Papers and Originals

THE LUNGS IN MITRAL STENOSIS*

BY

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Dynamic Changes

Any approach to the dynamics of lung function in mitral stenosis requires a brief survey of the mechanisms of respiration, bearing in mind the effect one might expect to find on them of the elevation of pressures and generalized structural changes of the type found by the pathologist. The lungs are gas-exchangers designed to enable blood to have its haemoglobin saturated with oxygen and to give up a nearly equivalent volume of carbon dioxide. These functions are achieved with an efficiency which in its precision, and particularly its range of adaptability, far surpasses the highest creative skill of the chemical engineer. The limits of tolerance to which the machinery operates are very close. The walls of several million alveoli constitute the diffusion membrane, and the rate of air exchange or ventilation of these and the rate of blood flow through the capillaries have to be so adjusted as to ensure that blood leaving the lungs has an oxygen tension of around 96 mm. Hg and a carbon-dioxide tension of 40 mm. Hg over a range of activity extending from an uptake of oxygen of 150 ml./min./sq. m. at rest to levels of thousands of millilitres during exercise. The same range of activity is associated with a pulmonary capillary blood flow of 2 to 15 l./min./sq. m.

The crucial adjustment is the ventilation/perfusion ratio, which need not be identical in all alveoli but which must, in the aggregate, have a statistical distribution of values that secures the necessary exchange with the minimum expenditure of ventilatory work. The attainment of this objective requires not only a variety of "feed-back" controls but smooth, well-balanced devices to regulate air flow in and out of alveoli and to adjust the calibre of small muscular pulmonary arteries so as to ensure optimal blood flow. It is to be expected, therefore, that the sort of changes in tissue density that occur in the pulmonary venous hypertension of mitral stenosis should seriously upset pulmonary function.

The concept that lung congestion caused rigidity of the lungs was advanced as long ago as 1887 by von Basch (1891–6), who introduced the term "lungenstarrung." Drinker, Peabody, and Blumgart (1922) occluded the pulmonary veins of animals and noted the diminished change of volume per unit pressure in the lung.

Work of Breathing

Christie and Meakins (1934) approached the problem from a different angle by inducing a small pneumothorax in patients and observing the pressure changes in the air-pocket during respiration. They found that patients with heart disease such as mitral stenosis showed an abnormally large pressure difference per unit/volume of air ventilated. It is clear that quite apart from the efficiency of air distribution and adjustment of ventilation/perfusion ratios the whole process of moving air in and out of the chest constitutes work in the mechanical sense and that more work has to be done when the lung is abnormally stiff.

Various methods have been used to measure the work of breathing. Theoretically the most satisfactory measurement would be of the oxygen consumed by the repiratory effort. Liljestrand (1918) attempted to do this by measuring the increase in oxygen uptake during hyperventilation but found the method subject to many inaccuracies. Otis, Fenn, and Rahn (1950) measured the work of passive respiration by placing in a Drinker type respirator a subject trained to relax to the extent of inhibiting his respiratory effort. The work done can be calculated from the volume of air moved in and out of the lungs and the pressures required to effect this. This value includes the work done in moving the thoracic cage as well as in moving the lungs themselves. The method requires a trained subject and is rarely suitable for the investigation of a pathological state.

To measure the work of ventilation in respect of the lungs apart from the thoracic cage it is of course necessary to know intrathoracic pressure changes, as well as the volumes of air moved. Christie's (1953) small artificial-pneumothorax method was physically very sound, but the induction of even a minute pneumothorax, particularly in a patient with severe emphysema, is not entirely free from risk. This difficulty was completely overcome when it was realized that changes of pressure recorded from a balloon placed in the lower part of the oesophagus (Dornhorst and Leathart, 1952) were, for this purpose, sufficiently representative of general intrathoracic pressure. This method of pressure measurement was used by Marshall, McIlroy, and Christie (1954), while the velocity of air flow in and out of the mouth was recorded with the use of a Lilly pneumotachograph. Changes in volume were measured by graphic integration of the areas under the curves of velocity of air flow. A pressure-volume diagram was constructed from the instantaneous values of pressure and flow during a complete respiratory cycle. We (Arnott, Butler, and Pincock, 1954) used a similar method except that the volume of air displaced was measured in a spirometer and the instantaneous values of intra-oesophageal pressure and volume were fed as rectangular co-ordinates into a mechano-optical integrator and the resulting trace was photographed. Nowadays we, and most other operators in this field, feed simultaneous pressure and volume signals into the "x" and "y" axes of a cathode-ray tube and photograph the trace or measure it with the aid of a screen with graticules.

Two Main Activities

The work of ventilation is absorbed in two main activities. One of these is concerned with stretching the lung and is maximal at the height of inspiration; in fact, at the top of a single breath, when air flow is zero, the only work done is in holding the lung out against its elastic recoil. If overcoming elastic resistance were the only activity then a graph of pressure (or tension)/volume values would lie along a sloping straight line, the inclination

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of which would depend upon the volume change per unit change of pressure (or vice versa); that is, provided the range of tensions observed lay on the long relatively straight portion of the approximately sigmoid curve of pressure/volume or tension/length relationships of an elastic structure. This regression value of volume on pressure is termed the "compliance" and is a valuable functional index of the degree of stiffness of lungs. The energy that is used in overcoming elastic resistance to inspiration is absorbed by the lungs, where it is stored until its release during expiration.

The other work which has to be done in breathing is non-elastic and is often referred to as viscous work. The chief demand for this component of effort is in moving air along the respiratory passages, while a small portion is concerned with the non-elastic resistance offered by the tissues of the lungs. During a single breath the maximum non-elastic effort is expended during mid-inspiration and mid-expiration, when the velocity of air flow is maximal. The faster the air flows the more energy is used up in moving it. Furthermore, the energy requirements of moving air in a co-axial stream vary approximately as the inverse of the square of the cross-sectional area of the tube, so that anything which narrows the bronchial tree, such as inflammatory swelling of the bronchial mucosa or tenacious mucus, greatly increases the non-elastic component of ventilatory effort. This expenditure of effort in moving air imparts to the graph of pressure–flow values an elliptical configuration often called a "hysteresis" loop.

The amount of work performed in these two ways can be calculated from this pressure–flow diagram. The elastic work is represented by the area of the triangle, of which the long axis of the ellipse is the hypotenuse, while the area of the loop represents the non-elastic or viscous work. Otis, Fenn, and Rahn (1950) constructed graphs of elastic work, viscous work, and total work per minute of respiration at various frequencies and amplitudes. These curves showed clearly that the slower the rate and therefore the greater the depth of the breaths required to ventilate any given amount of air, the greater the elastic effort, while the faster and shallower the breathing the less the elastic work but the greater the viscous work. They showed that there was a frequency and volume combination of minimal effort which in the case of a ventilatory volume of 6 l./min. was 15; this is the best compromise between these two tasks, and it means that if the lungs are to be ventilated at 6 l./min. the most economical rate in terms of respiratory work is about 15 a minute, which is the normal respiratory rate.

Respiratory Work and Compliance in Mitral Stenosis

Alterations in the haemodynamics of the pulmonary vascular bed have been shown to influence the compliance. The acute intravenous infusion of saline in dogs lowers the compliance (Heyer, Holman, and Shires, 1948). Similar intravenous infusions of albumin in man also lowers compliance (Pryor and Page, 1954). G-suit inflation momentarily squeezes blood into the trunk and causes a marked elevation of pressure in both systemic and pulmonary circulations; compliance is thereby diminished. In animal experiments a fall in compliance has been found to be significantly correlated with elevation of left atrial pressure but not with pulmonary arterial pressure or changes in pulmonary blood flow (Borst, Berglund, Whittenberger, Mead, McGregor, and Collier, 1957).

It is a fact that a considerable part of the resistance to distension of lungs originates in the surface tension of the fluid lining the alveoli. In 1929 von Neergaard pointed out that the compliance of a lung filled with water was much greater than when filled with air. Variations in the surfactant properties of this mono-molecular layer of fluid may be of importance in mitral stenosis, and we have the matter under investigation.

Although the theory of measurement of compliance by the hysteresis-loop method is simple there are many complications in its practical performance, particularly in the accurate delineation of the long axis of the ellipse and in the assessment of the compliance in terms which can be compared usefully in individuals of different size. For instance, to take an extreme example, unit change of pressure will produce twice the volume change in lungs of a particular size as compared with lungs of twice that size. In 1957 Butler, White, and Arnott published a study which attempted to assess the shape of the curve of static pressure–volume relationships in normal individuals breathing to the limits of vital capacity, to determine the normal range and day-to-day variation of lung compliance, and to standardize the results by relating them to the total lung volume predicted from anthropometric data.

One result of this study was the demonstration that with large breaths approaching vital capacity the loop becomes distorted and its long axis becomes curvilinear. It was found that a satisfactory method of identifying the location of the long axis was to superimpose on the film a series of records of breaths of different size. This can be done without the informed co-operation of the subject by allowing him to breathe consecutive breaths in and out of the spirometer. The accumulation of carbon dioxide ensures a progressive increase in amplitude of the respiratory cycles. Another method, which required instructed co-operation, was to record a large breath taken very slowly. The element of viscous work was then so small that the loop virtually collapsed, leaving a straight line. With both methods it was possible to recognize the points of departure from rectilinearity at the extremes of the cycle.

It is clear that comparison of the retractive properties of lungs of different size requires an expression like the cardiac index which relates cardiac output to surface area. The factor in the expression which varies with size must be independent of the lung compliance. It was therefore thought better to estimate the expected size of the total lung capacity from anthropometric data and to relate the distension pressure to this. The final value calculated was the pressure in centimetres of water required to produce a change of 10% of the predicted total lung volume. Divided out, this ratio is, of course, the tangent of the angle made by the loop axis with the volume axis in contrast to the compliance, which is the cotangent of that angle. The range of such distension–pressure values in the group, when the data were thus made comparable, was less wide than that of the unstandardized compliance values. An even better index of lung compliance divorced from the distorting effect of varying lung volumes is provided by the "specific compliance," which is the ratio of compliance to functional residual capacity.

Relation of Haemodynamic Changes and Lung Compliance

White, Butler, and Donald (1958), in our laboratory, investigated the relation between haemodynamic changes and lung compliance of patients with mitral disease. Lung compliance, pulmonary vascular pressures, and blood flow were measured simultaneously both at rest and on exercise. The methods used were those that have just been outlined. Eighteen patients, all with mitral stenosis, were studied as

part of their initial assessment. None of them had undergone mitral valvotomy. These patients had a significantly lower mean compliance of 0.12 l./cm. H_2O in the supine position at rest than normals (0.24 l./cm. H_2O). Mean values of compliance in groups of patients classified according to disability showed a progressive reduction with increasing disability. As resting wedge pressures increased above normal, compliance was reduced. The lung compliance fell as the pulmonary arterial pressure and wedge pressure rose during exercise. In discussing their results these workers suggest that the increase in lung retractive force which accompanies increasing disability may indicate that the subjective sensation of dyspnoea is related to the work of breathing.

A definite relationship therefore appears to exist between compliance and pulmonary vascular pressures in that patients with normal resting pressures have lungs of normal elasticity while those with raised wedge pressures have reduced compliance. These observations are in accord with the view that "lung congestion," of which the compliance is an index, is in large measure due to raised pulmonary vascular pressures.

Christie followed up his earlier work (Christie and Meakins, 1934) in which diminished lung distensibility in congestive cardiac failure was noted, with an analysis of the work of breathing in mitral stenosis (Marshall, McIlroy, and Christie, 1954). Twenty-five patients with mitral stenosis were studied by recording simultaneously intrathoracic pressure through an intra-oesophageal balloon and air-flow velocity at the mouth. Pressure–volume diagrams were prepared from these data. Observations were made both at rest and after exercise to the point of dyspnoea. The compliance was found to be lower at rest and to fall further as the result of exercise. A comparison of the work required to ventilate the lungs showed that patients with mitral stenosis have to do about two to three times as much work as normal people to achieve a given minute-volume.

The study also included observations on patients in the sitting and supine positions. Whereas in normal people the work of breathing increases when the person lies flat, with little change in compliance, in patients with orthopnoea there is a decrease in compliance when they lie flat accompanied by a greater increase in respiratory work. The work of breathing at different respiratory rates was calculated in some patients, the change in frequency being effected by exercise. It was found that at each level of activity the respiratory rate adopted corresponded closely to the value at which the minimum work was achieved. This observation indicates that patients with mitral stenosis, like normal people, adopt a rate and depth of breathing which represents the minimal expenditure of energy. Although these authors make no mention of it, a study of their graphs shows that not only did patients with mitral stenosis have to do more work to overcome the elastic resistance of the lungs but they also had to expend an abnormally large amount of energy in performing viscous work. A similar point had also been observed in our laboratory. The implications of this factor are considered when airway changes in mitral stenosis are discussed.

Air Distribution

It is important for normal respiratory function that each inspiration be uniformly distributed among the three hundred million alveoli. Any portion of the lung which is underventilated will have a low respiratory exchange ratio (<0.7) because the alveolar oxygen tension is not high enough to saturate the blood passing through its capillaries and the carbon-dioxide tension is too high to allow of normal transfer of that gas from blood to air. Conversely, if any portion be overventilated then there will be a high exchange ratio (>1) due to the low alveolar carbon-dioxide level, which allows too much gas to escape. It is one of the marvels of pulmonary physiology that in health each respiratory cycle ventilates the whole of both lungs with remarkable uniformity. This is shown by the rate of nitrogen dilution in normal lungs as they are respired with pure oxygen, which, taken expiration by expiration, is almost exponential until equilibrium is approached.

A more convenient and even more graphic method of assessing the efficiency of air-mixing is by the use of the nitrogen meter with which a record of the nitrogen content of a continuous sample of expired air can be obtained. The subject takes a breath of one litre of pure oxygen and then exhales. In a normal person the nitrogen content of the expirate rises rapidly during the emptying of the first few hundred millilitres, but thereafter the nitrogen content is uniform, indicating that the preceding inspiration of oxygen has been distributed uniformly throughout the lungs. Comparisons are made of the nitrogen concentration of that portion exhaled between the 750 and 1,250 ml. levels. Normally the increase in nitrogen concentration over that range should be no more than 2.5%.

Uneven distribution of inspired gas implies variation of time constants of ventilation in different parts of the lungs which leads to sequential emptying during expiration. This can be due to local differences of lung compliance and airway resistance. The change in nitrogen concentration during expiration provides an estimate of the degree of uneven ventilation. It can be expected that the sort of structural and functional changes in the lung that occur in mitral stenosis are likely to cause non-uniformity of air distribution, particularly as the compliance and work studies show not only decrease of compliance and increase of work but a definite increase of non-elastic or viscous work. Normal uniform air distribution demands of the lungs an extremely high degree of aerodynamic harmony, which must inevitably be impaired by anything that distorts tissue elasticity and calibre of airways.

My colleagues have published a study of the distribution of alveolar ventilation in mitral stenosis at rest and after exercise (Raine and Bishop, 1963). This was studied in 20 patients with mitral stenosis and 20 normal people selected so as to match the patients with mitral stenosis as closely as possible in age and sex. As part of their clinical assessment all the patients with mitral stenosis were studied by cardiac catheterization within a few days of the nitrogen-meter tests. Of the 20 patients, 12 gave a history of chronic cough and sputum indicative of bronchitis. The mean resting values of nitrogen concentration difference in the normal people was 2.25% (S.D. 0.61) and in the patients with mitral stenosis 3.21% (S.D.1.11). These means differed significantly ($P<0.001$). Initially, these investigators considered that a possible explanation of this impaired air distribution was that many of their patients had chronic bronchitis in the sense that they had chronic productive cough. It is known that patients with chronic bronchitis alone usually have an increased airways resistance and increased unevennesss of ventilation. However, there was no difference between the 12 patients with bronchitis and the eight without.

The possibility was then considered that the uneven ventilation might be the result of increased transudation of fluid from the pulmonary capillaries into the lung as the

result of the pulmonary venous hypertension. Such fluid might lie in the alveoli, the air passages, or the connective-tissue strata. This would alter compliance and cause airway stenosis. It was to clarify this possibility, therefore, that the tests were repeated immediately after the pulmonary capillary (wedge) pressure had been raised by exercise on the treadmill to the point of dyspnoea. This could be confidently anticipated to increase the rate of transudation. It was found that patients with mitral stenosis showed an increase of ventilatory unevenness after such exercise whereas no such change was found in the normal people nor in a group of patients with chronic bronchitis but no heart disease. The conclusion was reached that these experiments lend support to the view that the increased unevenness of ventilation in mitral stenosis is, at least in part, a consequence of the high pulmonary capillary pressures with an increased rate of transudation. Care was taken to point out that another variable in the mechanism of causation of this defect could be the rate of removal of transuded fluid along lymphatic channels which tend to be more and more restricted as the secondary pulmonary changes of mitral stenosis develop.

Ventilation/Perfusion Relationships

Emphasis has been placed already on the fact that efficient pulmonary function requires that the ventilation/perfusion ratios of the alveoli should be distributed normally, with comparatively little deviation around a mean determined by the respiratory quotient dictated by the current metabolic activities of the whole body. It has been shown that the structural lung changes of mitral stenosis interfere with the uniformity of alveolar ventilation. The question now arises, Do they interfere also with alveolar perfusion in such a way as to disorder ventilation/perfusion ratios? Judging by the structural abnormalities in the blood-vessels it would seem likely that patterns of capillary blood flow would be upset. While gross abnormalities of these ratios will so upset respiration that arterial oxygen unsaturation, with alteration of the plasma carbon-dioxide tension, will result, a considerable measure of inequality can exist before this occurs. Albeit, equilibrium may be preserved by balancing abnormal values at the cost of excessive ventilatory work with consequent dyspnoea.

A relatively crude indication of abnormality in these ratios can be got by analysing continuously the carbon-dioxide content of an exhalation. Normally this is reasonably uniform, with perhaps a slightly greater concentration at the end of the breath, but if the last part of the expired gas has a much greater carbon-dioxide content than the first part it means substantial inequality of ventilation/perfusion ratios. The gas with a high carbon-dioxide content has come from relatively underventilated alveoli. Riley, Cournand, and Donald (1951) have devised a much more accurate indirect method of assessing the degree of inequality of the ventilation/perfusion ratios. The ventilatory factor is assessed by calculating the "physiological dead space" by Bohr's equation, using the value of arterial P_{CO_2} as representing the mean alveolar P_{CO_2}. If the ventilation/perfusion ratios are absolutely uniform then "physiological dead space" equals the "anatomical dead space"; but if the former be larger, then it means that there are alveoli in which the ventilation is excessive for the degree of perfusion.

An index of inadequate ventilation is the degree of "venous admixture" or "physiological shunt." This can be calculated from the values for the arterial, mixed venous, and end-pulmonary capillary oxygen contents. The resulting value is an expression of the extent to which the pulmonary venous blood is contaminated by blood which has not been saturated with oxygen. The value for alveolar–arterial difference in oxygen tension is normally 9 mm. and is made up of several components. Firstly, there is the true anatomically shunted blood which has not been near respiratory capillaries. This comes mostly from bronchial and thebesian veins. Secondly, there is blood which has passed through underventilated respiratory capillaries and has not therefore been fully oxygenated. Thirdly, there may in pathological states be blood which, although it has come from alveoli with normal ventilation/perfusion ratios, has not been fully oxygenated because of a diffusion defect such as an increase in length of the air/blood pathway.

Riley and his colleagues have devised ingenious methods of identifying the proportion of this gradient which is due on the one hand to anatomical shunting plus deficient alveolar ventilation—that is, physiological shunting—and on the other hand to defective diffusion. After determining the physiological dead space and alveolar capillary gradient for oxygen while breathing air, the observations are repeated breathing 12% oxygen. This level of oxygen tension falls on the sigmoid oxygen-haemoglobin dissociation curve at its steep straight part where the effect of the admixture of 1–2% of shunted blood makes an insignificant contribution in terms of millimetres of oxygen tension to the A-a gradient, which now can be regarded as almost wholly due to the diffusion gradient.

A development of this technique is to repeat the measurements a third time while the subject is breathing 100% oxygen, which results in all blood passing through the respiratory capillaries being fully saturated but has no effect on anatomically shunted blood. The result is to magnify relatively the effect of such blood on the oxygen tension of arterial blood. The membrane or alveolar-capillary-wall component at this high oxygen tension is negligible. The A-a difference is therefore due entirely, at least in the normal person, to anatomical shunting; furthermore, as the A-a gradient at this high level of oxygen is proportionately large, being of the order of 30 mm., it can be measured much more accurately.

Blood/Gas Distribution

In 1959 Söderholm and Werkö reported that they had found that the oxygen saturation of arterial blood decreased during the infusion of acetylcholine in patients with mitral stenosis. It was suggested that this was due to the increased perfusion of poorly ventilated alveoli which had been previously poorly perfused. Bishop, Harris, Bateman, Davidson, Donald, and Raine (1961, 1962), in our department, have investigated, by the measurement of blood/gas tensions, the possible existence of such faulty gas/blood distribution in mitral stenosis. The work was greatly facilitated by the use of the Clark electrode, as modified by Bishop and Pincock (1959) for the estimation of oxygen tension polarographically. This enables high oxygen tensions to be measured easily. They began by investigating in 12 patients with mitral stenosis the alveolar and arterial (A-a difference) oxygen tensions and physiological dead spaces both at rest and while exercising during the infusion of acetylcholine into the right atrium.

The average value of the A-a difference in these patients at rest breathing 47% oxygen was found to be about twice the normal value. As it is thought that no appreciable end-capillary gradient should exist at the high alveolar oxygen tension used, the total A-a difference must therefore be

due to anatomical right-to-left shunting, with possibly a component due to inequality of ventilation/perfusion ratios. The increased values found in these patients with mitral stenosis might therefore be due to an increased volume of shunt or the admixture of blood from alveoli with a low V_A / Q_C ratio. It was concluded that anatomical shunting was not an adequate explanation of this abnormally high gradient for several reasons. Prominent among these was the fact that while the mean A-a gradient increased, increases and decreases of A-a difference occurred both during exercise and the infusion of acetylcholine at rest and during exercise. At the same time there occurred significantly correlated changes in the physiological dead spaces. This strongly suggests that a substantial fraction of the total A-a difference is due to unequal ratios of alveolar ventilation to pulmonary capillary blood flow.

It is necessary to emphasize that there is every reason to believe that the acetylcholine is inactivated so rapidly in the blood-stream that its action is limited to the pulmonary circulation. This is supported by the fact that in these studies there was no observed change in total pulmonary ventilation or respiratory frequency; neither was there any alteration in the amplitude of the respiratory variation in pulmonary wedge pressure during the infusion of acetylcholine. This excludes any possibility of the effects observed being due to acetylcholine influencing the bronchial or thebesian vessels or by influencing distribution of ventilation by action on airways. The existence of intrapulmonary arteriovenous shunts, such as could be influenced by acetylcholine introduced into the right atrium, is not known in mitral stenosis although these are recognized easily in some types of congenital heart disease.

As already stated, Bishop and his colleagues found that the alterations in A-a gradient induced by acetylcholine were sometimes increases and sometimes decreases. They noted that the increases were usually in patients with pulmonary arterial pressures of less than 45 mm. Hg—that is, the less severely involved—while the reduction in A-a gradients tended to occur in those with pulmonary arterial pressures of above 45 mm. Hg—that is, those who presumably have more severe pulmonary involvement. It is known that in mitral stenosis air distribution is impaired and that, as a consequence, underventilated areas exist. Local anoxia has the effect of constricting the blood-vessels to that area, thus constituting a self-regulating mechanism concerned with maintaining the proper level of ventilation/perfusion relationship.

These anoxic pulmonary vessels, being at a higher tonus, might be expected to show a preferentially greater degree of relaxation under the influence of acetylcholine, and this may account for the increase in A-a gradient. Admittedly this hypothesis rests on the assumption that even while breathing 47% oxygen-enriched air the vessels of underventilated areas are capable of reacting by constriction to what is a relative anoxia. In the later stages of mitral stenosis, when substantial muscle hypertrophy is present in the small muscular pulmonary arteries extending into the arterioles, the effect of acetylcholine will be to relax these vessels, causing an increase in local blood supply in parts of the lung, irrespective of their local ventilation and alveolar oxygen tension, so that the effect is to diminish the A-a difference and dead space, thus overriding the effect of anoxic vessels. In the later stages of mitral stenosis, therefore, the influence of maldistribution of blood predominates over the influence of maldistribution of air.

Having come to the conclusion that these studies supported the hypothesis of the existence of substantial ventilation/perfusion abnormalities in mitral stenosis my colleagues (Bateman *et al.*, 1962) tested the hypothesis by carrying out similar studies using the inhalation of 100% oxygen in addition to air and 47% oxygen. In this situation there can be no question of any recognizable distribution component of oxygen when the pure gas is being respired. It was found that the A-a difference when breathing 100% oxygen was less than when breathing 47% oxygen. There was no correlation between the A-a difference and physiological dead space when breathing 100% oxygen, in contrast with the situation when breathing air and 47% oxygen. Neither the A-a difference nor the physiological dead space changed significantly during the infusion of acetylcholine when the patients breathed 100% oxygen. These gas-tension studies therefore appear to support conclusively the existence in mitral stenosis of substantial abnormalities of ventilation/perfusion relationships.

Ventilatory Volume

In view of these changes of function and structure that occur in the lungs as the result of mitral stenosis it is not surprising that increased ventilation, and its subjective component of dyspnoea, is the most prominent clinical feature of chronic rheumatic heart disease. Some years ago my colleagues Donald, Bishop, and Wade (1954) studied the minute-to-minute changes of ventilation, oxygen uptake, arteriovenous oxygen difference, and cardiac output during exercise in 16 patients, all of whom had mitral stenosis and were candidates for mitral valvotomy. The patients were divided into three groups according to the level of work they could sustain for five minutes without distress. This was equivalent approximately to walking on the flat at 3, 2, and 1 mile an hour.

Group 1 patients achieved a maximum oxygen uptake of 550 to 750 ml./min./sq. m. for five minutes. One symptomless patient showed a normal respiration response of resting ventilation of 3.33 l./min./sq. m. rising to 9.3 l., at which level the oxygen uptake was 602 ml./min./sq. m., giving an oxygen extraction from the respired air of 6.48%. The other patients had resting ventilations of from 3.3 to 5.6 l. rising on exercise to maxima of 15.8 to 20.8 l., with maximum oxygen extraction rates of 3.79 to 4.95%. Group 2 patients were considerably disabled and were capable only of five minutes' exercise, involving a maximum oxygen uptake of 360 to 490 ml./min./sq. m. Their resting ventilation ranged from 3.8 to 6 l./min./sq. m., their maximum exercise ventilation from 10.5 to 25.8 l., and the oxygen extraction from 4.51 down to 1.7%. In this small group there is quite a striking correlation between the degree of disability and the elevation of the resting ventilation and the ventilatory response to exercise. Those with the highest resting ventilation and lowest oxygen extraction showed the greatest ventilatory response. The four patients in group 3 were all severely disabled, falling into grades IIIB or IV of the New York Heart Association classification, and were therefore unable to achieve exercise levels of more than 299 ml./min./sq. m. uptake of oxygen. The average resting ventilation lay between 4 and 5 l./min. and on exercise it rose as high as 12.1 l. The oxygen extraction was in the 2–3% zone.

Another abnormality of these patients with mitral stenosis is that when they begin to exercise the ventilatory rate increases abruptly without the lag of one to two minutes that normal people show. Because of this rapid augmentation of ventilation these patients do not show the rapid rise in oxygen extraction which characterizes the normal response to exercise. Some light on this latter feature may be shed by some observations which Armitage

and I (1949) reported. We found that in normal people the taking of a deep breath results in a swift elevation of the oxygen uptake, the only explanation for which seems to be that the act of deep inspiration draws into the thorax and lungs an extra volume of venous blood. From what we know of the state of the lungs and pulmonary circulation in mitral stenosis it would seem unlikely that such additional quanta of blood could be accommodated; the result of this inadequacy would be a slowing of the rise in oxygen uptake during a large breath. Donald (1959a), I am sure correctly, considers that this rapid increase of ventilation as soon as exercise begins is an important cause of these patients' discomfort, as they are deprived of this useful "buffering" of ventilation on transient exertion.

The important question arises whether ventilation in mitral stenosis is *adequate*. I think the answer is that on the whole it is if we take as criteria the maintenance of arterial oxygen and carbon-dioxide tensions at physiological levels; in fact, it is quite often excessive in that there is hyperventilation in the sense that the arterial P_{CO_2} is depressed down to levels approaching 30 mm. Hg. Exercise in the more severely affected patients often causes slight depression of arterial oxygen saturation percentage to values in the low 90's which, of course, means quite substantial falls in tension; but the alterations are in no way comparable with those seen constantly in the ventilatory failure of chronic bronchitis and alveolo-capillary block. If one, however, poses the question of whether ventilation is *efficient* in mitral stenosis, the answer is undoubtedly "No." It costs too much in terms of the most basic currency in Nature—that is, energy, expressed as oxygen consumed. My colleagues (Donald *et al.*, 1954, 1957b) and many others have found persistent elevation of resting oxygen consumption in mitral stenosis of up to as much as 200 ml./min./sq. m., which may well be due to the increased ventilatory effort. At exercise levels the ventilatory volume and work done in relation to oxygen uptake indicates excessive respiratory effort.

The excellent work of Christie and his colleagues, to which reference has already been made, shows that this excessive effort is spent not only in overcoming the increased resistance to distension of the indurated lungs but in moving air through the air passages. This latter defect is doubtless due to the state of chronic congestion with excessive moisture in the bronchial tree which is characteristic of mitral stenosis. It has been shown that the adjustment between the values of frequency and amplitude of respiration to produce any given ventilatory volume is closely related to the type of work involved; thus when elasticity is diminished, as in induration, the breathing is more rapid and shallow so as to minimize the elastic component. Such is a characteristic of the pattern of breathing in mitral stenosis, as indeed it is of all varieties of what is often collectively, and somewhat colloquially, referred to as "pulmonary fibrosis."

One result of this pattern is that the ratio of dead-space volume to tidal volume increases, with a consequent reduction in the ratio of alveolar ventilation to tidal volume. This in itself does not appear to impair ventilatory achievement in mitral stenosis, as the normal or low arterial P_{CO_2} indicates adequate alveolar ventilation. There is still no clear concept of the mechanism whereby ventilation is linked to cardio-respiratory dysfunction in mitral stenosis. The levels of P_{O_2} show so little departure from normal that it would seem unlikely that they stimulate the carotid sinus receptors at rest. During exercise, however, patients with mitral stenosis experience a marked reduction in ventilation while breathing oxygen, which suggests that anoxia may play some part in causing dyspnoea. Blood carbon-dioxide tension and *p*H play no part.

Regional Disturbances

It is known that the reduced cardiac output and increased arteriovenous oxygen difference across the lungs exposes the various regions of the body to greatly reduced mean oxygen tensions in their blood supply. In fact, the whole question of abnormal patterns of regional blood flow at rest and exercise in mitral stenosis has been one of the main research activities of our department over the last ten years (Donald *et al.*, 1957; Bishop *et al.*, 1958) and was reviewed by Professor Donald (1959b) in his Bradshaw Lecture. One fact emerges clearly, and that is the remarkable degree of preservation of cerebral blood flow in the face of severe restriction of cardiac output. Such an adjustment is a condition of survival. Other territories may have their blood supply so reduced that the venous blood leaves its capillaries almost completely stripped of oxygen. It therefore seems unlikely that any local defect in quality of blood supplied to the respiratory centre can play a part in stimulating ventilation.

It has been suggested that the unduly low oxygen tension in many parts of the body leads to an increase of anaerobic metabolism with the production of lactic acid, pyruvate, or some such substance. Harris, Bateman, and Gloster (1962a, 1962b), in our department, are studying the metabolism of glucose in resting and exercising muscle in patients with mitral stenosis. They have noted a close positive correlation between the lactate/pyruvate ratio of arterial blood and ventilation. While there may be an element of causality in this association they are not directly linked, as the lactate-pyruvate ratio changes throughout exercise while the ventilation remains relatively constant. There is a persistent belief in the hypothesis that the main factor in the production of these ventilatory phenomena is the operation of a reflex whose sensory organs are strain gauges situated in the lungs and are actuated by tissue tension—that is, the Hering–Breuer reflex. Direct proof of this is lacking, but it would explain many, if not all, of the reactions observed.

Effects of Mitral Valvotomy

We come now to the important matter of the effect of mitral valvotomy not only on the general well-being of the patient but on the many measurable aspects of cardio-respiratory function which we have discussed. There rests on all surgeons, and on the physicians who aid and abet them in their operations, the strong moral obligation to assess as scientifically as possible the effects of operative procedure on function. It is only thus that knowledge can grow and from it treatment can improve. To every good surgeon an operation is a scientific experiment as well as an act of treatment.

Wade, Bishop, and Donald (1954) reported the effects of mitral valvotomy on the cardio-respiratory function of 10 patients who had been operated on by Professor A. L. d'Abreu or Mr. J. L. Collis six to nine months previously. An arbitrary assessment of the results of operation was based on interviews, and resulted in five patients being regarded as having a "very good" result, three a "good" result, and two a "poor" result; in the last two the surgeon reported predominant mitral regurgitation. Of all the characteristics of cardio-pulmonary function measured in those patients, the characteristics which showed the greatest measure of change in the direction of normality were ventilatory. In all there was a consistent fall in resting

ventilation, but the really dramatic change was in the great reduction, as compared with the pre-operative measurements, in ventilation during the five-minute exercise test. The pattern of oxygen uptake was much less abnormal in that there was a marked increase of oxygen extraction during the first two minutes of exercise, or, to put it conversely, there was a return of the normal lag in the development of the hyperventilation of exercise. The maximum ventilatory capacity, which before operation had shown moderate impairment, was considerably improved. This change combined with the reduced exercise ventilation resulted in a striking reduction in the ratio of exercise ventilation to maximum ventilatory capacity. Pulmonary wedge pressures were reduced post-operatively in all patients, but in none to a normal level.

Neither the post-operative pressures nor the degree of reduction of these pressures showed any close correlation with the clinical state. As regards cardiac output, resting levels showed little change, but there was a marked improvement in five patients in whom during exercise the output rose to an extent which in one or two instances was not far short of normal. In fact, the improvement of output was of a greater proportionate magnitude than the reduction in pulmonary vascular pressures, which meant that pulmonary vascular resistance was higher and the work of the right ventricle was increased. At that time the authors expressed some concern about the ultimate effect of this load on the right ventricle.

Findings of a Study

A further report in 1957 by Donald and his colleagues gave the results of the study of 28 Birmingham patients before and after mitral valvotomy performed 17 to 51 months (mean 25 months) previously. They included 9 of the 10 patients who had been the subjects of the previous study. Of the 28 patients, 24 were greatly improved as judged by general clinical criteria. Calcification of the mitral valve, auricular fibrillation, and raised sedimentation rate had not precluded a good result. The most striking finding was that both resting and exercise ventilation were greatly reduced after operation in most of the patients. It was noted that there was a good correlation between the resting ventilation and the level of resting oxygen consumption, both of which fell after operation. It was suggested that the reduced resting oxygen uptake was the result of the greatly diminished work of breathing. If the increased oxygen uptake had been due entirely to increased work of ventilation it would have implied a ventilatory cost of around 4–6 ml./l. of ventilation in contrast to the normal figure of 0.5–1 ml./l.

Despite the marked clinical improvement the resting cardiac output fell after operation in 24 of the 28 patients, and in 20 it was below 2.5 l./min./sq. m. The response of the cardiac output to exercise was greater than before operation in only six patients, so that the improvement in exercise output noted in the earlier study was not found in this longer-term series. Frankly there is no satisfactory explanation of this persistent abnormality of behaviour of the cardiac output, it merely serves to emphasize how ignorant we are of the control of healthy cardiac output levels, without which we are not likely to understand pathological states.

Measurements of the pre- and post-operative wedge pressures at rest were obtained in all but three patients. Before operation the resting wedge pressures were elevated in every case. After operation the pressure fell in all but two patients, though not to normal levels, remaining mostly in the 30–15 mm. Hg zone as compared with pre-operative levels of 40–25 mm. Hg. There was a striking correlation between resting ventilation and wedge pressure both before and after operation. There is no certainty, however, that these two variables are causally related, although it is not at all unlikely that the reduction in pulmonary vascular pressures has an ameliorating influence on pulmonary turgidity and thus on ventilatory effort. On exercise the wedge pressure was extremely elevated even in those patients who now had no disability. Right ventricular work was reduced considerably in most members of this series owing to the fall in pulmonary vascular pressures and the continual low cardiac output; thus the trend towards increased right ventricular work noted in the earlier post-operative study was not maintained. There was no evidence in this later series of undue right ventricular hypertrophy.

Conclusion

All the measurements carried out in the post-mitral valvotomy patients strengthen the hypothesis that from the point of view of disability and mortality the principal disturbances of mitral stenosis are pulmonary and are mediated by elevation of pulmonary vascular pressures which cause structural abnormalities that result in functional disorganization. The low cardiac output that is a feature of mitral stenosis imposes quite abnormal patterns of regional distribution, some of which, particularly renal and splanchnic, have grave pathological significance; but, nevertheless, it spares the lung a substantial amount of pressure stress. If output were not reduced and normal amounts of blood were driven through at the very high pressures which would be necessary the lungs would be rapidly destroyed and would, among other abnormalities, come soon to present an insuperable block in the lesser circulation. The disease would in all probability pursue then a course to death in months rather than years.

Mitral stenosis, then, is, in its clinical aspects, largely a pulmonary disease. What help do all these many measurements, careful correlations, and continuous speculations bring to the patient? The answer is clear, "Everything must be done to minimize pulmonary venous hypertension." Mitral valvotomy should be done in every patient as soon as there is definite evidence of raised pulmonary pressures at rest. On the other hand, I think that normal pressures at rest with moderate elevation of oxygen uptake during exercise of up to 600–1,000 ml./min./sq. m. do not indicate immediate valvotomy, as there are patients with mitral stenosis in whom the obstruction is not enough to set in train the processes which lead progressively to severe pulmonary hypertension. Such patients, however, should have further haemodynamic assessment in two to three years, and if the pressures are rising then valvotomy should be done.

Such, then, is my message, "Pulmonary venous hypertension of mitral stenosis ruins lungs."

In conclusion I would emphasize again that these lectures do not attempt a review of the vast literature on this subject. They are simply the story of the studies over some 15 years of a group who have combined with the practice of medicine an attempt to unravel some of the cardio-pulmonary aspects of mitral stenosis. The story has been told by one who has played the part of an intensely interested and enthusiastic observer. I am greatly indebted to all my colleagues; their names are to be found in the bibliography.

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PULMONARY EMBOLISM

BY

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In a previous study of myocardial infarction (Honey and Truelove, 1957) it was concluded that: "The overall effect of anticoagulant therapy on the fatality-rate has not been very great, and the improvement can be accounted for by the almost complete abolition of deaths from pulmonary embolism." As an incidental observation it was noticed at that time that, although death from pulmonary embolism had become infrequent in patients with myocardial infarction since the introduction of anticoagulant therapy, pulmonary embolism was responsible for a considerable number of deaths in the whole hospital population and that the number was increasing from year to year. The present study is an analysis of the experience of two Oxford hospitals with respect to pulmonary embolism during the decade 1952–61.

Sources of Data

The case notes of all patients in the Radcliffe Infirmary and Churchill Hospital diagnosed as having sustained a pulmonary embolism during the period under review have been examined. Patients attending the maternity department, which keeps its own case notes, were excluded. Relevant information was extracted and put on punch-cards for mechanical sorting. As pulmonary embolism is frequently a subsidiary diagnosis, it is important to place on record the fact that the particular records clerk responsible for the diagnostic index makes an invariable practice of reading the entire case history of every patient in order that such subsidiary diagnoses should not be omitted. All case notes bearing the diagnosis of pulmonary embolism were examined in detail by one of us, and some of these were rejected because the evidence in them favouring a pulmonary embolism was judged to be inadequate. Among the patients who died, a considerable proportion of the diagnoses were either confirmed by post-mortem examination or were first made then. After rejecting the doubtful cases there were 853 case notes left for analysis.

Increasing Frequency of Pulmonary Embolism in the Hospital Population

During the decade under review there was an impressive rise in the frequency of recorded cases of pulmonary embolism, there being nearly five times as many in 1961 as in 1952. Throughout the whole period, in approximately one-half of the recorded cases, the patient died, so that the