagues, 1963), and investigations of the effects of anaesthetic agents in abolishing the radioprotective effect of anoxia (Ebert and Hornsey, 1958).

In any consideration of hyperbaric oxygenation it is important to think in terms of the Po_2 of the tissues. It is easy to think that, because a patient has an arterial Po_2 of 1,400 mm Hg, the tissue Po_2 must also be very high. In fact the simple calculations shown in *Table 37*, supported by experimental observations, show that large rises of venous (and presumably tissue) Po_2 do not occur until the Po_2 of the arterial blood is of the order of 2,000 mm Hg, and the whole of the tissue oxygen requirement can be met from dissolved oxygen. The situation varies from one tissue to another depending upon their oxygen extraction.

An interesting effect of hyperbaric oxygenation is the effect upon carriage of carbon dioxide in the blood. If the dissolved oxygen in the arterial blood is sufficient for the tissue requirements, it follows that the venous blood will contain a negligible quantity of reduced haemoglobin (Gessell, 1923). This causes a marked reduction of buffering power and carbamino carriage. It seems likely that this will result in some tissue retention of carbon dioxide although the elevation of Pco_2 is not likely to exceed about 7 mm Hg. In the brain this may increase cerebral blood flow and lead to a secondary rise of tissue Po_2.

Special Hazards of Hyperbaric Oxygenation

The most important toxic effect of oxygen in man is the convulsive effect which occurs during exposure to pressures in excess of 2 atmospheres absolute. This effect is known after Paul Bert who first described it. Its cause is still unknown although it is thought to result from interference with enzyme systems, and convulsions are encountered under conditions in which the tissue Po_2 rises steeply. The fact that more than 2 atmospheres of oxygen is required

accords with the relationship to tissue Po_2 shown in *Table 37*. Further evidence is the effect of an elevation of Pco_2 which diminishes the arterial Po_2 at which convulsions occur (Lambertsen, 1965). This, no doubt, results from the increase in cerebral blood flow which would reduce the difference between arterial and cerebral tissue Po_2.

The possibility of oxygen convulsions may be reduced by general anaesthesia and by hyperventilation. The onset of convulsions is variable ranging from 2 to 30 minutes at 3 atmospheres absolute. When a patient with normal arterial blood oxygenation is exposed to high pressures of oxygen (in excess of 3 atmospheres) it is usual to employ general anaesthesia. Others, however, have relied on curtailing the duration of exposure.

Many of the untoward effects associated with the use of hyperbaric oxygenation are due to the elevation of ambient pressure and are not related to oxygen at all. These effects are common to the circumstances of compressed-air working and include bends, ruptured air cysts (Walder, 1965) and avascular necrosis of bone (Davidson, 1965). Oxygen bends are very rare but have been described in goats (Donald, 1955).

It should also be remembered that patients in caissons are, to a greater or lesser extent, isolated from the normal facilities of a hospital. This reaches its greatest extent in one-man tanks which prevent the possibility of nursing or emergency medical attention. Access may depend on emergency decompression but there are certain patients who cannot be safely subjected to this procedure.

Clinical Applications of Hyperbaric Oxygenation which are under Evaluation

Space does not permit a full discussion of the difficult problem of the role of hyperbaric oxygenation in clinical medicine. Many of the factors have been presented in the last few pages but theory can only point the way to controlled clinical trials from which clear answers will probably not emerge for many years.

Prolongation of safe period of circulatory arrest would appear at first sight to be an obvious benefit to be expected from hyperbaric oxygenation. In fact, results have been very disappointing at normal temperature although somewhat better during hypothermia (Ledingham and Norman, 1965). *Table 37* shows that tissue Po_2 is not likely to be greatly increased by pressures up to 2 atmospheres absolute and therefore there is little additional stored oxygen dissolved in tissue fluids. However, during hypothermia, not only is the oxygen consumption decreased but the solubility of oxygen in tissue fluids is increased.

Symptomatic treatment of patients with gross shunts is not possible at atmospheric pressure when the shunt exceeds about 40 per cent of cardiac output. *Figure 116* shows that the administration of 100 per cent oxygen does very little to raise the arterial Po_2 in such cases. However, administration of high pressures of oxygen will restore normal arterial Po_2 up to a shunt of 50 per cent, as shown in *Table 38.*

Hypoxia due to hypoperfusion can be relieved by hyperbaric oxygenation provided that the perfusion is only marginally inadequate, since the small amount of additional oxygen carried in blood cannot compensate for a gross inadequacy

of circulation. In an organ suffering from partial ischaemia, the zone of surviving tissue may be enlarged. Satisfactory results have been obtained in experimental ligation of the left circumflex coronary artery in dogs (Smith and Lawson, 1958). Satisfactory protection has also been obtained during diffuse embolization of the coronary arteries of dogs at 3 atmospheres of oxygen (Jacobson and his colleagues, 1965). However, evidence of satisfactory results in clinical myocardial infarction has remained elusive (Cameron and his colleagues, 1965).

Table 38

Oxygen levels with 50 per cent shunt

Oxygen at:	*Pulmonary end-capillary blood*		*Arterial blood*		*Mixed venous blood*	
	Po_2 *(mm Hg)*	O_2 *content (ml./100 ml.)*	Po_2 *(mm Hg)*	O_2 *content (ml./100 ml.)*	Po_2 *(mm Hg)*	O_2 *content (ml./100 ml.)*
1 atm. abs.*	600	21	47	16	30	11
2 atm. abs.*	1,300	23	62	18	35	13
3 atm. abs.*	2,000	25	200	20	42	15

* The pressure in atmospheres absolute is equal to the sum of the barometric pressure and the gauge pressure (which shows the difference between the chamber pressure and the atmosphere). It is very important to distinguish clearly between absolute and gauge pressure since both scales are in routine use in different laboratories.

Isolated case histories have been reported of patients with cerebral ischaemia who have recovered consciousness during hyperbaric oxygenation. Improvement has been temporary and sustained recovery has not been reported (Ingvar, 1965).

There is a clinical impression that partially severed limbs have been saved with hyperbaric oxygenation at 2 atmospheres absolute, the remaining blood flow presumably being just insufficient to maintain life with conventional oxygen therapy. Such cases are rare but have been described (Smith and his colleagues, 1961). The value of such therapy would be lost if perfusion were to be reduced by the elevated Po_2. Mortality from haemorrhagic shock is reduced by hyperbaric oxygenation (Attar, Scanlan and Cowley, 1966).

Infection offers a promising field for the application of hyperbaric oxygenation. Good results have been claimed with anaerobic infections (Brummelkamp, 1965). Pulmonary infections also appear suitable for investigation since very high tissue Po_2 can be attained in the lung (Ross and McAllister, 1965).

Radiotherapy has been employed under conditions of hyperbaric oxygenation since 1955, the rationale being based on the influence of Po_2 on tissue radiosensitivity (*see* above). Technique has recently been reviewed by Foster (1965) but evidence of improved results in controlled trials is still awaited.

Carbon monoxide poisoning may be treated more effectively with oxygen at high pressure (Sharp, Ledingham and Norman, 1962). However, its clinical value will be maximal when hyperbaric facilities are unlikely to be available. This

consideration has led to interest in the possibility of mounting small chambers in ambulances (Williams and Hopkinson, 1965).

THE 'NORMAL' ARTERIAL OXYGEN TENSION

The arterial P_{CO_2} does not show any systematic change with age and, in healthy subjects, shows very little scatter, the standard deviation being of the order of 4 mm Hg (Raine and Bishop, 1963). In contrast, the arterial P_{O_2} shows a progressive decline with age and, for a particular age group, the standard deviation is about double that for P_{CO_2}.

It seems likely that some of the scatter of values for P_{O_2} is due to transient changes in ventilation, perhaps associated with arterial puncture. Because of the small body oxygen stores, such changes have a greater effect on P_{O_2} than on P_{CO_2}.

Values for arterial P_{O_2} within the range 70–110 mm Hg are commonly reported in healthy subjects breathing air, but recognition of the influence of age permits greater precision in the definition of normal values for particular age groups. *Table 39* is representative of the data of Raine and Bishop (1963), Loew and Thews (1962), Ulmer and Reichel (1963) and Marshall and Millar (1965).

Table 39

Age (years)	*Arterial* P_{O_2} *(mm Hg)*	
	Mean	*Range*
20–29	95	80–110
30–39	90	78–108
40–49	86	75–104
50–59	82	71–100
60–69	78	67–95

When breathing oxygen the most important factor causing scatter of values for arterial P_{O_2} is failure to exclude air from the breathing system. Provided that great care is taken to prevent dilution with air, very high values of arterial P_{O_2} may be obtained. A number of studies of normal conscious subjects have been reviewed by Raine and Bishop (1963) and by Laver and Seifen (1965). Mean values for arterial P_{O_2} in these studies range from 600 to 650 mm Hg, but individual values range from 550 mm Hg to values which are (no doubt erroneously) in excess of the alveolar P_{O_2}.

Reports of 'abnormalities' of oxygenation must be interpreted against the high degree of scatter in normal subjects under normal conditions.

OXYGEN LEVELS DURING ANAESTHESIA

There has been evidence of interest in oxygenation of patients under the effect of anaesthetic agents since the birth of the speciality. In Davy's *Researches* (1800) there is comment by Beddoes on the colour of blood flowing from leech bites,

and in Robinson's book of 1847 there is the remark that arterial blood presents its normal appearance during etherization.

Until about 1960, studies of oxygenation generally related to the saturation rather than the Po_2 of the arterial blood, and were of limited value since considerable reduction of Po_2 can occur without much change in saturation due to the shape of the oxygen dissociation curve. However, since 1960, the introduction of the polarograph has led to many studies of arterial Po_2 which have shed a great deal of light on factors governing the oxygenation of the arterial blood during anaesthesia. The contributions of most of these studies to the fundamental understanding of the problems have already been discussed in the appropriate parts of this book, and all that now remains is to summarize the principal factors in relation to anaesthesia.*

Inspired oxygen concentration probably exceeds all other factors in importance. When the inspired oxygen concentration exceeds 80 per cent, the arterial Po_2 of apparently healthy anaesthetized patients is almost never found to be below

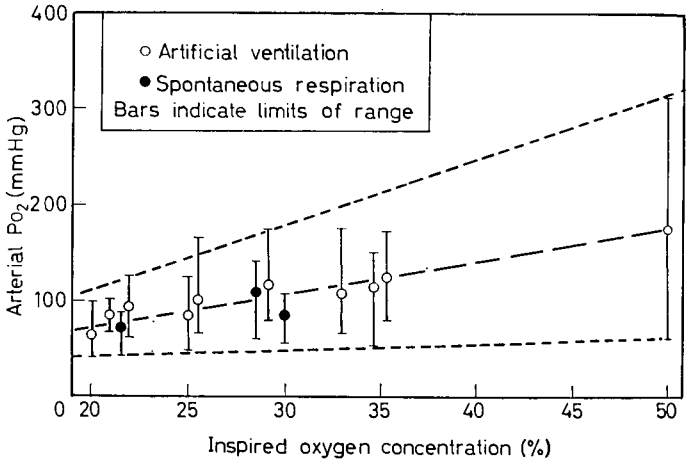


Figure 123. Pooled data on arterial Po_2 *levels during anaesthesia reported by the following authors as a function of the inspired oxygen concentration: Campbell, Nunn and Peckett (1958); Theye and Tuohy (1964a and b); Nunn (1964); Slater and his colleagues (1965); Sykes, Young and Robinson (1965); Nunn, Bergman and Coleman (1965); Webb and Nunn (1967). Note the high correlation between mean arterial* Po_2 *and inspired oxygen concentration. Mean arterial* Po_2 *is about half the inspired gas* Po_2*. Factors varying between the different studies seem to have surprisingly little effect and most studies contain one or more patients whose* Po_2 *is inexplicably low*

250 mm Hg. When the inspired oxygen concentration is below 21 per cent, the arterial Po_2 is usually below 100 mm Hg. Inspired oxygen concentrations within the range 30–40 per cent usually result in an arterial Po_2 between 80 and 150 mm Hg (*Figure 123*) but surprisingly low values are occasionally found in patients who show no signs of respiratory or circulatory disease.

An increase in inspired oxygen concentration will usually produce a corresponding increase in alveolar Po_2 (page 336). However, other factors

* Appropriate references are given in the legend of *Figure 123* and in *Table 40.*

remaining constant, the alveolar/arterial P_{O_2} difference is increased (page 340) and the improvement in arterial P_{O_2} is thus less than might be expected.

There is a school of thought which believes that oxygenation is of such importance that all anaesthetized patients should receive an inspired gas with at least 80 per cent oxygen. This virtually guarantees adequate arterial oxygenation under almost all exigencies of anaesthesia, including gross hypoventilation (*Table 40*). However, it obliges the anaesthetist to forgo the use of nitrous oxide and seems to engender an attitude which tolerates elevation of P_{CO_2} to levels which many would regard as dangerous.

Table 40

Values for arterial P_{O_2} reported during anaesthesia with an inspired gas concentration close to 100%

Year	*Authors*	*Type of respiration*	*Arterial P_{O_2} (mm Hg)*		
			Minimum	*Mean*	*Maximum*
1960	Stark and Smith	Spontaneous	272	332	388
		Artificial	211	343	445
1963	Bendixen, Hedley-Whyte and Laver	Artificial	150	440	608
1964	Nunn	Spontaneous	259	476	569
1964	Bendixen and his colleagues	Spontaneous	—	402	—
		Artificial	—	553	—
1965	Nunn, Bergman and Coleman	Artificial	421	517	636
1968	Panday and Nunn	Spontaneous	332	450	530

A number of studies have been omitted where there was inadequate evidence of nitrogen elimination. These studies included those in which the patients were allowed to breathe from closed circuits with an inflow of a few hundred millilitres of oxygen per minute. Measurements have shown that there is still about 20 per cent nitrogen circulating after 1 hour of such conditions, sufficient to reduce the arterial P_{O_2} by about 140 mm Hg.

Ventilation is of critical importance below the normal value of alveolar ventilation (*Figure 111*). At higher levels of ventilation and when breathing 100 per cent oxygen, changes of ventilation have relatively little effect upon the alveolar P_{O_2}, although an increased tidal ventilation may re-expand collapsed lung.

The alveolar/arterial P_{O_2} difference is a major factor influencing the arterial P_{O_2} during anaesthesia and has been accorded considerable attention in this chapter (page 337). Its magnitude is influenced by the following factors: (1) shunt; (2) scatter of ventilation/perfusion ratios; (3) cardiac output; (4) the alveolar P_{O_2}; and (5) haemoglobin, pH, temperature and other minor factors.

Although there is no doubt that the alveolar/arterial P_{O_2} difference is increased during anaesthesia, it is less certain how far this is due to an abnormal degree of shunting or pulmonary venous admixture. In the early studies the shunt was calculated on the basis of assumed values for mixed venous oxygen. However, later studies have demonstrated unexpectedly low values for cardiac output and mixed venous oxygen during anaesthesia, particularly with hypocapnia. Estimates of shunt based on more realistic values for mixed venous oxygen content have shown that the shunt during anaesthesia with artificial

ventilation is scarcely increased above the normal range (Kelman and his colleagues, 1967). During anaesthesia with spontaneous respiration, the mean values for shunt are of the order of 10 per cent which is well above the normal range.

There is an even greater degree of uncertainty regarding the cause of the increased shunting which appears to be a normal accompaniment of certain types of anaesthesia (page 255). In their classical paper, Bendixen, Hedley-Whyte and Laver (1963) reported progressive falls of arterial Po_2 during anaesthesia with restoration of Po_2 following inflation of the lungs. Progressive collapse with re-expansion of the lungs following inflation seemed a reasonable explanation, and it appears likely that this does occur in some patients. However, more recent studies have failed to confirm that progressive fall of arterial Po_2 is an invariable accompaniment of anaesthesia (Theye and Tuohy, 1964a; Askrog and his colleagues, 1964; Sykes, Young and Robinson, 1965; Nunn, Bergman and Coleman, 1965; Panday and Nunn, 1968), and some of these workers have been unable to elevate the arterial Po_2 by manual inflation of the lungs to 30 cm H_2O.

It seems likely that elucidation of the nature of the shunt which occurs during anaesthesia will require a broadening of the investigational front beyond a study of blood gas tensions. Unfortunately, it seems that chest radiography is of limited value (Prys-Roberts and his colleagues, 1967b), and it appears likely that other methods must be sought. In particular, it seems pointless to speculate further on the scatter of ventilation/perfusion ratios which occurs during anaesthesia until measurements have been made, difficult though these may be (*see* 'Note added in proof', page 383). Factors influencing the venous admixture during anaesthesia are considered on pages 256 et seq.

In the post-operative period, there are many possible causes of arterial hypoxaemia. Withdrawal of nitrous oxide at the end of an anaesthetic causes dilution of alveolar gas with nitrous oxide. Alveolar and arterial Po_2 are reduced by this mechanism originally known as 'diffusion anoxia' (page 336). Marshall and Millar (1965) considered this to be the principal cause of early post-operative hypoxaemia but reductions of arterial Po_2 commonly occur in patients who have not received nitrous oxide and, in patients who have received nitrous oxide, the hypoxaemia usually outlasts the period of nitrous oxide wash-out (Nunn and Payne, 1962). A study by Bay, Nunn and Prys-Roberts (1968) showed that there was no universal cause for early post-operative hypoxaemia. In some patients there was a large venous admixture, while in others the main abnormality was excessive desaturation of mixed venous blood caused by a high oxygen consumption which was not matched by the cardiac output. Substantial increases in oxygen consumption were found in shivering patients. Surprisingly, hypoventilation was not a major cause of arterial hypoxaemia in the patients studied, and minute volumes as high as 25 l./min. were recorded in shivering patients. Clearly the ventilation might be limited in other patients by pulmonary disease or faulty anaesthetic technique with, for example, residual neuromuscular block.

The severity of early post-operative hypoxaemia has no obvious connection with the nature of the operation except that there is a relation to duration of anaesthesia (Marshall and Millar, 1965) and hypoxaemia is not seen after

operations lasting less than 20 minutes (Taylor, Scott and Donald, 1964). Hypoxaemia is more marked in older patients and there is a negative correlation between arterial Po_2 and the age of the patient (Nunn, 1965), the regression line lying below and parallel to that observed in conscious patients. There is a great deal of scatter in individual observations but mean results of pooled data from many sources yield the following regression equation:

$$\text{early post-operative arterial } Po_2 = 94{\cdot}3 - 0{\cdot}455 \text{ (age)}$$

(Nunn, 1965)

Early post-operative arterial hypoxaemia does not last beyond the day of operation and persistent hypoxaemia, when it occurs, is usually due to overt pulmonary collapse (Palmer and Gardiner, 1964; Palmer, Gardiner and McGregor, 1965).

In the pre-operative period it has been shown that patients awaiting surgery (without premedication) have a normal arterial Po_2 for their age (Conway, Payne and Tomlin, 1965). Atropine was found to have no effect on arterial Po_2 of volunteers (Daly, Ross and Behnke, 1963; Nunn and Bergman, 1964) but Tomlin, Conway and Payne (1964) reported a fall of arterial Po_2 of 15 mm Hg after intramuscular administration of atropine to patients awaiting surgery. Papaveretum and hyoscine administered together were found to result in a fall of arterial Po_2 of about 10 mm Hg, patients acting as their own control (Prys-Roberts, 1966).

In the intensive care department normal arterial oxygenation is the exception rather than the rule. Hypoventilation is now an unusual cause of hypoxaemia, since those concerned with intensive care are generally quick to diagnose and treat underventilation. It is, in fact, usual to find a low arterial Pco_2 in patients undergoing intensive care whether the respiration is spontaneous or artificial. However, the alveolar/arterial Po_2 difference is increased in almost all patients for one reason or another and hypoxaemia would be prevalent were it not for the enrichment of the oxygen concentration of inspired gas which is a widespread feature of management. In difficult cases, titration of the inspired oxygen concentration against the arterial Po_2 may be required to ensure a safe level of arterial Po_2.

CYANOSIS

The commonest method of detection of hypoxia is by the appearance of cyanosis, and the change in colour of haemoglobin on desaturation affords the patient a safeguard of immense value. Indeed, it is interesting to speculate on the additional hazards of anaesthesia if gross hypoxia could occur without overt changes in the colour of the blood. There must have been countless occasions in which the appearance of cyanosis has given warning of hypoventilation, pulmonary shunting, stagnant circulation or decreased oxygen concentration of inspired gas.

Central and Peripheral Cyanosis

If shed arterial blood is seen to be purple, this indicates arterial desaturation. However, when skin or mucous membrane is inspected, most of the blood which

colours the tissue is lying in veins and its oxygen content is related to the arterial oxygen content as follows:

$$\begin{matrix}\text{venous} \\ \text{oxygen} \\ \text{content}\end{matrix} = \begin{matrix}\text{arterial} \\ \text{oxygen} \\ \text{content}\end{matrix} - \begin{matrix}\text{arterial/venous} \\ \text{oxygen content} \\ \text{difference}\end{matrix}$$

The last term may be expanded in terms of the tissue metabolism and perfusion:

$$\begin{matrix}\text{venous} \\ \text{oxygen} \\ \text{content}\end{matrix} = \begin{matrix}\text{arterial} \\ \text{oxygen} \\ \text{content}\end{matrix} - \frac{\text{tissue oxygen consumption}}{\text{tissue blood flow}}$$

The oxygen consumption by the skin is usually very low in relation to its circulation so that the quantity in the bracket is generally small. Therefore, the venous oxygen content is close to that of the arterial blood and inspection of the skin gives a reasonable indication of arterial oxygen content. However, when circulation is reduced in relation to skin oxygen consumption, cyanosis may occur in the presence of normal arterial oxygen levels. This occurs typically in cold weather and in the Trendelenburg position, but may occur in a wide range of circulatory disorders.

The Influence of Anaemia

Lundsgaard and Van Slyke (1923) stressed the importance of anaemia in appearance of cyanosis. There is general acceptance of their statement that cyanosis is apparent when there are 5 g. of reduced haemoglobin per 100 ml. of capillary blood. They defined capillary blood as having a reduced haemoglobin concentration which was the mean of the levels in arterial and venous blood. If, for example, the arterial blood contained 3 g./100 ml. of reduced haemoglobin (80 per cent saturation at normal haemoglobin concentration) and the arterial/venous difference for the skin were 4 ml./100 ml. of oxygen (corresponding to the reduction of 3 g./100 ml. of haemoglobin), the 'capillary' blood would contain 4·5 g./100 ml. of reduced haemoglobin and the degree of hypoxaemia would be just below the threshold at which cyanosis should be evident. In cases of severe anaemia, the reduced haemoglobin concentration of the capillary blood is unlikely to attain the level of 5 g./100 ml., which is said to be required for the appearance of cyanosis and, clearly, cyanosis could never occur if the haemoglobin concentration were only 5 g./100 ml.

There seems little doubt that qualitatively the views of Lundsgaard and Van Slyke are sound. There has been little quantitative confirmation of their theory but it is generally found that cyanosis can be detected at an arterial oxygen saturation of about 85 per cent although there is much variation (Comroe and Botelho, 1947). Such a level would probably correspond to a 'capillary' saturation of more than 80 per cent and a reduced haemoglobin of about 3 g./100 ml.

Sites for Detection of Cyanosis

Kelman and Nunn (1966a) carried out a comparison of the appearance of cyanosis in different sites with various biochemical indices of hypoxaemia of arterial blood. Best correlations were obtained with buccal mucosa and lips, but there was no significant correlation between the oxygenation of the arterial blood and the appearance of cyanosis in the ear lobes, nail bed or conjunctivae.

The Importance of Colour-rendering Properties of Source of Illumination

Kelman and Nunn also compared the use of five types of fluorescent lighting in use in hospitals. There was no significant difference in the correlation between hypoxaemia and cyanosis for the different lights. None was therefore more *reliable* than the others for the detection of hypoxaemia. However, there was a striking difference in the *degree* of cyanosis with the different lights, some tending to make the patients pinker and others imparting a bluer tinge to the patients. The former gave false negatives (no cyanosis in the presence of hypoxaemia) while the latter gave false positives (cyanosis in the absence of hypoxaemia), the total number of false results being approximately the same with all tubes.

It is potentially dangerous for patients to be inspected in different places under lamps of different colour-rendering properties, particularly if the medical and nursing staff do not know the characteristics of each type of lamp. It would be too much to suggest that the staff should calibrate their impressions of cyanosis for a particular lamp by relation to arterial oxygen levels, but it is not too much to expect that hospitals will standardize their lighting and acquaint staff with the colour-rendering properties of the type which is finally chosen.

Sensitivity of Cyanosis as an Indication of Hypoxaemia

It has been stressed above that the appearance of cyanosis is considerably influenced by the circulation, haemoglobin concentration and lighting conditions. Even when all these are optimal, cyanosis is by no means a precise indication of the arterial oxygen level and should be regarded as a warning sign rather than a measurement. Kelman and Nunn (1966a) detected cyanosis in about 50 per cent of patients who had a saturation of 93 per cent. Cyanosis was detected in about 95 per cent of patients with a saturation of 89 per cent. It should be remembered that 89 per cent saturation corresponds to about 58 mm Hg Po_2, a level which many anaesthetists would consider unacceptable. Absence of cyanosis does not necessarily mean normal arterial oxygen levels.

PRINCIPLES OF MEASUREMENT OF OXYGEN LEVELS

Oxygen Concentration in Gas Samples

For many years the use of the Haldane apparatus, or its modification by Lloyd (1958), has been the standard method of measurement of oxygen concentrations in physiological gas samples. Recently analysers working on the paramagnetic properties of oxygen (Pauling, Wood and Sturdivant, 1946) have attained a degree of accuracy and reliability which has enabled them to supplant the older chemical methods of analysis (Nunn and his colleagues, 1964; Ellis and Nunn, 1968). A particularly attractive feature of the method is that interference by other gases likely to be present in anaesthetized patients does not cause major inaccuracies and, if particularly high accuracy is required, correction factors may be employed. The apparatus manufactured by Servomex Controls Ltd. has proved to be reliable and is based on a robust measuring cell developed by the Distillers Company.

Measurement of breath-to-breath changes in oxygen concentrations of

respired gases requires an instrument with a response time of less than about 300 milliseconds. Until recently the only suitable technique for oxygen measurement has been the mass spectrometer (Fowler and Hugh-Jones, 1957). However, a number of alternative methods have now been described although their use has remained limited at the time of writing. The first of these was a modification of the polarograph (Severinghaus, 1963), followed by a fast-response version of the Servomex D.C.L. 83 paramagnetic oxygen analyser (Cunningham, Kay and Young, 1965). A hitherto unapplied principle was employed in the oxygen-sensitive solid electrochemical cell described by Elliot, Segger and Osborn (1966). All of these instruments are capable of giving a continuous indication of the oxygen concentration of respired gases from which it is possible to observe the end-expiratory concentration.

Oxygen Content of Blood Samples

The older chemical methods are those of Van Slyke and Neill (1924) and Haldane (1920). More recently, the Natelson apparatus (1951) appears a simpler alternative to the Van Slyke manometric apparatus but many have found it unexpectedly difficult to obtain reliable results for oxygen content.

Still more recently, the polarographic method of measurement of Po_2 (*see* page 380) has been utilized to measure oxygen content. Chemically combined oxygen is liberated from blood by saponin-ferricyanide solution and the Po_2 of the resultant solution is proportional to the oxygen content of the blood sample (Linden, Ledsome and Norman, 1965). This method is uninfluenced by the presence of inhalational anaesthetic agents, and has proved to be simple, accurate and reliable.

Blood Oxygen Saturation

The classical method of measurement of saturation is in the form of the ratio of content to capacity (with dissolved oxygen subtracted from each):

$$\text{saturation} = \frac{HbO_2}{Hb + HbO_2} = \frac{\text{oxygen content} - \text{dissolved oxygen}}{\text{oxygen capacity} - \text{dissolved oxygen}}$$

Oxygen capacity is determined as the content after saturation of the blood by exposure to oxygen.

Nowadays, it is more usual to measure saturation photoelectrically. Methods are based on the fact that the absorption of monochromatic light of wavelength 805 nm is the same for reduced and oxygenated haemoglobin. At other wavelengths (particularly 650 nm) there is a marked difference between the absorption of transmitted or reflected light by the two forms of haemoglobin (Zijlstra, 1958). Various devices are marketed which depend upon the simultaneous absorption of light at these two wavelengths and so indicate the saturation directly. Unfortunately, these instruments tend to be used uncritically and their calibration is seldom checked for the simple reason that such a check is a difficult and time-consuming operation.

Saturation may be derived from Po_2. This is reasonably accurate above a Po_2 of about 55 mm Hg where the dissociation curve is flat. However, it is inaccurate at lower tensions since, on the steep part of the curve, the saturation changes by 3 per cent for a tension change of 1 mm Hg.

At a superficial glance the concept of saturation appears simple enough. However, on further consideration there are seen to be difficulties which cannot easily be overcome. They arise chiefly from the presence of abnormal forms and compounds of haemoglobin. Methaemoglobin is usually present as about 5 per cent of total haemoglobin, and carboxyhaemoglobin may be as high as 10 per cent of total haemoglobin in smokers. These compounds also explain the difficulty in demonstrating the theoretical relationship between oxygen capacity and haemoglobin concentration (1·39 ml. oxygen/g. haemoglobin).

Blood Po_2

Four methods of measurement are available.

(1) A tiny bubble of gas may be equilibrated with blood at the patient's body temperature and then analysed quantitatively for oxygen (Riley, Campbell and Shephard, 1957). Po_2 is derived from the oxygen concentration of the bubble. The technique is difficult and inaccurate when the Po_2 is more than 95 mm Hg. It cannot be used in the presence of anaesthetic gases.

(2) If the dissociation curve is known, the Po_2 may be derived from the saturation (*see* above). This method is quite accurate on the steep part of the dissociation curve, but is of limited value when the Po_2 is more than 55 mm Hg and quite inaccurate when the Po_2 is over about 85 mm Hg.

(3) Po_2 of blood is directly proportional to the oxygen content of the plasma. This relationship may be used for deriving Po_2 from content, provided that blood can be separated anaerobically without change in the distribution of oxygen between plasma and erythrocytes. The solubility of oxygen in the patient's plasma must be accurately known. The method is difficult because of the small quantities of oxygen dissolved in plasma. However, Stark and Smith (1960) successfully used the method of Smith and Pask (1959) for measuring plasma oxygen content and derived values for blood Po_2 in a pioneer study.

(4) Since 1960, polarography has virtually displaced all other methods of measurement of blood Po_2. This technique has been of immense value in anaesthesia since it is uninfluenced by the presence of anaesthetic agents. It has been used both for research and for the management of patients who present difficult problems of oxygenation. The apparatus consists essentially of a cell formed by a silver anode and a platinum cathode, both in contact with an electrolyte in dilute solution. If a potential difference of about 700 millivolts is applied to the cell, a current is passed which is directly proportional to the Po_2 of the electrolyte in the region of the cathode. In use, the electrolyte is separated from the sample by a thin membrane which is permeable to oxygen. The electrolyte thus attains the same Po_2 as the sample and the current passed by the cell is proportional to the Po_2 of the sample, which may be gas, blood or other liquids. A disturbing source of error in the polarographic measurement of blood Po_2 is the difference in reading between blood and gas of the same Po_2. Estimates of the ratio vary between 1·0 and 1·17 but it may change unexpectedly for reasons which are not understood. This error may be avoided by calibration with tonometer-equilibrated blood, but some workers prefer to calibrate on gas and then use a correction factor. A third approach is to calibrate with a solution of 30 per cent glycerol in water. This solution gives the same reading as blood of the same Po_2. Studies of the performance of

polarographs for the measurement of blood Po_2 include those by Polgar and Forster (1960), Staub (1961) and Bishop and his colleagues (1966). The subject has been reviewed with special reference to anaesthesia by Laver and Seifen (1965) and Adams, Morgan-Hughes and Sykes (1967).

The major errors in the measurement of blood oxygen levels usually arise from faulty sampling and handling of the sample (Nunn, 1962b) and from failure to correct for differences in temperature between the patient and the measurement system. The following points require attention.

(1) The blood sample must be collected without exposure to air.

(2) Oxygen is consumed by blood (Greenbaum and his colleagues, 1967), and avoidance of error due to the consequent fall in Po_2 after sampling requires one or more of the following actions:

(*a*) immediate analysis after sampling;

(*b*) storage of sampled blood at 0°C;

(*c*) application of a correction factor for oxygen consumed during the interval between sampling and analysis (Kelman and Nunn, 1966b).

(The first is the most and the last the least satisfactory method.)

(3) If blood Po_2 is measured at a lower temperature than the patient, the measured Po_2 will be less than the Po_2 of the blood while it was in the patient. It is often difficult to maintain the measuring apparatus at the patient's body temperature, and significant error results from a temperature difference of more than about 1 degree C. Correction is possible but the factor is variable depending upon the saturation (Nunn and his colleagues, 1965a). A convenient nomogram has been described by Kelman and Nunn (1966b).

Cutaneous Oximetry

On superficial acquaintance, cutaneous oximetry appears an attractive alternative to direct measurement of arterial oxygen levels. The blood which is visualized by the apparatus is venous or capillary rather than arterial and the method is, therefore, dependent upon a brisk blood flow being maintained through the skin. Perhaps the most serious objection is that the apparatus is usually standardized according to a routine provided by the manufacturers and few users calibrate the apparatus against measurements on arterial blood. An indirect method of calibration suggested by Campbell (unpublished) has been described by Nunn and his colleagues (1965b). Generally speaking, arterial puncture and direct measurement of oxygen levels is no more difficult and a great deal more reliable.

Measurement of Mixed Venous Po_2

The usual method of measurement of mixed venous Po_2 (or oxygen content) is to sample blood from the right ventricle or pulmonary artery and analyse it according to the methods described above. It has, however, been suggested that a rebreathing technique might be used to derive mixed venous Po_2 indirectly along the same lines as the Campbell and Howell technique for measurement of mixed venous Pco_2 (page 324). The technique for oxygen was described by Cerretelli and his colleagues (1966) and requires the rebreathing of a mixture of carbon dioxide in nitrogen. This procedure inevitably reduces the arterial Po_2 which, although of short duration, may be unacceptable for some patients. There is, however, a more serious objection to the method.

Calculations show that the cardiac output in most patients will not be sufficiently high for the alveolar P_{O_2} to be brought into equilibrium with the mixed venous P_{O_2} in one circulation time (Spence and Ellis, 1969). Furthermore, the change in alveolar P_{O_2} is likely to be so slow that there may be a false impression that equilibrium has been attained.

Indirect Methods of Measurement of Arterial P_{O_2}

Unfortunately, indirect methods of measurement of arterial P_{O_2} are of limited value in the healthy subject, and of no value in the anaesthetized patient or in patients with respiratory disease. The arterial/venous P_{O_2} difference is so large that the rebreathing method of measurement of mixed venous P_{O_2} (*see* above) is valueless for indirect assessment of the arterial P_{O_2}. The end-expiratory P_{O_2} differs from the arterial P_{O_2} in patients with increased alveolar dead space, for reasons identical to those producing a difference in the P_{CO_2} (page 189). End-expiratory P_{O_2} will not therefore indicate the actual level of arterial P_{O_2} during anaesthesia, although it may give some indication of changes. Cutaneous venous or capillary blood P_{O_2} may, under ideal conditions, be close to the arterial P_{O_2}, but a modest reduction in skin perfusion will cause a substantial fall in P_{O_2} since the oxygen is consumed at a point on the dissociation curve where small changes in content correspond to large changes in tension. For these reasons, if a reliable indication of the arterial P_{O_2} is required, there appears to be no alternative to arterial puncture and direct measurement.

Tissue P_{O_2}

Clearly the tissue P_{O_2} is of greater significance than the P_{O_2} at various intermediate stages higher in the oxygen cascade. It would therefore appear to be logical to attempt the measurement of P_{O_2} in the tissues, but this has proved difficult both in technique and in interpretation. Technical difficulties arise from the extremely small size of the polarographic electrode which is needed to avoid excessive damage to the tissues. Difficulties of interpretation arise from the fact that P_{O_2} varies from one cell to another and from one part of a cell to another, the most important factor being the relation of the electrode to the capillaries (*Figure 93*). The significance of measurements of tissue P_{O_2} depends upon the precise location of the electrode and the degree of damage caused by its insertion: this requires meticulous attention to detail. Cater and his colleagues (1961) have inserted electrodes by a stereotaxic technique, fixed the tissues before removal and then examined serial sections cut along the track of the electrode to determine its position in relation to blood vessels and to exclude the possibility of a haematoma around the tip of the electrode.

Such are the difficulties of measurement of tissue P_{O_2} that many prefer to measure the venous P_{O_2} of blood draining a particular tissue. Even the significance of this measurement is not entirely clear, but the venous P_{O_2} is roughly related to the mean pressure head of oxygen for diffusion into the cells of the area drained by the blood.

Oxygen Consumption

Oxygen consumption may be measured either as the loss of oxygen from a closed rebreathing system or, more accurately, by the subtraction of the

quantity of oxygen exhaled from the quantity inhaled. Measurement of the minute volume and the concentration of oxygen in the inspired and expired gas presents no great difficulty and the main problem centres on the measurement of the difference between the inspired and expired minute volumes. This is easy enough when a patient is in equilibrium with the nitrogen in ambient air but, when he is breathing an artificial gas mixture, the difficulties increase (Nunn and Pouliot, 1962).

NOTE ADDED IN PROOF

Effect of 2, 3-Diphosphoglyceric Acid on the Oxyhaemoglobin Dissociation Curve

When this chapter was written, it was generally accepted that the oxyhaemoglobin dissociation curve was governed almost entirely by the molecular structure of the globin part of the haemoglobin and the pH, P_{CO_2}, temperature, etc. It has now become apparent that the high concentration of 2,3-diphosphoglyceric acid (2,3-DPG) within the erythrocyte has a most important effect upon the position of the dissociation curve, increased values causing a shift to the right. Many implications of this discovery have still to be explored but it seems that reductions of 2,3-DPG (causing a shift to the left) occur during storage of banked blood. In contrast, a comparatively short stay at high altitude causes an increase in 2,3-DPG concentration associated with a shift of the curve to the right. Other substances may also have the property of shifting the dissociation curve.

It seems likely that these considerations will strike at the very foundations of work on the oxyhaemoglobin dissociation curve and many aspects of the field will require re-evaluation. A useful introduction to the subject and list of references will be found in the editorial written by Astrup, Garby and de Verdier (1968).

APPENDIX A

PHYSICAL QUANTITIES AND UNITS OF MEASUREMENT

In each case dimensions are given in mass/length/time (MLT) units. These units provide a most useful check of the validity of equations and other expressions which are derived in the course of studies of respiratory function. Only quantities with identical MLT units can be added or subtracted and the units must be the same on the two sides of an equation.

Volume (Dimensions: L^3)

In this book we are concerned with volumes of blood and gas. The units are litres and millilitres (which have replaced cubic centimetres for the measurement of volumes of fluid). For practical purposes, we may ignore changes in the volume of liquids which are caused by changes of temperature. However, the changes in volume of gases caused by changes of temperature or pressure are by no means negligible and constitute an important source of error if they are ignored. Gas volumes are usually measured at ambient (or environmental) temperature and pressure, either dry (as from a cylinder passing through a rotameter) or saturated with water vapour at ambient temperature (e.g. an expired gas sample). Customary abbreviations are A.T.P.D. (ambient temperature and pressure, dry) and A.T.P.S. (ambient temperature and pressure, saturated).

It is not good practice to report gas volumes under the conditions prevailing during their measurement. In the case of oxygen uptake, carbon dioxide output and the exchange of 'inert' gases, we need to know the actual quantity (i.e. number of molecules) of gas exchanged and this is most conveniently expressed by stating the gas volume as it would be under standard conditions, i.e. 0°C, 760 mm Hg pressure and dry (S.T.P.D.). Conversion from A.T.P.S. to S.T.P.D. is by application of Charles' and Boyle's laws (*see* page 1). A table of conversion factors is given in Appendix B. In the case of volumes which relate to anatomical measurements (e.g. vital capacity, tidal volume and dead space) it is necessary to express gas volumes as they would be at body temperature and pressure, saturated with water vapour (B.T.P.S.). Conversion from A.T.P.S. to B.T.P.S. is also based on Charles' and Boyle's laws and factors are listed in Appendix B.

Fluid Flow Rate (Dimensions: L^3/T, i.e. L^3T^{-1})

In the case of liquids, flow rate is the physical quantity of cardiac output, regional blood flow, etc., and the usual units are litres per minute (l./min.) or millilitres per minute (ml./min.). For gases, the dimension is applied to the delivery rate of fresh gases in anaesthetic gas circuits, minute volume of respiration, oxygen consumption, etc. The units are the same as those for liquids except that litres per second are used for the high instantaneous flow rates which occur during the course of inspiration and expiration.

In the case of gas flow rates, just as much attention should be paid to the matter of temperature and pressure as when volumes are being measured. Measurement is usually made at ambient temperature, but gas exchange rates are reported after correction to S.T.P.D. while ventilatory gas flow rates should be corrected to B.T.P.S. As a very rough rule, gas volumes at S.T.P.D. are about 10 per cent less than at A.T.P.S., while volumes at B.T.P.S. are about 10 per cent more.

Force (Dimensions: MLT^{-2}) (LT^{-2} or L/T^2 are the units of acceleration)

In respiratory physiology we are chiefly concerned with force in relation to pressure, which is force per unit area. An understanding of the units of force is essential to an understanding of the units of pressure. Force, when applied to a free body, causes it to change either the magnitude or the direction of its velocity.

The units of force are of two types. The first is the force resulting from the action of gravity on mass. This is synonymous with weight. Examples include the pound-force, the gramme-force and the kilogramme-force. Each has a value equal to the product of the mass (pound, gramme or kilogramme) and the acceleration produced by the earth's gravitational field (981 cm./sec./sec. or **g**).

$$\text{mass} \times \text{acceleration} = \text{force}$$
$$M \times LT^{-2} = MLT^{-2}$$

Note that these units of force have no value when gravitation is zero as in an orbiting satellite.

The second type of unit of force is absolute and does not depend upon the magnitude of the gravitational field. The dyne is the absolute unit of force in the centimetre/gramme/second (c.g.s.) system, and is the force which, when acting upon a free mass of 1 g., will give it an acceleration of 1 cm./sec./sec.

The relationship between the two types of unit is governed by the earth's gravitational field. Thus a gramme-force (the weight or force exerted by a mass of 1 g. in the earth's gravitational field) equals **g** dynes, where **g** equals approximately 981. This relationship would be different on another planet, in a centrifuge, in space or in a lift which is accelerating or decelerating. The difference between the two types of units of force is reflected in the units of pressure which are of greater importance in the biological field.

Pressure (Dimensions: MLT^{-2}/L^2, i.e. $ML^{-1}T^{-2}$)

Pressure may be considered as force per unit area. Tyre or cylinder pressures are commonly indicated in the units of kilogrammes per square centimetre (kg./sq. cm.) or pounds per square inch (p.s.i.). Both units are misnomers since kilogrammes and pounds are masses and not forces. The units are more correctly described as kilogramme-force (kgf) per square centimetre and pound-force (lbf) per square inch. Both units are gravity-dependent and in the same class is the centimetre of water (cm H_2O), a unit which is widely used in the laboratory and hospital. If we consider a centimetre cube of water, it will be clear that the undersurface will have a force of one gramme-force (the weight

of a cubic centimetre of water) acting on a surface area of one square centimetre. Thus:

$$1 \text{ cm } H_2O = 1 \text{ gf/sq. cm.}$$

and

$$1{,}000 \text{ gf/sq. cm.} = 1 \text{ kgf/sq. cm.}$$

Similarly, the mm Hg can be considered as the weight of one cubic millimetre of mercury acting upon one square millimetre. This gives the relationship:

$$1 \text{ mm Hg} = 1{\cdot}36 \text{ cm } H_2O$$

(13·6 is the specific gravity of mercury)

It may well be wondered why two different units should be used when they are so close together. Their *raison d'être* derives directly from the traditional method of measurement of pressure with liquid-filled U-tubes and it seems absurd that we should perpetuate the use of both these units of pressures, simply because water or mercury are more convenient manometer liquids in different circumstances.

All the units of pressure described above are directly influenced by the earth's gravitational field. The independent and absolute units of pressure are based upon the dyne (*see* above) which is an absolute unit of force, independent of gravity. The absolute unit of pressure in c.g.s. units will thus be the dyn/sq. cm.* This is an extremely small pressure and is called a microbar. The millibar is within 2 per cent of a cm H_2O and the bar is fairly close to an atmosphere.

The standard atmosphere (physical) is defined as 1·013,250 bars, and thence the Torr (Torricelli) is defined as 1/760 of a standard atmosphere. The Torr is practically identical to the mm Hg (within two parts in ten million) and, at the time of writing, the Torr is used interchangeably with mm Hg in the field of respiratory physiology.

It is understandable that the multiplicity of units of pressure causes a good deal of unnecessary confusion which could be avoided by using the true metric units of bar, millibar, etc. The inter-relationship of some of the units is set out in Appendix B.

Compliance (Dimensions: $L^3/ML^{-1}T^{-2}$, i.e. $M^{-1}L^4T^2$)

The term 'compliance' is used in respiratory physiology to denote the volume change of the lungs in response to a change of pressure. The dimensions are therefore volume divided by pressure and the commonest units are litres (or millilitres) per cm H_2O. Elastance is the reciprocal of compliance.

Resistance to Gas Flow (Dimensions: $ML^{-1}T^{-2}/L^3T^{-1}$, i.e. $ML^{-4}T^{-1}$)

Under conditions of laminar flow (Chapter 4) it is possible to express resistance to gas flow as the ratio of pressure difference to gas flow rate. This is analogous to electrical resistance which is expressed as the ratio of potential difference to current flow. The dimensions of resistance to gas flow are pressure

* At the time of writing, there is a strong tendency towards replacement of the c.g.s. system with the m.k.s. system (metre, kilogramme, second). While this has advantages for the engineer, the only apparent advantage to the physician is in standardization. The m.k.s. unit of pressure is the newton per square metre (the newton is the force required to give a mass of 1 kilogramme an acceleration of 1 metre per second per second). Since a newton per square metre is only 10 microbars it is no more convenient than the c.g.s. pressure units.

difference divided by gas flow rate, and typical units in the respiratory field are cm H_2O/l./sec. Absolute units are dyn sec. cm^{-5}.

Work (Dimensions: ML^2T^{-2}, derived from $MLT^{-2} \times L$ or $ML^{-1}T^{-2} \times L^3$)

Work is done when a force moves its point of application or gas is moved in response to a pressure gradient. The dimensions are therefore either force times distance or pressure times volume, in each case simplifying to ML^2T^{-2}. The absolute unit of work is the dyne-centimetre or erg. This is inconveniently small and it is often more convenient to use the joule which equals 10^7 ergs. The joule is a link with electrical units since it is the work done when a power of one watt is used for one second. It is also a link with calorimetry since one calorie equals 4·2 joules. (A kilocalorie or Calorie equals 10^3 calories and is the preferred unit for metabolic studies in man.)

Power (Dimensions: ML^2T^{-2}/T, i.e. ML^2T^{-3})

Power is the rate at which work is done and so has the dimensions of work divided by time. The absolute metric unit is the watt, which equals one joule per second. Power is the correct dimension for the rate of continuous expenditure of biological energy, although one talks loosely about the 'work of breathing', for example (Chapter 6). This is incorrect and 'power of breathing' is the correct term.

Surface Tension (Dimensions: MLT^{-2}/L, i.e. MT^{-2})

Surface tension has become important to the respiratory physiologist since the realization of the part it plays in the 'elastic' recoil of the lungs (page 56). The usual units are dynes per centimetre (of interface). Tension in the wall of a bubble or an alveolus causes the pressure inside to be greater than the pressure outside by an amount equal to:

$$\frac{2T}{R}$$

where T is the surface tension at the interface, and R is radius of the bubble. (Note that $2T/R$ has the units $MT^{-2}/L = ML^{-1}T^{-2}$ which are the units of pressure.)

APPENDIX B

CONVERSION FACTORS FOR GAS VOLUMES AND UNITS OF PRESSURE

Table 41

Factors for conversion of gas volumes measured under conditions of ambient temperature and pressure, saturated (A.T.P.S.) to the volumes which would be occupied under conditions of body temperature and pressure, saturated (B.T.P.S.)

Ambient temperature (°C)	*Conversion factor*	*Saturated water vapour pressure (mm Hg)*
15	1·129	12·8
16	1·124	13·6
17	1·119	14·5
18	1·113	15·5
19	1·108	16·5
20	1·103	17·5
21	1·097	18·6
22	1·092	19·8
23	1·086	21·0
24	1·081	22·4
25	1·075	23·7
26	1·069	25·2

These conversion factors are applied to gas volumes measured by spirometry and derived methods, to express the volumes as they would be in the lungs of the patient. Conditions of B.T.P.S. should be used for the expression of values for ventilation, dead space and all lung volumes.

Derivation of correction factors:

$$\text{volume}_{(\text{B.T.P.S.})} = \text{volume}_{(\text{A.T.P.S.})} \left(\frac{273 + 37}{273 + t}\right) \left(\frac{P_B - P_{H_2O}}{P_B - 47}\right)$$

P_B is barometric pressure and the table has been prepared for a barometric pressure of 750 mm Hg: variations within the range 740–760 mm Hg have a negligible effect upon the factors.

t is ambient temperature (°C). The table has been prepared for a body temperature of 37°C: variations within the range 35–39°C are of small importance.

P_{H_2O} is the water vapour pressure of the sample.

Table 42

Factors for conversion of gas volumes measured under conditions of ambient temperature and pressure, saturated (A.T.P.S.) to the volumes which would be occupied under conditions of standard temperature and pressure, dry (S.T.P.D.)—0°C, 760 mm Hg

Ambient temperature (°C)	*Barometric pressure (mm Hg)*			
	730	*740*	*750*	*760*
15	0·895	0·907	0·919	0·932
16	0·890	0·903	0·915	0·928
17	0·886	0·899	0·911	0·923
18	0·882	0·894	0·907	0·919
19	0·878	0·890	0·902	0·915
20	0·873	0·886	0·898	0·910
21	0·869	0·881	0·893	0·906
22	0·865	0·877	0·889	0·901
23	0·860	0·872	0·885	0·897
24	0·856	0·868	0·880	0·892
25	0·851	0·863	0·875	0·887
26	0·847	0·859	0·871	0·883

These conversion factors are applied to gas volumes measured by spirometry and derived methods, to express the volumes as they would be under standard conditions (0°C, 760 mm Hg). Conditions of S.T.P.D. should be used for the expression of values for gas exchange and blood gas contents.

Derivation of correction factors:

$$\text{volume}_{(\text{S.T.P.D.})} = \text{volume}_{(\text{A.T.P.S.})} \left(\frac{273}{273 + t}\right) \left(\frac{P_B - P_{H_2O}}{760}\right)$$

P_B is barometric pressure.

t is ambient temperature.

P_{H_2O} is the saturated vapour pressure of water at ambient temperature (*see Table 41*).

Table 43

Conversion factors for units of pressure

1 standard atmosphere	(physical)	
=	1·013	bars
=	1,013	millibars
=	1,013,000	microbars (= dyn/sq. cm.)
=	1·033	kg./sq. cm.
=	1,033	g./sq. cm. (= cm H_2O)
=	760·0	mm Hg (almost equal to the Torr)
=	33·90	ft. H_2O (fresh water)
=	14·70	lb./sq. in.
=	0·9447	ton/sq. ft.
1 cm H_2O		
=	0·9806	millibars
=	0·7355	mm Hg
1 mm Hg		
=	1·333	millibars
=	1·360	cm H_2O

All factors are given correct to 4 significant figures.
Note the closeness of: (1) the atmosphere, the bar and the kg/sq. cm.; (2) the millibar, the cm H_2O and the mm Hg.

APPENDIX C

SYMBOLS, ABBREVIATIONS AND DEFINITIONS

Symbols

Symbols used in this book are in accord with the recommendations of the committee for standardization of definitions and symbols in respiratory physiology (Pappenheimer and his colleagues, 1950). The use of these symbols is very helpful for an understanding of the quantitative relationships which are so important in respiratory physiology.

Primary symbols (large capitals) denoting physical quantities.

F fractional concentration of a gas
P pressure, tension or partial pressure of a gas
V volume of a gas
$\dot{Q}$ volume of blood
C content of a gas in blood
S saturation of haemoglobin with oxygen
R respiratory exchange ratio (R.Q.)
D diffusing capacity

$\dot{}$ denotes a time derivative; e.g. $\dot{V}$ ventilation
$\dot{Q}$ blood flow

Secondary symbols denoting location of quantity.

in gas phase (small capitals)	*in blood* (lower case)
I inspired gas	a arterial blood
E expired gas	v venous blood
A alveolar gas	c capillary
D dead space	t total
T tidal	
B barometric (usually pressure)	

$\bar{}$ denotes mixed or mean; e.g. $\bar{v}$ mixed venous blood
$\bar{E}$ mixed expired gas

′ denotes end; e.g. E′ end-expiratory gas
c′ end-capillary blood

Tertiary symbols indicating particular gases.

O_2 oxygen
CO_2 carbon dioxide
N_2O nitrous oxide
etc.

f denotes the respiratory frequency

B.T.P.S., A.T.P.S. and S.T.P.D. *see* Appendix B

Examples of Respiratory Symbols

$P_{A_{O_2}}$ alveolar oxygen tension
$C\bar{v}_{O_2}$ oxygen content of mixed venous blood
$\dot{V}O_2$ oxygen consumption

The system is well adapted to the expression of quantitative relationships.

$$\dot{Q}\,(Ca_{O_2} - C\bar{v}_{O_2}) = \dot{V}O_2 \qquad \text{(Fick equation)}$$

$$V_D = V_E\left(\frac{Pa_{CO_2} - P\bar{E}_{CO_2}}{Pa_{CO_2}}\right) \qquad \text{(Bohr equation)}$$

$$R = \frac{\dot{V}CO_2}{\dot{V}O_2}$$

Definitions of Words used in a Special Sense or which have Little General Use

Ambient: surrounding or environmental (e.g. room air)

Parameter: a quantity which is a constant in a particular relationship, but which varies from one relationship to another; e.g. a and b in the equation $y = a + bx$ (x and y are variables).

Variable: any quantity of which the value is likely to change; e.g. haemoglobin concentration might be considered as a variable over a number of days but as a parameter when a series of blood samples are drawn in rapid succession without there being a change of haemoglobin concentration. P_{O_2} would probably be a variable in both situations.

Phase: a continuous fluid medium. The lungs contain a gas phase and a blood phase, separated by the alveolar-capillary membrane.

APPENDIX D

THE EXPONENTIAL FUNCTION*

Examples of exponential functions recur throughout this book. They are, in fact, so common in biological systems that the exponential function is sometimes referred to as the law of organic growth.

The anaesthetist is deeply implicated in practical applications of exponential functions. The examples quoted below will show that much of his work is devoted to guiding certain variables of his patients along exponential curves. The success which attends his work depends to a large extent upon his skill in performing this task.

Many anaesthetists have had no formal instruction in exponential functions and lack much of the background knowledge which is needed for their comprehension. This is unfortunate since orthodox mathematical texts tend to proceed in an orderly manner with the assumption that the student has understood all that has gone before. It is, therefore, difficult for the anaesthetist to pick up a textbook of mathematics and 'read up exponential functions'. The best approach is without doubt a friendly mathematician. Failing that, the less orthodox books such as *Mathematics for the Million*, by Lancelot Hogben (1951), and *Calculus Made Easy*, by Silvanus P. Thompson (1946), will be found helpful.

General Statement

An exponential function describes a change in which the rate of change of one variable, in relation to the other, is proportional to the magnitude of the first variable. Thus, if y varies with respect to x, the rate of change of y with respect to x (i.e. $\mathrm{d}y/\mathrm{d}x$)† varies in proportion to the value of y at that instant. That is to say:

$$\frac{\mathrm{d}y}{\mathrm{d}x} = ky$$

where k is a constant.

This general equation appears with minor modifications in three main forms. To the biological worker they may be conveniently described as the tear-away, the wash-out and the wash-in.

THE TEAR-AWAY EXPONENTIAL FUNCTION

This must be described first as it is the simplest form of the exponential function. It is, however, the least important of the three to the anaesthetist.

* *See also* Waters and Mapleson (1964).

† $\mathrm{d}y/\mathrm{d}x$ is the mathematical shorthand for rate of change of y with respect to x. The 'd' means 'a very small bit of'; $\mathrm{d}y/\mathrm{d}x$ thus means a very small bit of y divided by a very small bit of x. This is equal to the slope of the graph of y against x at that point. In the case of a curve, it is the slope of a tangent drawn to the curve at that point.

Simple Statement

In a tear-away exponential function, the quantity under consideration increases at a rate which is in direct proportion to its actual value—the richer one is, the faster one makes money.

Examples

Classical examples are compound interest, and the mythical water-lily which doubles its diameter every day (*Figure 124*). A typical biological example is the free spread of a bacterial colony in which (for example) each bacterium

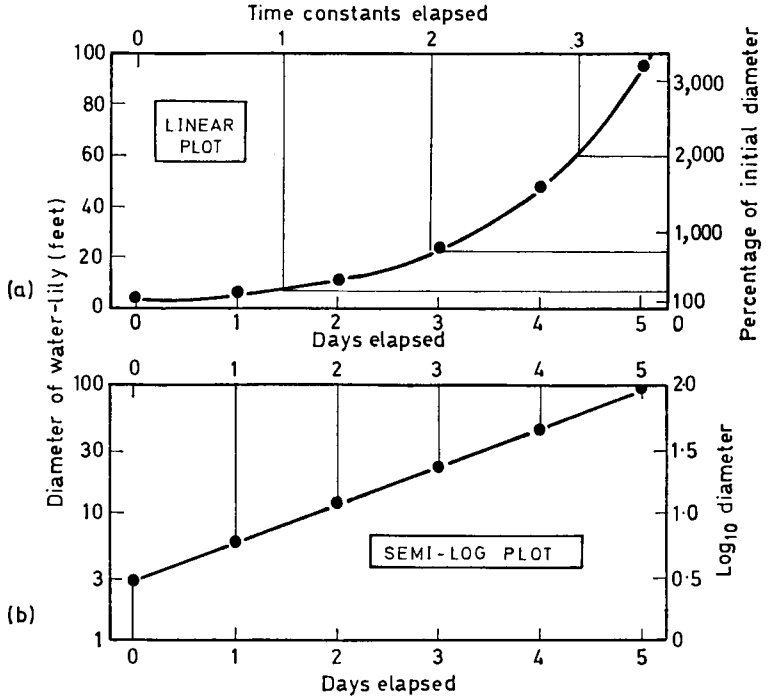


Figure 124. The growth of a water-lily which doubles its diameter every day—a typical tear-away exponential function. Initial diameter, 3 feet; size doubled every day (i.e. doubling time = 1 day). Compare the figures in the table below with those in Table 44.

Diameter of water-lily = $3e^{t/1\cdot44}$
(t is measured in days, diameter in feet)

Elapsed time (days)	*Diameter of water-lily*	
	Feet	*Percentage of initial diameter*
0	3	100
1	6	200
1·44	6·5	217
2	12	400
2·88	22·2	739
3	24	800
4	48	1,600
4·32	60·3	2,009
5	96	3,200

divides every 20 minutes. The doubling time of this example would be 20 minutes.

Mathematical Statement

By convention we consider y as the quantity which is changing in relation to x. However, for the anaesthetist, x almost invariably represents time and so we shall take the liberty of replacing x with t throughout. The tear-away function may thus be represented as follows:

$$\frac{dy}{dt} = ky$$

A little mathematical processing will convert this equation into a more useful form, which will indicate the instantaneous value of y at any time, t.

First multiply both sides by dt/y:

$$\frac{1}{y}\,dy = k\,dt$$

Next integrate both sides with respect to t:

$$\log_e y^* + C_1 = kt + C_2$$

(C_1 and C_2 are constants of integration and may be collected on the right-hand side.)

$$\log_e y = (C_2 - C_1) + kt$$

Finally, take antilogs of each side to the base e:

$$y = e^{(C_2 - C_1)} \times e^{kt}$$

At zero time, $t = 0$ and $e^{kt} = 1$. Therefore the constant $e^{(C_2 - C_1)}$ equals the initial value of y which we may call y_0. Our final equation is thus:

$$y = y_0\, e^{kt}$$

y_0 is the initial value of the variable y at zero time.

e is the base of natural or Napierian logarithms (discovered in 1619 before the circulation of the blood was known). It appeared as a result of integrating $(1/y)\,dy$.* This constant (2·71828...) possesses many remarkable properties which are lucidly expounded by Hogben (1951).

k is a constant which defines the speed of the particular function. For example, it will differ by a factor of two if our mythical water-lily doubles its size every 12 hours instead of every day. In the case of the wash-out and wash-in, we shall see that k is directly related to certain important physiological quantities, from which we may predict the speed of certain biological changes.

To the anaesthetist, e is unfamiliar and fairly alarming. We may, if we wish, avoid it by using the more familiar base 10:

$$y = y_0 10^{k_1 t}$$

* This is a difficult step for most of us. *See* page 165 of Thompson (1946).

This is a perfectly valid way of expressing a tear-away exponential function, but you will notice that the constant k has changed to k_1. This new constant does *not* have the simple relationships to physiological variables mentioned above. It does, however, bear a constant relationship to k, as follows:

$$k_1 = 0{\cdot}4343k \quad \text{(approx.)}$$

When an exponential function is considered to proceed by steps of whole numbers, it is known as a geometrical progression.

Graphical Representation

On linear graph paper, a tear-away exponential functional rapidly disappears off the top of the paper (*Figure 124*). If plotted on semi-logarithmic paper (time on a linear axis and y on a logarithmic axis), the plot becomes a straight line and this is a most convenient method of presenting such a function. The logarithmic plots in *Figures 124–126* are all plotted on semi-log paper.

THE WASH-OUT OR DIE-AWAY EXPONENTIAL FUNCTION

The account of the tear-away exponential function has really been a curtain-raiser for the wash-out or die-away exponential function, which is of great importance to the biologist in general, and the anaesthetist in particular.

Simple Statement

In a wash-out exponential function, the quantity under consideration falls at a rate which decreases progressively in proportion to the distance it still has to fall. It approaches but, in theory, never reaches zero.

Examples

Classical examples are cooling curves, radioactive decay and (nearer home) water running out of the bath. In the latter example the rate of flow down the plug-hole is proportional to the pressure of water, which is proportional to the depth of water in the bath, which in turn is proportional to the quantity of water in the bath (assuming that the sides are vertical). Therefore, the flow rate of water down the plug-hole is proportional to the amount of water left in the bath, and decreases as the bath empties. The last molecule of bath water takes an infinitely long time to drain away. A similar example is the mountaineer who each day ate half of the food which he carried. In this way he made his food last indefinitely.

Biological examples include:

(1) Passive expiration (*Figure 125*)
(2) The elimination of inhalational anaesthetics
(3) The fall of arterial P_{CO_2} to its new level after a step increase in ventilation
(4) The fall of arterial P_{O_2} to its new level after a step decrease in ventilation
(5) The fall of blood P_{CO_2} towards the alveolar level as it progresses along the pulmonary capillary
(6) The fall of blood P_{O_2} towards the tissue level as blood progresses through the tissue capillaries

Mathematical Statement

When a quantity *decreases* with time, the rate of change is *negative*. Therefore, the wash-out exponential function is written thus:

$$\frac{dy}{dt} = -ky$$

Integrating and taking antilogs (as described above for the tear-away function), we find:

$$y = y_0 e^{-kt}$$

which is simply another way of saying:

$$y = \frac{y_0}{e^{kt}}$$

y_0 is again the initial value of y at zero time. In *Figure 125* y_0 is the initial value of (lung volume − F.R.C.) at the start of expiration; that is to say, the tidal volume inspired.

e is again the base of natural logarithms (2·71828...).

k is the constant which defines the rate of decay, and really comes into its own in the wash-out exponential function. It is the reciprocal of a most important quantity known as the *time constant*. There are three things which should be known about the time constant.

(1) *Figure 125* shows a tangent drawn to the first part of the curve. This shows the course events would take if the initial rate were maintained instead of slowing down in the manner characteristic of the wash-out curve. The time which would then be required for completion would be $1/k$ which is called the *time constant* and designated by the Greek letter *tau* (τ). The wash-out exponential function may thus be written:

$$y = y_0 e^{-t/\tau}$$

(2) After one time constant, y will have fallen to $1/e$ of its original value. After two time constants, y will have fallen to $1/e^2$ of its initial value, and so on.

After 1 time constant, y will have fallen to approximately 37 per cent of its initial value.

After 2 time constants, y will have fallen to approximately 13½ per cent of its initial value.

After 3 time constants, y will have fallen to approximately 5 per cent of its initial value.

After 5 time constants, y will have fallen to approximately 1 per cent of its initial value.

(More precise values are indicated in *Table 44*.)

(3) The time constant is often determined by physiological factors. When air escapes passively from a distended lung, the time constant is governed by two variables, compliance and resistance (Chapters 3 and 4).

Let V represent the lung volume (above F.R.C.) then $-(dV/dt)$ is the

instantaneous expiratory gas flow rate. Assuming Poiseuille's law is obeyed (page 75):

$$-\frac{dV}{dt} = \frac{P}{R}$$

when P is the instantaneous alveolar-to-mouth pressure gradient and R is the airway resistance.

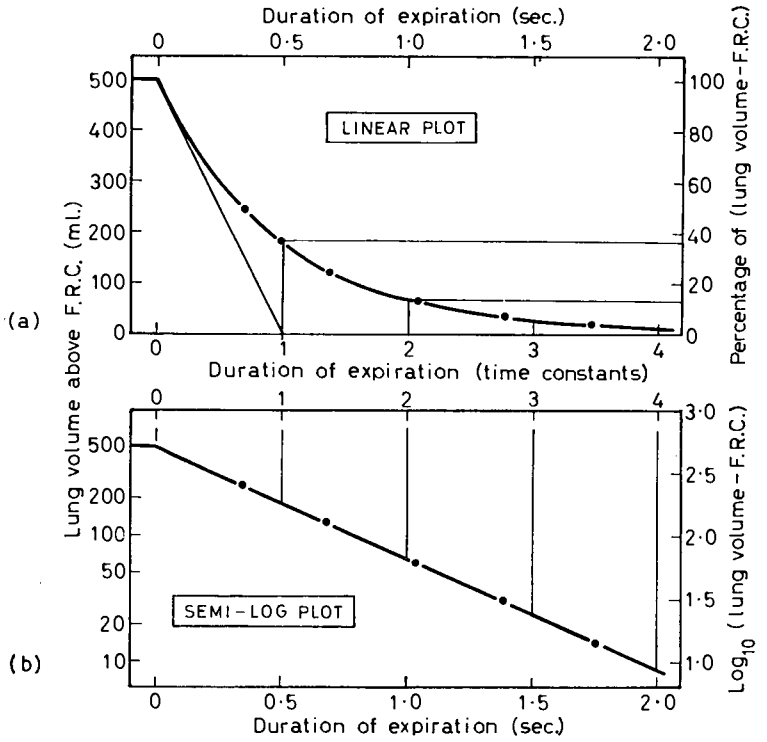


Figure 125. Passive expiration—a typical wash-out exponential function. Tidal volume, 500 ml.; compliance, 50 ml./cm H_2O; airway resistance, 10 cm H_2O/1,000 ml./sec.; time constant, 0·5 sec.; half-life, 0·35 sec. The points on the curves indicate the passage of successive half-lives

Lung volume above F.R.C. $= 500e^{-(t/0.5)}$

Elapsed time (constants)	*Lung volume remaining above F.R.C.*	
	ml.	*Percentage of tidal volume*
0	500	100
0·69	250	50
1	184	36·8
2	67·5	13·5
3	25	5·0
4	9	1·8

Note that the logarithmic co-ordinate has no zero. This accords with the lung volume approaching, but never actually equalling, the F.R.C.

But

$$\text{compliance } C = \frac{V}{P} \quad \text{(page 51)}$$

therefore

$$-\frac{dV}{dt} = \frac{1}{CR} V$$

or

$$\frac{dV}{dt} = -\frac{1}{CR} V$$

Then by integration and the taking of antilogs as described above:

$$V = V_0 e^{-(t/CR)}$$

By analogy with the general equation of the wash-out exponential function, it is clear that $CR = 1/k = \tau$ (the time constant). Thus the *time constant equals the product of compliance and resistance.** This is analogous to the discharge of an electrical capacitor through a resistance, when the time constant of discharge equals the product of the capacitance and the resistance. Rather similar is the wash-out of anaesthetic from a body or organ. Here the 'capacitance' equals the product of the mass of the body or organ and the solubility in it of the agent. The agent's 'resistance' to escape is inversely related to ventilation, diffusion, blood flow, renal function, etc.

In the more complex situations, wash-out curves remain exponential in form, but are compounded of a number of individual wash-out curves. Each has its own time constant which equals the product of capacitance (for the anaesthetic) and resistance (to wash-out) for each part. An example of the technique for separation of individual components from an over-all wash-out curve is the analysis of nitrogen clearance curves (Comroe and his colleagues, 1962).

Wash-out of a substance from an organ by perfusion with blood which is free of the substance is another example of a wash-out exponential function where the time constant may be stated in terms of certain physiological factors.

Let Q represent the volume of an organ and C be the concentration in the organ of a substance whose solubility in the organ equals its solubility in blood.

Imagine a small quantity of blood (dQ) to enter the organ. The concentration is then reduced by dC:

$$\frac{C - dC}{C} = \frac{Q + dQ}{Q}$$

Subtracting 1 from each side:

$$-\frac{dC}{C} = \frac{dQ}{Q}$$

* It is strange at first sight that two quantities as complex as compliance and resistance should have a product which boils down to anything as simple as time. In fact the mass/length/time units check perfectly well (*see* Appendix A).

$$\text{compliance} \times \text{resistance} = \text{time}$$
$$M^{-1}L^4T^2 \times ML^{-4}T^{-1} = T$$

If blood enters the organ at a constant rate, dQ/dt may be represented by $\dot{Q}$ (the usual symbol for blood flow rate). It then follows that:

$$-\frac{dC}{C} = \frac{\dot{Q}.dt}{Q}$$

and so

$$-\frac{dC}{dt} = \frac{\dot{Q}}{Q}C$$

from which it follows that:

$$C = C_0 e^{-(\dot{Q}/Q)t}$$

Again, by analogy, it is clear that $Q/\dot{Q} = 1/k = \tau$ (the time constant). Thus the *time constant equals the tissue volume divided by its blood flow.*

Similarly, the time constant of wash-out of a substance from the alveolar gas equals the F.R.C. divided by the alveolar ventilation (assuming that none of the substance crosses the alveolar-capillary membrane during the process, as is nearly true with helium, for example).

This important relationship is used in the nitrogen wash-out test of uniformity of intrapulmonary gas mixing, in which gas is considered as being washed out of two compartments, one fast and one slow. A compound wash-out curve is obtained and is subsequently analysed for different components (Comroe and his colleagues, 1962). It is also the basis of the Lassen and Ingvar (1961) technique for measurement of organ blood flow. The theory is delightfully simple. The time constant is determined for the wash-out of a freely diffusible radioactive substance from the organ. Since the reciprocal of the time constant equals the organ blood flow divided by the organ volume, the answer is immediately available in blood flow per unit volume of tissue (usually expressed as ml./min./100 ml. of tissue). This again makes the assumption that the solubility of the substance is the same for blood and tissue. If it is not, a correction factor can easily be applied.

Half-life.—It is often convenient to use the half-life instead of the time constant. This is the time required for y to change by a factor of two (or a half). The special attraction of the half-life is its ease of measurement. The half-life of a radioactive element may be determined quite simply. First of all the degree of activity is measured and the time noted. Its activity is then followed and the time noted at which its activity is exactly half the initial value. The difference between the two times is the half-life and is constant at all levels of activity. Half-lives are shown in *Figures 124–126* as dots on the curves. For a particular exponential function there is a constant relationship between the time constant and the half-life.

Half-life = 0·69 times the *time constant*
Time constant = 1·44 times the *half-life*

(For practical purposes, the time constant is 1·5 times the half-life.)

Graphical Representation

Plotting a wash-out exponential function is similar to the tear-away function (*Figure 125*). Semi-log paper may be used in the same way and is of considerable

practical importance as the curve (being straight) may then be defined by far fewer observations. It is also easy to extrapolate backwards to zero time if the initial value is required but could not be measured directly for some reason. It is, for example, an essential step in the measurement of cardiac output with a dye which is rapidly lost from the circulation (page 229).

THE WASH-IN EXPONENTIAL FUNCTION

The wash-in function is of special importance to the anaesthetist and is the mirror image of the wash-out function.

Simple Statement

In a wash-in exponential function, the quantity under consideration rises towards a limiting value, at a rate which decreases progressively in proportion to the distance it still has to rise.

Examples

A typical example would be a mountaineer who each day manages to climb half the remaining distance between his overnight camp and the summit of the mountain. His rate of ascent declines exponentially and he will never reach the summit. A graph of his altitude plotted against time would resemble a 'wash-in' curve.

Biological examples include the reverse of those listed for the wash-out function.

(1) Inflation of the lungs of a paralysed patient by a sustained increase of mouth pressure (*Figure 126*).

(2) The uptake of inhalational anaesthetics.

(3) The rise of arterial P_{CO_2} to its new level after a step decrease of ventilation.

(4) The rise of arterial P_{O_2} to its new level after a step increase of ventilation.

(5) The rise of blood P_{O_2} to the alveolar level as it progresses along the pulmonary capillary.

(6) The rise of blood P_{CO_2} to the venous level as blood progresses through the tissue capillaries.

Mathematical Statement

With a wash-in exponential function, y increases with time and therefore the rate of change is positive. As time advances, the rate of change falls towards zero. The initial value of y is often zero but y approaches a final limiting value which we may designate y_∞, that is the value of y when time is infinity (∞). A change of this type is indicated thus:

$$\frac{dy}{dt} = k(y_\infty - y)$$

As y approaches y_∞ so the quantity within the bracket approaches zero, and the rate of change slows down. The corresponding equation which indicates the instantaneous value of y is:

$$y = y_\infty\ (1 - e^{-kt})$$

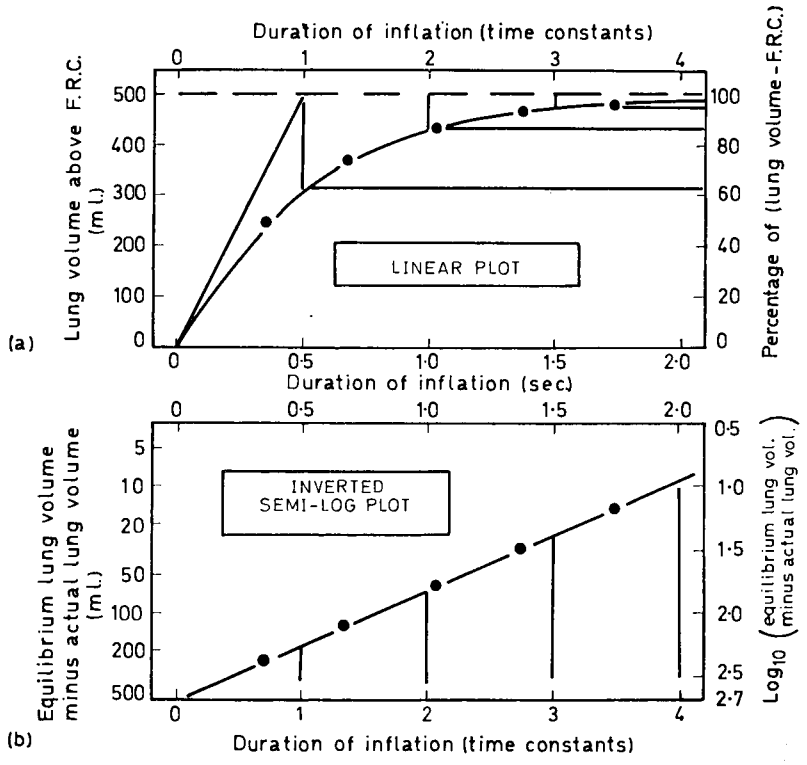


Figure 126. Passive inflation of the lungs with a sustained mouth pressure—a typical wash-in exponential function. Eventual tidal volume, 500 ml.; compliance, 50 ml./cm H_2O; airway resistance, 10 cm H_2O/1,000 ml./sec.; time constant, 0·5 sec.; half-life, 0·35 sec. The points on the curves indicate the passage of successive half-lives.

Lung volume above F.R.C. $= 500\ (1 - e^{-(t/0.5)})$

Elapsed time (constants)	*Lung volume attained above F.R.C.*	
	ml.	*Percentage of tidal volume*
0	0	0
0·69	250	50
1	316	63·2
2	433	86·5
3	475	95·0
4	491	98·2

Note that, for the semi-log plot, the log scale (ordinate) is from above downwards and indicates the difference between the equilibrium lung volume (inflation pressure maintained indefinitely) and the actual lung volume

y_∞ is the limiting value of y (attained only at infinite time).

e is again the base of natural logarithms.

k is a constant defining the rate of build-up and, as is the case of the wash-out function, it is the reciprocal of the *time constant* the significance of which is described above. It is the time which would be required to reach completion, if the initial rate were maintained without slowing down.

After 1 time constant, y will have risen to approximately 100 − 37 = 63 per cent of its final value.

After 2 time constants, y will have risen to approximately 100 − 13½ = 86½ per cent of its final value.

After 3 time constants, y will have risen to approximately 100 − 5 = 95 per cent of its final value.

After 5 time constants, y will have risen to approximately 100 − 1 = 99 per cent of its final value.

(More precise values are indicated in *Table 44*.)

Table 44

Percentage change of y *after the lapse of different numbers of time constants*

Time elapsed in time constants	*Tear-away function* $y = y_0 e^{kt}$ (*expressed as % of* y_0)	*Wash-out function* $y = y_0 e^{-kt}$ (*expressed as % of* y_0)	*Wash-in function* $y = y_\infty(1 - e^{-kt})$ (*expressed as % of* y_∞)
0	100	100	0
0·6931*	200	50	50
1	272	36·8	63·2
2	739	13·5	86·5
3	2,009	4·98	95·02
4	5,460	1·83	98·17
5	14,841	0·67	99·33
10	2,202,650	0·0045	99·9955
∞	∞	0	100

* Half-life or doubling time.

Note: $272 = 100 \times e$
$739 = 100 \times e^2$
$2{,}009 = 100 \times e^3$
etc.

Finally, the time constant for a wash-in exponential function equals the product of compliance and resistance, tissue volume divided by blood flow, or F.R.C. divided by alveolar ventilation. As above, the time constant is approximately 1·5 times the half-life.

There are many examples of both a wash-in and a wash-out in a single system with fixed parameters. The time constant for each function will then be the same. A classical example is the charging of an electrical capacitor through a resistance, and then allowing it to discharge to earth through the same resistor. The time constant is the same for each process and equals the product of capacitance and resistance. *Figure 126* shows inflation of the lung by a sustained pressure applied to the mouth. Assuming that compliance and airway resistance are the same for inflation and expiration, the inflation curve in

Figure 126 will be the mirror image of the expiration curve in *Figure 125*, and each will have the same time constant (equal to compliance times resistance).

Graphical Representation

The wash-in function may be represented on linear paper as for the other types of exponential function. However, for the semi-log plot, the paper must be turned upside down and the plot made as indicated in *Figure 126*. The curve will then be a straight line.

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