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Blood Flow to the Lung and Gas Exchange

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THERE HAVE BEEN substantial advances in our understanding of pulmonary gas exchange, particularly the role played by pulmonary blood flow, in the last few years. The introduction in the late 1950's of radioactive gases to measure the topographic distribution of blood flow resulted in a rapid advance in this area. More recently, new insights into the relationships between blood flow, ventilation, and gas exchange have been provided by numerical analysis by means of the digital computer. We can identify three stages in the history of understanding the difficult subject of ventilation–perfusion relationships. In the first, exemplified by the work of Haldane,[1] Krogh and Lindhard,[2] and others in the early part of this century, the principle that the gas exchange in any part of the lung is determined by the relative amount of ventilation and blood flow was clearly established. Then, in the late 1940's and 1950's, Fenn, Rahn and Otis[3] on the one hand, and Riley and Cournand[4] and their colleagues on the other, developed the graphic analysis of pulmonary gas exchange. This was a major advance because the oxygen and carbon dioxide dissociation curves are not only nonlinear but interdependent, and they defy all attempts at algebraic manipulation. Then, in the last few years, it has been possible to fit the oxygen and CO_2 dissociation curves by computer subroutines,[5,6] and this allows us to answer questions about gas exchange which only a few years ago seemed impossibly complicated.

This review looks first at the influence of total pulmonary blood flow on gas exchange. Then some recent advances in the field of the topographic inequality of blood flow are reviewed. Finally, some new data on distributions of blood flow and ventilation–perfusion ratio within the lung are discussed.

Total Pulmonary Blood Flow and Gas Exchange

The lung is the only organ of the body which is required to receive the whole of the cardiac output under a variety of conditions. As a result, total pulmonary blood flow may vary between less than 5 to more than 20 liters per minute from conditions of rest to strenuous exercise. The vascular resistance of the normal pulmonary circulation is remarkably low, and it has the ability to become even smaller as total blood flow increases. This fall in vascular resistance is brought about partly through the opening up of new vessels and also through the increase in caliber of those already open, as is discussed in the next section. As a consequence, pulmonary arterial pressure rises much less with exercise than would otherwise be the case.

In terms of gas exchange, variations in total pulmonary blood flow are of relatively minor importance compared with inequalities of its distribution. If there is no ventilation–perfusion inequality within the lung, or if this is minimal in terms of impairment of overall gas exchange, as is the case in the normal lung, arterial P_{O_2} and P_{CO_2} are virtually unaffected by large alterations in total blood flow. However, as pulmonary blood flow increases, the proportion of the oxygen in the arterial blood which is extracted by the tissues is reduced, and therefore P_{O_2} in the tissues and in the mixed venous blood rises. This can be seen from a version of the Fick equation:

$$C\bar{v}_{O_2} = Ca_{O_2} - \frac{\dot{V}_{O_2}}{\dot{Q}}$$

where $C\bar{v}_{O_2}$ and Ca_{O_2} refer to the oxygen contents of mixed venous and arterial blood

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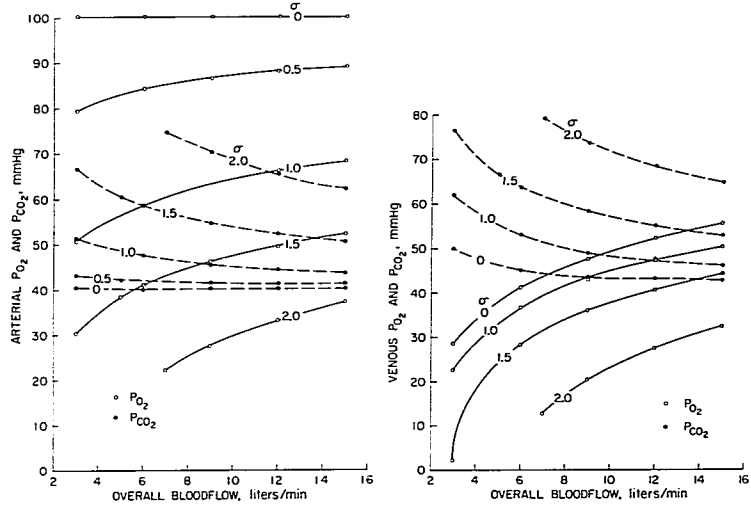

FIG. 1. Effects of changes in total pulmonary blood flow on P_{O_2} and P_{CO_2} in arterial (*A, left*) and mixed venous (*B, right*) blood. Solid lines show P_{O_2}, broken lines P_{CO_2}. The numbers on the lines are the standard deviations (σ) of the $\dot{V}_A/\dot{Q}$ distributions of the lung models. Note that an increase in blood flow results in modest gains of P_{O_2} and falls of P_{CO_2} in arterial blood, but the changes are greater in mixed venous blood.

respectively, $\dot{V}_{O_2}$ is the oxygen uptake by the tissues, and $\dot{Q}$ is cardiac output. Thus, an increase in cardiac output will result in an increase in the oxygen content and therefore the P_{O_2} of mixed venous blood. By the same token, a decrease in pulmonary blood flow such as may occur in oligemic shock may cause a profound fall in the P_{O_2} of the tissues and the mixed venous blood. However, it would be possible for the P_{O_2} and P_{CO_2} in arterial blood to be virtually unaffected by the fall in pulmonary blood flow if there were no ventilation–perfusion inequality in the lung. In practice, however, most patients with oligemic shock do have some uneven ventilation and blood flow in the lung.

When ventilation–perfusion inequality is present, changes in total pulmonary blood flow will influence the P_{O_2} and P_{CO_2} of arterial blood as well as mixed venous blood. There has been some confusion in this area. It has sometimes been argued that if the pulmonary blood flow is reduced in the presence of ventilation–perfusion inequality, the overall ventilation–perfusion ratio of the lung will increase, and therefore the P_{O_2} of arterial blood will rise and the P_{CO_2} will fall. This is a fallacy. By and large, the more ventilation and/or blood flow the lung receives, the higher the arterial P_{O_2} and lower the P_{CO_2} of arterial and mixed venous blood.

Quantitatively, the effects of changing total pulmonary blood flow on the arterial blood gases in lung models with various ventilation–perfusion inequalities can be seen from figure 1. These calculations[7] were made assuming that the lung had a log normal distribution of ventilation–perfusion ratios, that is, that the plots of ventilation and blood

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flow with respect to ventilation–perfusion ratio had the shape of a normal distribution curve when ventilation–perfusion ratio was plotted on a log scale. This is explained further below. If we fix on one particular value of ventilation–perfusion inequality, say a log standard deviation of 1.5, it can be seen that as total pulmonary blood flow was increased, there was a moderate gain in arterial P_{O_2} but a faster increase in the P_{O_2} of mixed venous blood (solid lines). These changes were accompanied by modest falls in the P_{CO_2} of both arterial and mixed venous blood (broken lines). Thus, we can conclude that in a lung with a considerable ventilation–perfusion inequality, arterial P_{O_2} will rise and P_{CO_2} fall if total pulmonary blood flow is increased. Larger changes are seen in the mixed venous blood. However, in general, the arterial blood gases are much more sensitive to alterations in total alveolar ventilation than total capillary blood flow.

Topographic Inequality of Pulmonary Blood Flow and Gas Exchange

The topographic inequality of blood flow in the normal upright human lung and the changes which occur with posture, exercise, and various types of heart and lung disease have been reviewed extensively over the last few years. Only a summary is given here. Figure 2A shows the normal distribution of blood flow in the upright human lung,[8] and it can be seen that blood flow decreases strikingly from bottom to top and that the apex is very poorly perfused. With the subject in the supine position, the apex and base have the same blood flow but the anterior part of the lung, which is uppermost, has less blood flow than the posterior dependent region. In the left lateral position, the blood flow to the dependent left lung exceeds that to the right. On exercise in the upright position both apical and basal blood flows increase so that the proportional difference between apex and base decreases.

Figure 2*B* shows a simple three-zone model which has been useful in understanding the roles of the various pressures in the pulmonary circulation in determining the topographic distribution of blood flow.[9] There may be a region, zone 1, near the top of the lung where there is no blood flow. If this occurs it is always at the top because of the hydrostatic differences of pressure within the pulmonary arterial tree, as a result of which the pulmonary arterial pressure falls off at the rate of 1 cm H_2O per cm of distance up the lung. If there is a region where pulmonary arterial pressure is less than alveolar pressure the capillaries collapse because the pressure outside them exceeds the pressure inside. Since no gas exchange is possible in this region, it constitutes an alveolar deadspace.

It should be emphasized that there is no zone 1 in the lung under normal conditions, but this may occur either if pulmonary arterial pressure is reduced, as in oligemic shock, or if alveolar pressure is increased, as in positive-pressure ventilation. Under these conditions it is known that pulmonary arterial pressure rises as well but not as fast as alveolar pressure, particularly when alveolar pressure exceeds 10 cm H_2O. Thus, an unperfused region is particularly likely to develop in a patient who is oligemic and who is ventilated with positive pressure. There have been several demonstrations of the large increase in physiologic deadspace in such patients and the appearance of unperfused zone is one of the mechanisms involved. Others include an increase in the number of units which are poorly perfused (see below) and also the increase in anatomic deadspace which results from the increase in lung volume.

Figure 2*B* shows that further down the lung, there is a region, zone 2, where pulmonary arterial pressure exceeds alveolar pressure, and therefore there is blood flow. Here, alveolar pressure exceeds venous pressure, and it can be shown that blood flow is determined by the difference between arterial and alveolar pressures rather than the more conventional arterial–venous pressure difference.[10] The explanation for this is not entirely clear, but a thin-walled rubber tube set up in the laboratory under similar pressure conditions shows a collapse point at the downstream end which regulates the

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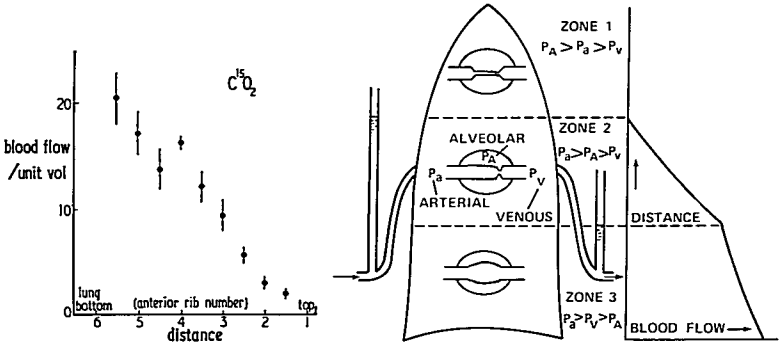

FIG. 2. *A (left)*, distribution of blood flow in the normal upright human lung as measured with radioactive carbon dioxide. *B (right)*, a three-zone model to account for the distribution of blood flow under a variety of conditions (see text for details).

flow of liquid through it. This phenomenon goes by various names, including the "Starling resistor," "waterfall," or "sluice" effect. Since pulmonary arterial pressure is increasing down this region of the lung but alveolar pressure is constant, the driving pressure increases and therefore blood flow increases. Finally, near the bottom of the lung there is a region, zone 3, where venous pressure exceeds alveolar pressure and blood flow is determined in the ordinary way by the arterial–venous pressure difference. Here, the increase in blood flow cannot be caused by a change in driving pressure, since the arterial–venous pressure difference is constant. However, the pressure inside the capillaries increases down the zone because of the hydrostatic effect, whereas the pressure outside them is constant. Thus, the transmural pressure difference of the capillaries rises and their caliber increases. This appears to be the main factor determining the increase in blood flow down zone 3.

This three-zone model summarizes the roles of various pressures operating on the capillaries in the pulmonary circulation. It has also been shown that the larger blood vessels which are outside the influence of alveolar pressure can determine the topographic distribution of blood flow under some conditions. Careful measurements made with subjects at their functional residual capacity show a zone of reduced blood flow in the lowermost few cm of the upright lung.[11] This is apparently caused by an increase in vascular resistance of the larger blood vessels, which are relatively compressed in this region because of the poor expansion of the pulmonary parenchyma. Other measurements show that with a normal subject at residual volume, the influence of these so-called "extra-alveolar vessels" dominates to such an extent that there is no increase in blood flow down the upright lung, and indeed blood flow at the apex may slightly exceed that at the base. However, at lung volumes above functional residual capacity, the resistance in the capillaries appears to control the topographic distribution of blood flow over most of the height of the lung.

It should not be thought that at any particular level in the lung, all the blood vessels have the same morphology. Rather, histologic measurements of rapidly frozen lungs of experimental animals show that there is considerable variation in the numbers of blood vessels that are open and also in the calibers of the capillaries. There has been considerable

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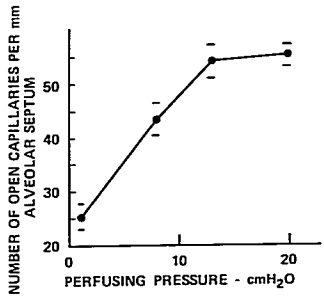

FIG. 3. Number of open capillaries plotted against pulmonary arterial pressure in rapidly frozen dog lungs. The rapid increase presumably reflects the situation near the apex of the upright human lung.

recent interest in the roles of the two possible factors, recruitment and distention, which may be responsible for the increase in capillary filling from top to bottom of the lung. Permutt and colleagues[12] have argued that most of the change in the capillary blood volume which occurs as the vascular pressures are raised is caused by recruitment, that is, opening up of previously unopened vessels or onset of flow in vessels which previously had none. These investigators found that changes in capillary blood volume, as reflected by the diffusing capacity for carbon monoxide, for example, were closely related to changes in pulmonary arterial pressure but not to pulmonary venous pressure. They concluded that the only reasonable model to explain these findings was one in which virtually all the changes in blood volume in the capillaries were caused by recruitment.

By contrast, Fung, Sobin and associates[13–15] have attributed the changes in capillary blood volume to the distensibility of the pulmonary capillary bed. Their studies are based on measurements of the thickness of the small pulmonary blood vessels in preparations in which the vascular bed is filled with silicone elastomer at various pressures. They find an almost linear relationship between the thickness of the alveolar "sheet" of blood and capillary pressure over the range 6 to 27 cm H_2O. This linear relationship can be explained by the distortion which occurs in a thin layer of tissue (the blood–gas barrier) when it is exposed to a lateral pressure (like the membrane of a base drum).

Evidence from histologic measurements of rapidly frozen dog lung suggests that both mechanisms play roles. Glazier and colleagues[16] found a very rapid increase in the number of erythrocytes per unit length of alveolar septum in very thin histologic sections as the pulmonary arterial pressure was increased, and concluded that this could be explained only by extensive recruitment of new vessels. This was the case, particularly in zone 2, when the pulmonary arterial pressure was relatively low. Warrell and coworkers[17] confirmed these observations by finding that the number of open capillaries per unit length of alveolar septum in thin sections increased rapidly with pulmonary arterial pressure under zone 2 conditions. Figure 3 shows that the numbers of open

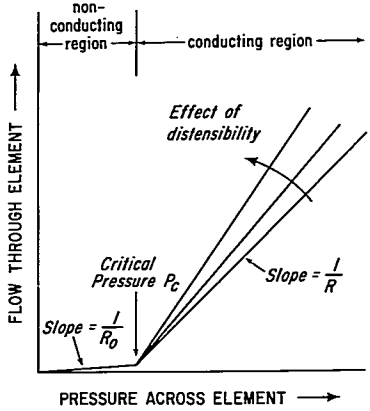

FIG. 4. Assumed pressure–flow characteristics of a capillary segment in an alveolar wall. Virtually no flow occurs until a critical pressure is exceeded. The flow that occurs is then influenced by the distensibility of the vessel.

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capillaries (defined as those which contained an erythrocyte or whose walls were more than 1 μ apart) increased from about 25 per mm length of alveolar septum at a pulmonary arterial pressure of 1 cm H_2O to about 55 at a pressure of 12 cm H_2O. Thus, there seems little doubt that recruitment occurs to a striking extent when pulmonary arterial pressure increases from low values in zone 2, conditions which occur near the apex of the upright human lung. Thus, we should regard this region of the lung (or the anterior region of the supine lung) as forming a reserve of unopened capillaries that can be called upon when the pulmonary arterial pressure rises, as on exercise. This reserve is presumably responsible for much of the decrease in pulmonary vascular resistance that also occurs in other conditions where pulmonary blood flow is greatly increased, such as left-to-right shunts.

An interesting question is the mechanism of recruitment of the capillaries. Fowler[18] and Permutt and colleagues[12] have suggested that as pulmonary arterial pressure rises, critical opening pressures of muscular arterioles are exceeded, and as a result, more of the capillary bed opens up. Warrell *et al.*[17] tested this hypothesis by comparing the amount of capillary filling (as evidenced by the number of intracapillary erythrocytes) in capillaries that were closely adjacent, with that in those that were widely separated from each other. These workers argued that if recruitment were caused by critical opening pressures in arterioles, it should be possible to recognize arteriolar "domains" which contained either very few or very many open capillaries. However, it was found that the filling of the capillary bed was far more patchy than this hypothesis would suggest. In fact, there was as much unevenness of capillary filling within arteriolar domains as between them. This finding suggested that the recruitment process had more to do with the properties of the network of capillaries than critical opening pressures in muscular arterioles.

Recently, we have studied the pressure–flow properties of networks of blood vessels

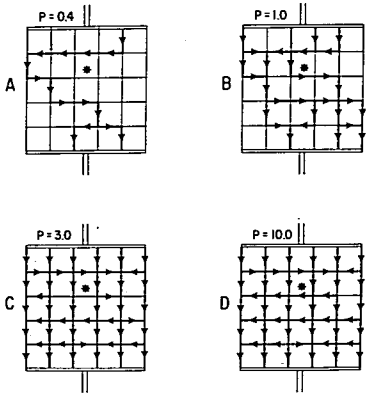

FIG. 5. Examples of the pattern of flow found in a network model of pulmonary capillaries using the pressure–flow characteristic of figure 4. Upper and lower borders of each large square represent inflow and outflow, respectively. P is arterial pressure and venous pressure is zero. Notice that as the arterial pressure is increased in steps, flow begins in more elements of the network. The asterisk shows a segment in which reverse flow occurred.

and shown that such a network may show recruitment of individual segments (that is, onset of flow) as arterial pressure is raised over a large range.[19] Each element of the network is assumed to require a certain pressure difference across it[20] before any flow occurs (critical pressure), as shown in figure 4. Thereafter the flow is assumed to be linearly related to pressure across the element, although the slope of the line can be altered to simulate distensibility. Figure 5 shows an example of the flow patterns which are observed in such a model as the arterial pressure is increased in steps. In this network the values of the critical pressures (figure 4) and the resistances of the elements were randomly chosen from distributions.

It can be seen that initially a preferential channel of flow opened up at a relatively low arterial pressure. This channel consisted

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of elements that had low critical pressures. As arterial pressure was increased, additional elements began to conduct. This process of recruitment occurred over a large range of arterial pressures, with the result that vascular resistance decreased even in the absence of distention. A feature of such a network is reversals of flow in some elements. Thus, in the example shown in figure 5, the link indicated by the asterisk first had no flow, then flow from left to right, then no flow again, and finally flow from right to left. This can be explained by the pressure difference across the element which was first below the critical pressure, then above, then below it again because of an increase in its downstream pressure, and finally, above the critical pressure again. This type of behavior has frequently been seen in capillary networks and is usually ascribed to active control, but indeed may be a passive feature of such a network.

Whether the pulmonary microcirculation behaves in this way is not known, but it is worth pointing out that it is one of the densest networks of capillaries in the body. For example, Weibel's data[21] indicate that in the human lung an erythrocyte will encounter of the order of 100 branch points in the capillary bed from an arteriole to a venule. We calculate that the critical pressures required for such behavior in the human pulmonary microcirculation would be extremely small, of the order of 0.02 cm H_2O. Such a mechanism would satisfactorily explain the remarkable ability of the human lung to decrease its vascular resistance as pulmonary blood flow increases.

In addition to its capacity for recruitment, the pulmonary capillary bed is able to distend as the capillary pressure increases. Figure 6A shows a plot of the mean width of the capillaries against capillary pressure, and it can be seen that there is a substantial increase in the caliber of the vessels up to capillary pressures of approximately 30 cm H_2O.[16] Beyond this value there is no further consistent change. These measurements were made on histologic sections of rapidly frozen dog lung by measuring the widths of all

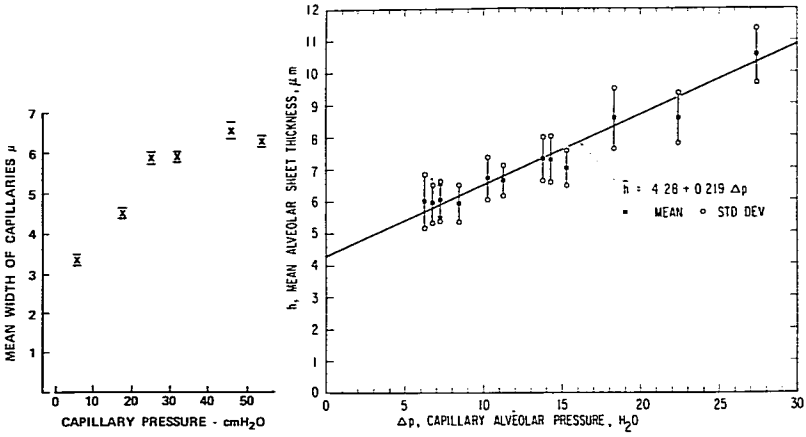

FIG. 6. Evidence for distention of the pulmonary capillaries. *A (left)*, mean width of capillaries plotted against capillary pressure in rapidly frozen dog lungs. *B (right)*, data from Sobin *et al.*, obtained in the cat.

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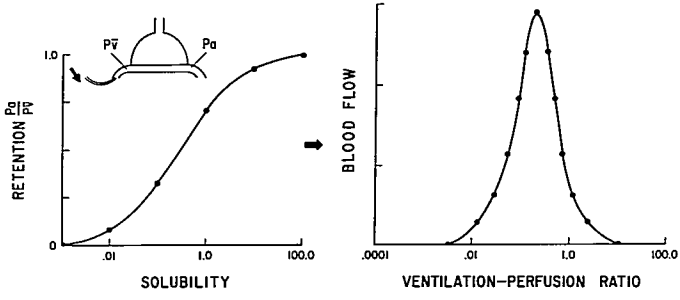

FIG. 7. Principle of measurement of continuous distributions of ventilation–perfusion ratios. A retention–solubility curve is drawn, based on the pattern of elimination of a series of infused inert gases, and this can be transformed by numerical analysis into a plot of blood flow against ventilation–perfusion ratios.

open capillaries at 5-μ intervals along alveolar septa. The resulting values for mean width are therefore smaller than the maximum diameters of the capillaries. Figure 6*B* shows data from Sobin, Fung, and colleagues[13] obtained using silicone elastomer injections of cat lung. Here, the rate of increase in the thickness of the alveolar sheet (corresponding to the maximum width of the capillaries) appears greater than in the dog.

There is evidence that some of the capillaries in the systemic circulation, for example, those in mesentery, can accommodate very large pressures without measurable distention. Fung and colleagues[22] have shown that this behavior can be ascribed to the rigidity of interstitial tissues surrounding the capillaries rather than to the mechanical properties of its wall. Thus, the capillaries may be regarded as holes through Swiss cheese. By contrast, the pulmonary capillaries have exceedingly thin walls less than half a micron thick, and are therefore free to bulge into the alveolar spaces. In view of the differences in histology between pulmonary and systemic capillaries, it is hardly surprising that the former show considerable distention as intracapillary pressure is raised.

Ventilation–Perfusion Inequality and Gas Exchange

The topographic differences of blood flow discussed above can seriously impair pulmonary gas exchange under certain conditions, for example, in oligemic shock. However, in practice, most of the inequality of blood flow responsible for defective gas exchange is not on a topographic basis but exists between closely neighboring units of lung. Although the importance of uneven distribution of ventilation–perfusion ratios has been recognized for many years, actual measurement of the distributions has proved very elusive. Until now, we have had to be satisfied with models such as the three-compartment analysis introduced by Riley and Cournand,[4] where the lung is divided into three imaginary compartments, one which is perfused but not ventilated (shunt), one which is ventilated but not perfused (dead-space), and an ideal compartment. Although this type of "as if" analysis has proved useful in clinical practice, it would clearly be preferable to know something of the position, shape, and dispersion of the distribution of ventilation and blood flow with respect to ventilation–perfusion ratio.

Wagner and colleagues[23] have recently

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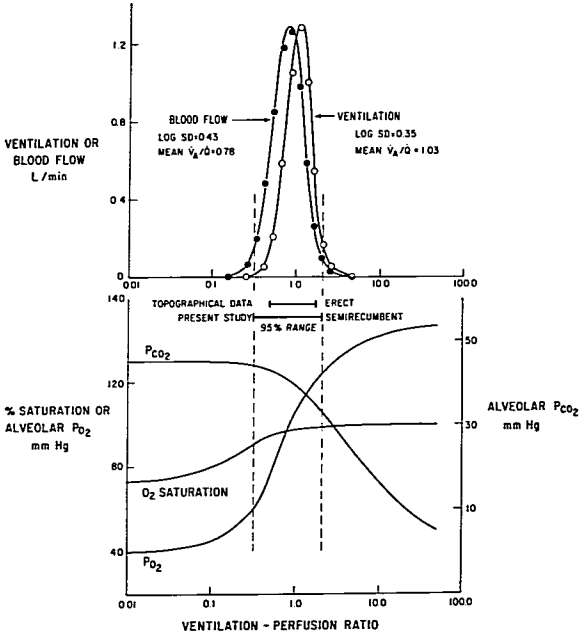

FIG. 8. Upper graph shows the average distribution of ventilation–perfusion ratios in young semirecumbent normal subjects. The 95 per cent range covers ventilation–perfusion ratios from 0.3 to 2.1. The corresponding variations of P_{O_2}, P_{CO_2} and oxygen saturation in the end-capillary blood can be seen in the lower panel.

described a method of determining these distributions based on the pattern of elimination of a series of infused inert gases. A mixture of six gases, sulfur hexafluoride, ethane, cyclopropane, halothane, diethyl ether, and acetone, is dissolved in physiologic saline solution and infused into a peripheral vein for about 20 minutes at the rate of 5 ml/min. Towards the end of the infusion period, samples of arterial blood and mixed expired gas are collected and total ventilation and cardiac output are measured, the latter by dye dilution. The concentrations of each gas in the blood and gas samples are measured by gas chromatography, using flame ionization and electron capture detectors. The concentrations are within the range 0.001 to 100 parts per million, well below the levels that produce measurable changes in cardiopulmonary or central nervous system function.

For each gas the ratio of arterial to mixed venous concentration (retention), and the ratio of expired to mixed venous concentration (excretion) are calculated and retention–solubility and excretion–solubility curves are drawn. Figure 7A shows a typical retention–solubility curve, and it can be seen that the

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retention of poorly soluble gases is much less than that of the gases with high solubility. This retention–solubility curve can be regarded as a "fingerprint" of the particular distribution of ventilation–perfusion ratios that gave rise to it. In other words, a particular distribution of ventilation–perfusion ratios result in a unique retention–solubility curve.

In practice, it is possible to derive the corresponding plot of blood flow against ventilation–perfusion ratio, as shown in figure 7. This transformation is made using techniques of numerical analysis by means of the digital computer. In the same way, the excretion–solubility curve can be transformed into a plot of ventilation with respect to ventilation–perfusion ratio, although this is not shown in figure 7. This new method is relatively simple to use and has now been tested extensively in a series of 12 normal subjects, more than 30 patients with various types of heart and lung disease, and a large number of anesthetized dogs. The technique is well suited to clinical investigation and has been used to measure the distributions of ventilation and blood flow in acutely ill patients in the intensive care unit.

Figure 8 shows the type of distributions found in young normal subjects breathing air in the semirecumbent position.[24] It can be seen that the distributions of both ventilation and blood flow are relatively narrow. The dispersions of the distributions can conveniently be described by the log standard deviation and the values are 0.35 and 0.43 for ventilation and blood flow, respectively. These data are based on a series of measurements made in a study of normal undergraduate student volunteers. The normal values of the 95 per cent limits for ventilation–perfusion ratios were calculated by taking two standard deviations towards the low $\dot{V}_A/\dot{Q}$ values for blood flow, and towards the high $\dot{V}_A/\dot{Q}$ values for ventilation. The upper and lower 95 per cent limits shown correspond to ventilation–perfusion ratios of 0.3 and 2.1, respectively. Notice that these young normal subjects had no blood flow going to areas with very low ventilation–perfusion ratios, nor did they have any blood

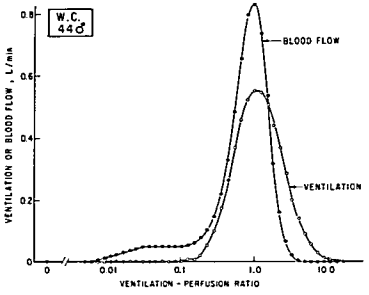

FIG. 9. Example of distribution found in an apparently normal 44-year-old man. Note that there is an appreciable amount of blood flow going to areas with low ventilation–perfusion ratios.

flow to unventilated areas or shunt. It should be emphasized that this method measures only intrapulmonary or intracardiac shunts and separates these from other causes of hypoxemia, such as bronchial and Thebesian venous blood, which are traditionally included as shunts.

Figure 8 also shows end-capillary P_{O_2}, P_{CO_2}, and oxygen saturation in units having different ventilation–perfusion ratios. These graphs were drawn assuming that the P_{O_2} and the P_{CO_2} of mixed venous blood were 40 and 45 mm Hg. It can be seen that the 95 per cent range of ventilation–perfusion ratios in these normal subjects causes a P_{O_2} range of 60 to 123 mm Hg, while the corresponding P_{CO_2} range is 44 to 33 mm Hg. These can be compared with the ranges of P_{O_2} and P_{CO_2} calculated from the topographic distribution of ventilation–perfusion ratios in the normal upright human lung,[8] where the range of P_{O_2}, for example, was 89 to 132 mm Hg and that of P_{CO_2}, 41 to 28 mm Hg. In fact, the inequality of ventilation and blood flow in the normal lung is greater in the erect than the semirecumbent position. The large range found by the multiple inert gas elimination technique reflects the fact that not all the ventilation–perfusion inequality exists on a topographic basis but, in addition, there is some inequality between

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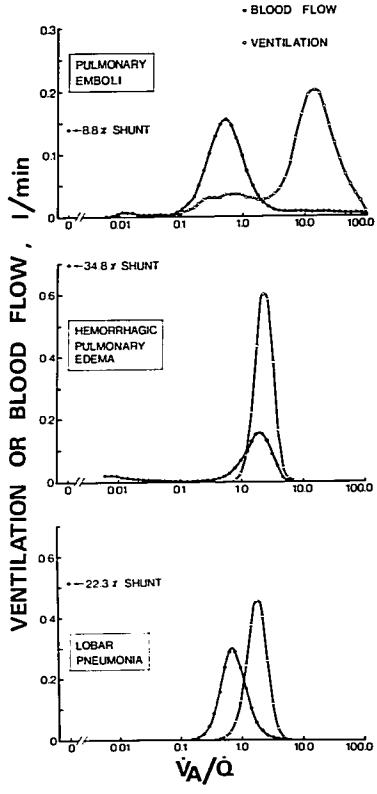

FIG. 10. Examples of abnormal distributions of ventilation–perfusion ratios measured in anesthetized dogs with various types of abnormal lungs (see text for details).

adjacent lung units at the same topographic level. The inert gas technique does not, of course, give topographic information, but instead describes the total inequality of ventilation and blood flow as it affects pulmonary gas exchange.

Figure 9 shows an example of the distributions of ventilation and blood flow in an older, apparently normal volunteer.[21] This subject had no history of lung disease, was a nonsmoker, and physical examination, chest x-ray, and spirometry showed no abnormality. It can be seen that, in contrast to the distribution found in the young normal subjects (figure 8), the older man had appreciable amounts of blood flow going to regions with low ventilation–perfusion ratios. This tail to the distribution caused some skewing to the left. Again, however, there was no shunt, and indeed none of the normal subjects had any shunt during oxygen breathing. In general, the dispersion of the blood flow distribution increased with age, and this presumably explains the inverse correlation between arterial P_{O_2} and age in normal subjects.

The effects of pathologic changes in the lungs on the distributions of ventilation–perfusion ratios have been studied in anesthetized dogs. Figure 10A shows the result of producing experimental pulmonary embolism by infusing a large number of small glass beads into the venous blood: it can be seen that a very abnormal distribution of ventilation and blood flow resulted. The distribution of ventilation was virtually bimodal, with large amounts going to regions with extremely high ventilation–perfusion ratios. There was some blood flow to areas with abnormally low ventilation–perfusion ratios, and also a shunt of 8.8 per cent. Figure 10B shows the results of infusing oleic acid into the right ventricle. Oleic acid is a toxic agent known to cause hemorrhagic pulmonary edema. It can be seen that there was relatively little broadening of the main body of the distributions of ventilation and blood flow, but that a large shunt of 34.8 per cent appeared. Figure 10C shows the distributions in a dog which developed pneumococcal lobar pneumonia as a result of the experimental instillation of pneumococci into the right lower lobe. Again, there was little broadening of the main bodies of the distributions, but a shunt of 22.3 per cent appeared. It is of interest that there were no regions of reduced ventilation–perfusion ratios such as might be expected in the vicinity of the consolidated lung.

A striking finding has been the effect of breathing oxygen on the distributions of

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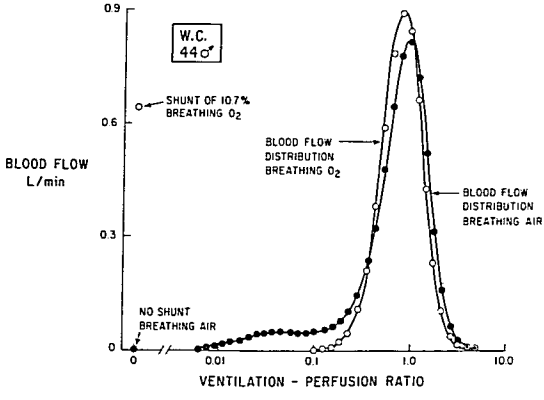

FIG. 11. Effects of oxygen breathing on the distribution of ventilation–perfusion ratios in the normal subject whose distribution during air breathing is shown in figure 9. Note the loss of the "tail" of the distribution and development of a 10.7 per cent shunt.

ventilation–perfusion ratios.[24] Figure 11 shows the effect of 45 minutes of breathing 100 per cent oxygen on the distribution of blood flow of the old normal subject whose distributions were depicted in figure 9. It can be seen that there was a striking reduction in the amount of blood flow going to units with low ventilation–perfusion ratios such that the tail to the distribution curve was virtually abolished. However, at the same time, a shunt of 10.7 per cent of the cardiac output appeared. Thus, it appears that the effect of breathing oxygen was to convert units which had low ventilation–perfusion ratios into unventilated but perfused areas.

The example shown in figure 11 was the most extreme in terms of the development of shunt during oxygen breathing. However, all but one of the eight normal subjects who were given oxygen to breathe developed some shunt, averaging 2.2 per cent of cardiac output. The effects of breathing oxygen on the distribution of blood flow have also been examined extensively in anesthetized dogs, in which acute respiratory failure has been produced by several techniques. These include the injection of numerous glass-bead emboli into the venous circulation, and the infusion of oleic acid into the right ventricle. All these animals with pathologic changes in the lungs show some shunt during breathing of air, and without exception this increases when enriched oxygen mixtures are given. The increase in shunt is related to the amount of blood flow going to areas with low ventilation–perfusion ratios during breathing of air. If there is a large tail of blood flow to areas with low ventilation–perfusion ratios, as shown in figure 11, the development of a large shunt during breathing of oxygen is likely. The relationship between the concentration of inspired oxygen and the amount of shunt has not yet been fully worked out, but it is clear that concentrations as low as 50 per cent can produce large shunts under some conditions.

The cause of the shunt during oxygen breathing is presumably the increase in oxygen uptake by lung units with low ventilation–perfusion ratios, as suggested by Briscoe and colleagues.[25] A unit that has a low ventilation–perfusion ratio during breathing of air will have a low alveolar P_{O_2}. When an enriched oxygen mixture is given, alveolar P_{O_2} will rise and, therefore, the rate at which oxygen moves from the alveolar gas to the capillary blood will greatly increase. Under some circumstances this oxygen flux may rise so much that the net flow of gas into the blood exceeds the inspired alveolar ventilation, and under some conditions the unit can then close. Collapse is

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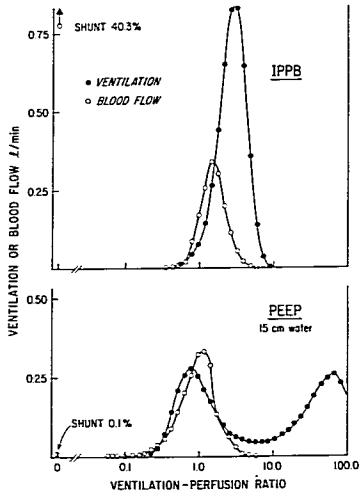

FIG. 12. Effect of positive end-expiratory pressure (PEEP) on the distributions in a dog with oleic acid-induced acute hemorraghic pulmonary edema. Notice that the shunt fell from 40.3 per cent to virtually zero and that a considerable amount of ventilation went to units with high ventilation–perfusion ratios.

most likely to occur if the inspired oxygen concentration if high and the content of oxygen in the mixed venous blood is low. This phenomenon is of considerable significance in the clinical situation for two reasons. First, enriched oxygen mixtures are often used therapeutically, and it is important to know whether this therapy is causing atelectasis. Second, the amount of shunt is often estimated during breathing of 100 per cent oxygen, and if this maneuver results in shunt, the measurement will clearly be in error.

Figure 12 shows the effects of positive end-expiratory pressure (PEEP) on the distributions of blood flow and ventilation in an anesthetized dog in which acute respiratory failure was induced by infusion of oleic acid. It can be seen that when the animal was ventilated with intermittent positive pressure by means of a Harvard respirator, the main bodies of the distributions of ventilation and blood flow were relatively narrow, but there was a shunt of 40.3 per cent. When 15 cm H_2O PEEP was added there was a substantial decrease in the amount of shunt, from 40.3 to 0.1 per cent. Presumably this can be explained by the opening up of previously obstructed areas. At the same time, the distribution of ventilation was changed, in that a larger proportion went to units with high ventilation–perfusion ratios. This can presumably be explained by the reduction of blood flow in some areas as a result of the increased alveolar pressure, giving rise to a high ventilation–perfusion ratio. Accompanying these changes was a large increase in ventilation to unperfused regions (not shown in figure 12), which was presumably made up of an increase in anatomic deadspace as lung volume increased, together with an increase in the number of lung units that were unperfused. The findings shown in figure 12 are typical of those obtained in a series of dogs in which the effects of PEEP have been studied.

It is possible to calculate the arterial P_{O_2} and P_{CO_2} which are caused by the observed patterns of distribution of ventilation and blood flow as measured with this technique. These predicted values can then be compared with the measured P_{O_2} and P_{CO_2} of arterial blood, and figure 13 shows the results in a series of anesthetized dogs with various types of induced respiratory failure. It can be seen that, in general, the correlation was very close. These data suggest that the new method accurately determines the total amount of inequality of ventilation and blood flow within the lung. They also indicate that in these experimental animals, virtually all of the hypoxemia and hypercarbia can be explained by ventilation–perfusion inequality.

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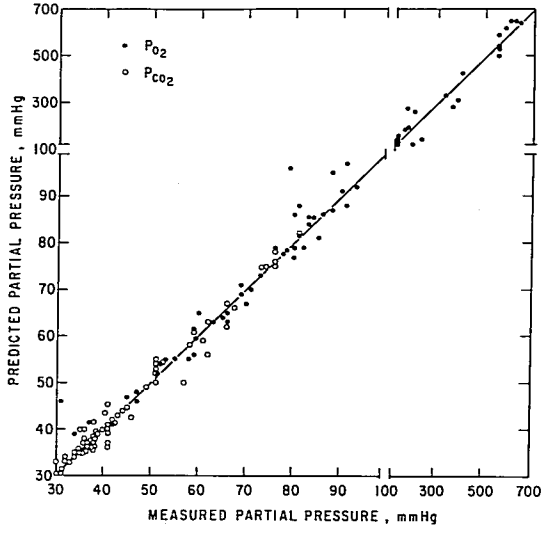

FIG. 13. Correlation of the arterial blood gases predicted from the distributions compared with the values measured in arterial blood. These data, from a series of anesthetized dogs with various types of induced respiratory failure, suggest that most of the hypoxemia and hypercarbia could be explained by the ventilation–perfusion inequality.

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