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Pulmonary Circulation

Its Control in Man, with Some Remarks on Methodology

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The development of our knowledge of the pulmonary circulation in man has followed the introduction of the cardiac catheter into clinical investigation. In 1943, this new tool was only the key in the lock—although this is in no way to minimize W. Forssmann's brilliant and courageous experiment. To guide our hand in turning this key, we had all the knowledge accumulated through the years by physiologists in their studies of animals; and to one, William F. Hamilton, I owe a more personal debt of gratitude for his constant advice and kind criticism. Basically, our difficulties were then, as they are still, those of measuring pulmonary blood flow, pressures, and volume. And, since the reliability of experimental data is no better than the reliability of the measuring techniques employed, I should like, before discussing our present understanding of the pulmonary circulation, to consider the limitations of our methods.

Measurement of Blood Flow

As D. W. Richards has pointed out (*1*), at first the measurement of pulmonary blood flow in man did not appear to pose an important problem; once catheterization of the pulmonary artery, cannulation of a peripheral artery, and spirometry supplied the data necessary to apply the principle described by Fick in 1870 (*2*). But the application of the Fick principle involves more than the simple substitution of analytic values into a ready-made equation, and the problem which had to be solved is an illustration of the caution necessary when physical principles are applied to biologic measurements (*3–5*).

The Fick principle can be used to measure flow in a physical system in which a stream of constant velocity enters a chamber of constant volume, the volume being sufficiently small so that an indicator substance continually added to the chamber is instantaneously mixed with the volume therein. Then, if the rate at which the indicator enters the chamber is measured, and if the difference in concentration of the indicator in the fluid entering and leaving the chamber is determined, flow can be calculated by dividing the volume of indicator added per unit of time by the volume of indicator gained per unit of fluid flow.

But these ideal conditions are not realized in the body, since pulmonary blood flow is pulsatile and since the rate of transfer of oxygen, the indicator substance, into the pulmonary capillaries is influenced by the cyclic character of ventilation and may be measured only at the mouth rather than at the alveolocapillary membrane. Furthermore, blood samples required for the determination of the oxygen content of the blood entering and leaving the lungs are integrated in respect to time rather than in respect to volume; in addition, they must be collected for a finite period instead of from instant to instant, as would be necessary in order to make a continuous measurement of flow.

However, as a result of extensive investigations in animal and in man, it would appear that these theoretical considerations do not introduce an error of large magnitude in the measurement of pulmonary blood flow, provided that certain criteria regarding the maintenance of a steady state of ventilation, circulation, and gas exchange are met. Thus the problems of periodic variations in flow velocity and of arteriovenous oxygen difference, and the matter of time-integrated, rather than volume-integrated, samples, do not affect the measurement of flow except under the most extreme circumstances. It was pertinent to the solution of this question to demonstrate that the volume of flow measured by the dye-dilution technique, which involves a somewhat different principle, agrees rather closely, under a wide variety of conditions, with that obtained by application of the Fick principle (*6*).

Measurement of Blood Pressures

In the early days, pressures in the right atrium and in the right ventricle were recorded (*7, 8*) through a single-lumen catheter, connected to a Hamilton manometer, a coupling which raised important technical questions. Whereas in animals it had been possible to limit the distance between the heart and the manometer to the length of a short metal needle, the use of a catheter interposed a column of fluid at least 100 centimeters long between the pressure to be measured and the pressure-measuring device. Moreover, the fluid was contained inside a tube, the stiffness of which was considerably less than that of metal; this is an important consideration in view of the fact that the fidelity of a recording system is a function of the stiffness of its parts.

It was necessary, therefore, to construct a catheter in which a compromise was made; the catheter had to be sufficiently stiff to transmit pressures accurately, but not so stiff that its introduction into the heart would be dangerous. In addition, damping had to be considered because of the low natural frequency of the system and in order to minimize the artifacts imposed by the

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mechanical impact of the beating heart (Fig. 1). In general, the proper degree of damping is best determined empirically, since it varies with heart rate, height of pressure, and the location of the tip of the catheter. An important progress in technique was the development of a double-lumen catheter through which simultaneous pressures in two contiguous heart chambers and large vessels could be recorded.

The first two tracings of blood pressure pulses recorded simultaneously within the right ventricle and the pulmonary artery are presented here (Fig. 2). They served to illustrate a paper published in 1945 (*8*) in collaboration with Henry Lauson and Richard Bloomfield, on the use and advantages of this newly designed double-lumen catheter. For me, this tracing holds a unique place, for it is the first demonstration that the tip of a catheter was placed in the pulmonary artery of man in order to record pressure pulses. Subsequent progress in our knowledge of the dynamics of the pulmonary circulation in man (*10*) owes much to the technique of catheterization of the pulmonary artery. The part played by Lewis Dexter and his associates in this latter technical development deserves special mention (*11*).

Apart from our efforts to evolve a satisfactory catheter, considerable attention was also required for proper operation of the Hamilton manometer. Stanley Bradley, who was assigned by Homer Smith to the team studying shock at Bellevue Hospital, New York, during the years of World War II, was initially in charge of this delicate and essential function. Although the Hamilton manometer was subsequently replaced by strain gages in association with electronic recorders, it is well to recall that most of our early knowledge of pressure pulses was obtained by using this device.

During the past few years, recording machines have become increasingly complex and useful. But no matter how sensitive may be the manometer employed, the catheter system itself still remains the limiting factor in reproducing faithfully human pulse pressures, under all circumstances.

An estimation of the pressure drop across the entire pulmonary vascular system had been of particular concern to physiologists interested in the dynamics of the pulmonary circulation. Catheterization of the pulmonary artery supplied the necessary data concerning pressures at the origin of the system; but the pressure at the end of the system—that is, in the left atrium—although predictable from the diastolic pressure in the pulmonary artery of the normal subject, could not be accurately determined.

A first step in the proper direction was made when pressures were recorded from the left atrium and large pulmonary veins in human subjects under the abnormal conditions provided by interatrial septal defects (*12*); however, it was not until very recently that, by means of needles, direct measurements of the left atrial pressure in intact man have been secured. Prior to the latest development, an ingenious indirect method for making this measurement had been developed separately in 1949 by Hellems and Dexter (*13*) and by Lagerlöf and Werkö (*14*). It consists in advancing a cardiac catheter in a peripheral branch of the pulmonary artery until it is firmly wedged.

At first it was assumed that the recorded pressure was that in the first freely anastomosing segment of the pulmonary vascular bed distal to the point of wedging—that is, the capillary bed. Theoretical considerations suggest, and recent comparisons indicate, that the pulse contour and the mean pressures recorded after wedging correspond with those obtained from the left atrium, particularly in subjects with pulmonary venous congestion. This pressure, therefore, can be used with caution to derive a fairly accurate figure for the pressure drop across the entire vascular bed, particularly in cases where vascular pressures throughout the pulmonary circuit are elevated.

Measurement of Blood Volume

Since the pulmonary circulation constitutes a distensible reservoir interposed between the right and the left ventricles, measurements of pulmonary blood volume and of its variations under various physiologic conditions has attracted the interest of clinical investigators. The use

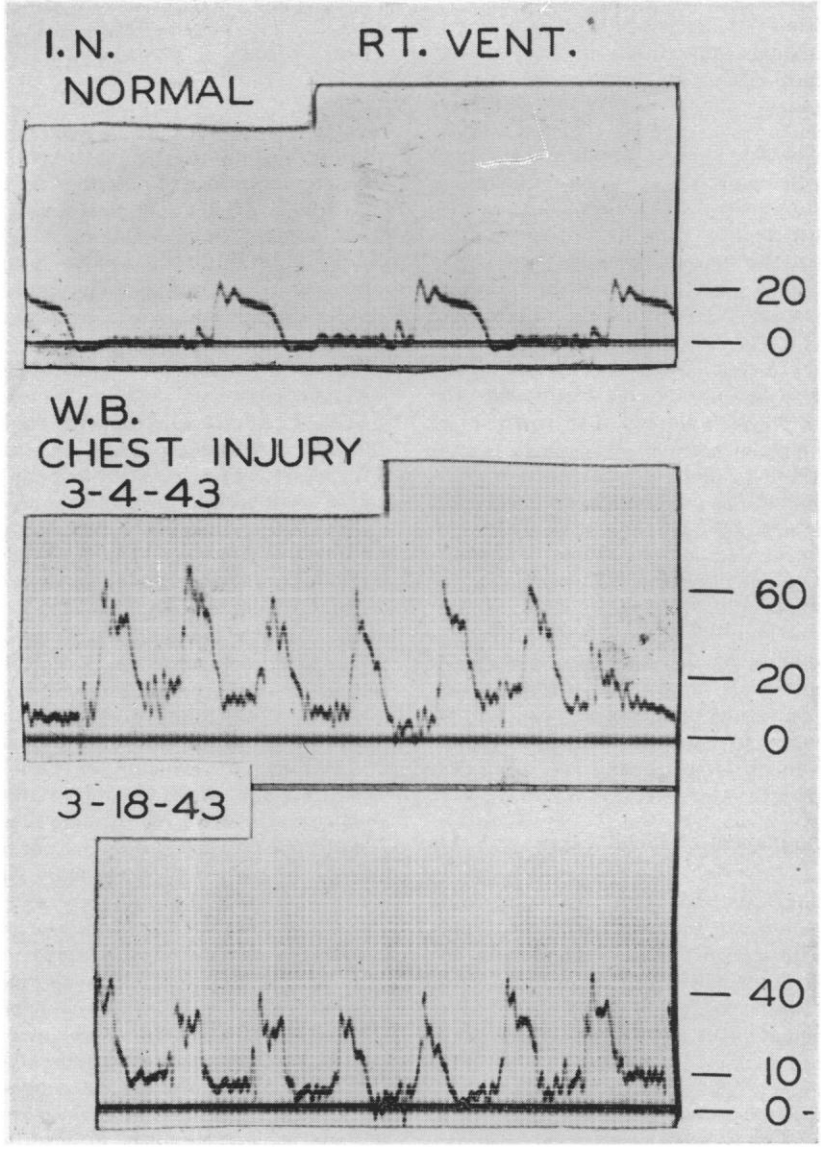

Fig. 1. The first reported pressure pulses recorded in the right ventricle of a normal man and of a patient with severe traumatic chest injury (*7*, chart 13). The tracings were obtained through a catheter attached to a Hamilton manometer; they are undamped. The coarse vibrations were caused by impacts on the catheter.

of the dye-dilution technique referred to in a previous section provides an indirect means of measuring this volume, according to a principle first correctly stated and then experimentally established by Hamilton and his school. However, the "central blood volume" thus measured has somewhat vague limits, and it includes the volume in the left heart and that in a large part of the arterial tree. Furthermore, the error of the technique is of the order of 15 percent of the volume measured; hence, variations of volume amounting to 150 to 200 milliliters may not be significant.

Concluding this long preamble on methodology, I now turn to the main theme of my article—the control of the pulmonary circulation in normal man.

Control of Normal Pulmonary Circulation

From the large body of previous work in animals, particularly in dogs, it was already evident at the inception of our investigation that the relationship between pressure and flow in the pulmonary circulation was quite different from that in the systemic circuit. Although the stroke output of each ventricle is approximately the same, except for temporary differences, the mean pressure in the aorta is 6 times that in the pulmonary artery. This is an expression of a much higher viscous resistance to flow in the systemic circulation—a resistance located mainly at the arterioles, the walls of which are endowed with a thick and circular layer of smooth muscles. By contrast, the walls of the small branches of the pulmonary artery have only a very thin muscular media.

Mechanical Factors

From these anatomic observations, it might be expected that the influence of the activity of this thin muscular coat on the viscous resistance to flow in the small pulmonary arteries would be a relatively weak one. Moreover, if the vasomotor tone is weak, the part played by purely mechanical factors, such as variations in blood flow and blood volumes in controlling the pressure in the pulmonary artery, becomes proportionally more important.

However, the effects of such mechanical factors are not simple. For instance, if the resistance to flow in the pulmonary vessels remained constant, then the pulmonary arterial pressure should be directly influenced by variations in flow and by variations in left atrial pressure. Since, however, the whole vascular system is distensible, the resistance in the circuit is itself dependent on variations in distending pressure. Thus, an increased flow, or an increased left atrial pressure, will by itself increase the distending pressures in the various pulmonary vessels, thus changing the geometry of the system by opening up new channels, and thereby lowering the pulmonary vascular resistances. From this it follows that the relationships between pressure and flow in the pulmonary circulation should not be expected to be rectilinear.

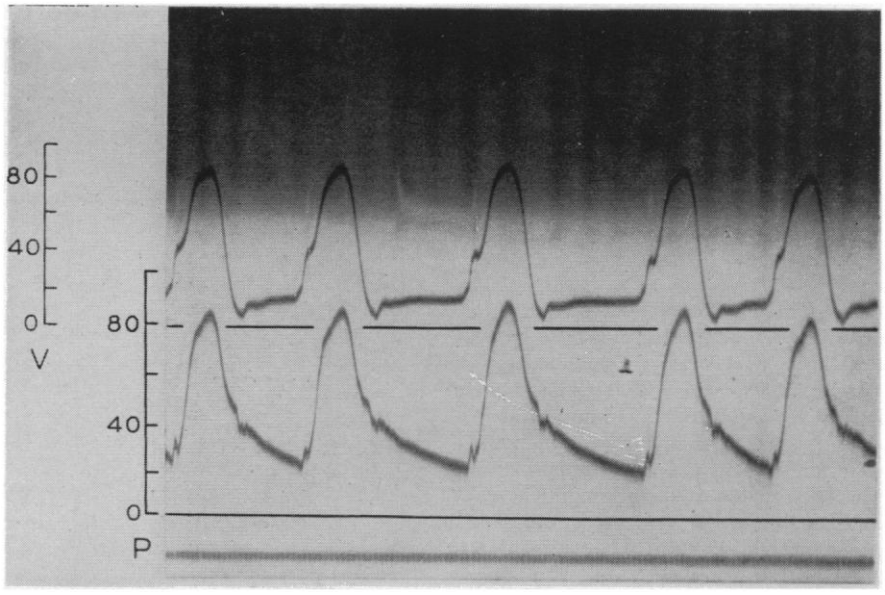

Fig. 2. The first reported pressure pulses recorded in the pulmonary artery of man (*9*). The simultaneous tracings in the pulmonary artery and the right ventricle were obtained through a double-lumen catheter attached to the Hamilton manometer in a patient with severe hypertension. The scale is in millimeters of mercury.

Indeed, it was soon apparent, from our studies, that there was not a linear relationship. For example, measurements made before and after pneumonectomy showed that the pressure in the pulmonary artery rose very little when the entire output of the right ventricle flowed through one single normal lung (*15*). Hence, the vascular resistance is strikingly dependent on the rate of flow, and the pulmonary vessels appear to be remarkably distensible within this range. Further support of this observation is provided by the relatively small rise in the pulmonary arterial pressure which is associated with a large increase in pulmonary blood flow observed during exercise in normal subjects and in patients with large left-to-right intracardiac shunts.

Beyond a certain point, however, increases in pulmonary blood flow cause greater increments in pulmonary arterial pressure, and this is presumably an indication of the shape of the curves which relate distending pressure to cross-sectional areas in the pulmonary vessels. In this respect, it is interesting to recall that Lilienthal and Riley have recently called attention to the relationship existing between the critical level at which pressure in the pulmonary artery increases significantly and the maximum oxygen diffusing capacity, a function closely related to the size of the total alveolocapillary interface (*16*).

Our experiments on the effects of the normal respiratory cycle, positive-pressure breathing, and the Valsalva maneuver (*17*) showed also the mechanical results of altering the effective, or net distending, pressure in the pulmonary vessels. In addition, they revealed that the hemodynamic situation is further complicated by differential changes in the filling pressure and thereby in the stroke output of each ventricle. These results directed our attention to the important notion of heterodynamism of both ventricles, which is particularly fruitful in the understanding of isolated ventricular failure.

Vasomotor Factors

Since remarkably wide variations in vascular resistance can normally occur in a purely passive fashion, the task of demonstrating the active part that the smooth muscles in the wall of the small vessels may play in its alterations becomes very difficult. Nevertheless, we have knowledge of two agents which appear to affect the resistance to flow in the pulmonary circulation by modifying the muscular tone of its vessels. These two agents are hypoxia and acetylcholine.

Hypoxia

Our interest in hypoxia was stimulated by the observations of von Euler and Liljestrand, who in 1946 demon-

strated a rise in the pulmonary arterial pressure of cats breathing low concentrations of oxygen (*18*). In man, we were able to confirm this phenomenon in collaboration first with Motley, Werkö, and Himmelstein (*19*). More recently, we established with Fishman, McClement, and Himmelstein that the rise of pressure in the pulmonary artery is associated with some increase in the pulmonary blood flow, and we suggested that this increase in flow is not by itself sufficient to account for the change in pressure (*4*).

Others have shown that the pulmonary wedge pressure in man and the left atrial pressure in animals and in man are not altered by hypoxia. There is, therefore, very strong evidence that hypoxia causes pulmonary vasoconstriction.

At what site has this vasoconstriction happened? We are not sure. How is it caused? We do not know. We assume that it arises directly or indirectly from the action of a low partial pressure of oxygen at some point in the body. Is it a local reflex activated at the level of the alveoli or of the pulmonary veins? Does it involve the autonomic system as a result of the stimulation of chemoreceptors in the carotid body or the aorta? Is it due to a direct action of excessively hypoxic mixed venous blood in the precapillary segment of the pulmonary vascular bed? Is there some other vasoconstricting substance liberated in the body under the influence of hypoxemia and carried by venous blood up to the lungs, or is such a substance activated in the pulmonary tissue itself under the influence of local hypoxia? Does severe hypoxemia cause a shift of blood from the systemic to the pulmonary circulation as a result of systemic vasoconstriction?

Although we are in no way near to a final solution to this problem, there are observations which give a partial answer to some of these questions as far as man is concerned. In the first place, we have not been able to demonstrate a significant increase in central blood volume under the influence of severe arterial hypoxemia. In the second place, we have studied the effect of hypoxia in a patient before and after he underwent extensive bilateral sympathectomy for Raynaud's disease. The sympathectomy, which included the stellate ganglion, the upper three thoracic ganglia on each side, and the midcervical ganglion on one side, had no influence on the rise in pulmonary arterial pressure caused by hypoxia. Thus, we reached timidly the tentative conclusion that this effect is not mediated by the sympathetic system.

Liljestrand (*20*) and von Euler (*21*) pointed out that, if the pulmonary vascular resistance were regulated on a regional basis, by a purely local action of the alveolar and blood oxygen partial pressures, this action could provide an important mechanism for maintaining the most effective ratio of ventilation to perfusion throughout the lungs. To examine this attractive hypothesis, several workers have studied the local effects on blood flow of a hypoxic gas mixture given to one lung in animals, and we have in association with Himmelstein, Fishman, and Fritts (*22*), made similar observations in man. The technique is difficult, because it includes the simultaneous use of bronchospirometry, cardiac catheterization, and arterial cannulation. By means of this technique, the flow of blood through each lung can be separately measured.

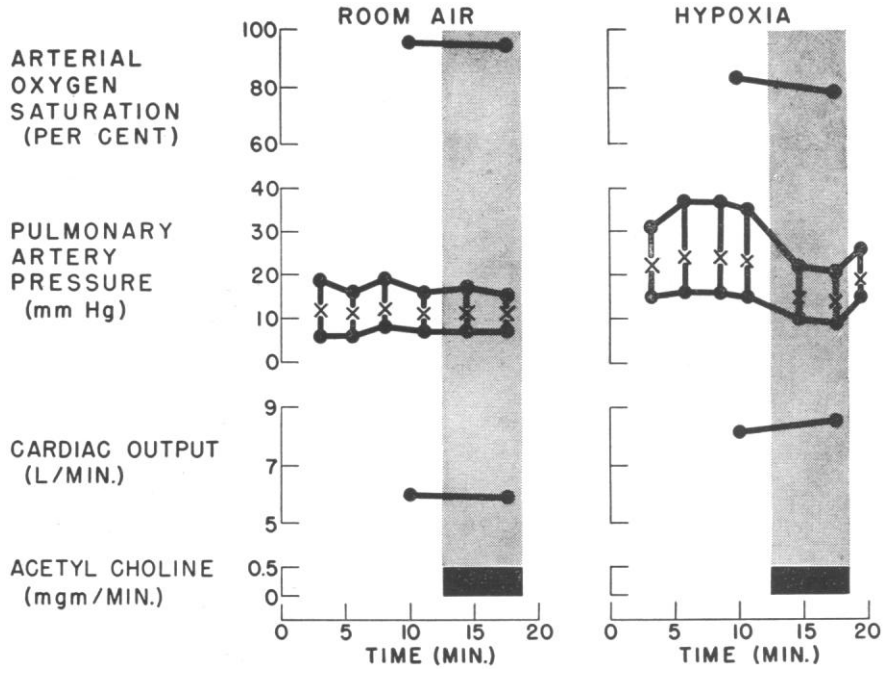

Fig. 3. Effects of acetylcholine on the pulmonary arterial pressure in a normal man. Acetylcholine was given in a continuous infusion of the main pulmonary artery at the rate of 0.5 milligram per minute (shaded areas). (Left) The subject was breathing 21 percent oxygen in nitrogen. (Right) The subject was breathing 12 percent oxygen in nitrogen.

It was found that concentrations of 8 to 10 percent oxygen in the inspired gas given to *one* lung caused no modification in the partition of flow of blood between the two lungs and no change in the pulmonary arterial pressure. Yet, giving a somewhat higher concentration of oxygen (12 percent) to both sides causes a considerable rise in pressure in the pulmonary artery. The role of a local viscerovascular reflex arising from the low oxygen tension in the alveolar gases has, therefore, been questioned. The pulmonary capillaries and venules, however, cannot be excluded as a site of origin for such a vasoconstricting reflex, since the calculated oxygen saturation of the pulmonary venous blood on the hypoxic side did not fall below the 80-percent level, which in bilateral experiments is the critical level for pulmonary hypertension.

We have, however, four observations on the effect of giving concentrations of oxygen as low as 6 percent to one lung. Here the calculated pulmonary venous oxygen saturation fell below 80 percent. In three of these studies, there was no change in the partition of flow, as compared with the control period. In one of them, there was a diminution of flow to the hypoxic lung; suggestively enough, this is the only instance in which mixed venous blood and pulmonary venous blood had an identical oxygen saturation, and where, therefore, no oxygen uptake in the hypoxic lung could be measured. Further work with even lower oxygen concentration is in progress and may well resolve the discrepancy between some of our results in man and experiments on animals in which the giving of pure nitrogen to one lung caused, indisputably, a diminution in blood flow on this side.

Acetylcholine

Here, then, the problem of the effects of hypoxia on the pulmonary vessels lies partly unsolved, and tantalizing. I turn now to the effects of acetylcholine on the pulmonary circulation. This drug has been known, since the early experiments of Sir Henry Dale, to have a strong vasodilating influence throughout the systemic arterial tree. As far as the pulmonary circulation is concerned, however, reports on the effects of this preparation in animals have been contradictory. In normal man, we have found, in collaboration with Harris, Fritts, Clauss, and

Odell (*23*), that infusion of acetylcholine into the main pulmonary artery at a rate of 0.5 milligram per minute causes a slight questionable fall in pulmonary arterial pressure. When the pulmonary arterial pressure had been previously increased by hypoxia, however, the fall in pressure due to acetylcholine was very significant (Fig. 3), although the hypoxic stimulus was maintained. This fall in pressure in the pulmonary artery was associated with no change in pulmonary wedge pressure. The cardiac output, which had increased as the result of hypoxia, remained unchanged or rose slightly further. When given in these small amounts, acetylcholine had no effect on the systemic blood pressure or pulse rate, presumably because of its rapid rate of destruction in the blood stream.

It seems fairly certain, therefore, that the action of the drug is limited to the pulmonary circulation, that this action is one of vasodilatation, and that the degree of vasodilatation is largely dependent, as one might expect, on the preexisting tone of the smooth muscles of the pulmonic vessels' wall. As in hypoxia, we do not know whether the site of action is in the precapillary, or the capillary, or the postcapillary segments of the pulmonary vascular bed. Again, as in hypoxia, we do not know through what mechanisms the drug acts.

Although they left these questions unsolved, the experiments nonetheless have to their credit three important results. They revealed that, first, blood-borne substances can act directly on the wall of some segment of the pulmonary vascular bed, second, that the effects of hypoxia in causing both an increase in blood flow and a vasoconstriction can be neatly separated, and third, that the vasoconstriction associated with hypoxia, whatever the site of its action, can be reversed.

Interplay of Factors in Disease

Although I am here mainly concerned with the relative importance of mechanical and vasomotor factors in the pulmonary circulation of normal man, it might be of interest to dwell briefly on the question of how such factors are altered by disease. In certain diseases high pressure develops in the pulmonary artery, and this is associated with a high vascular resistance and thickening of the walls of the small branches of the pulmonary artery. The hemodynamics of such a natural experiment provide an interesting contrast to those which hold good under normal conditions. The pulmonary artery pressure of these patients is found to be considerably more dependent on variation in flow and volume than it normally would be, and one may well ascribe this to a diminished distensibility of the thickened pulmonary arterial branches.

The results of experiments with sympathetic blocking agents in this group of diseases have led other workers to assign to the autonomic nervous system an important role in the control of the pulmonary circulation. I am inclined to believe that there are other alternative explanations for the striking drop of pressure in the pulmonary artery following the use of these agents rather than to claim that it is the result of blocking the nervous supply to the pulmonary vessels. For instance, translocations of even small amounts of pulmonary blood following systemic vasodilatation could have the same effect in a poorly distensible pulmonary vascular bed.

Conclusions

To summarize our present knowledge, it can be said that we have acquired some understanding of the relations between pressure and flow in the pulmonary vessels of normal man. We know also that these relations can be influenced by mechanical factors and by at least two chemical stimuli—hypoxia and acetylcholine. However, the mechanism of action of these stimuli is but poorly understood. And, when we come to fit them into an integrated concept of the control of the pulmonary circulation, we are troubled by several doubts.

The first doubt is how far such unphysiological concentrations of inspired oxygen and doses of acetylcholine throw any light on what happens under normal circumstances. The second is how to extrapolate into indefinite time the results from very short-term observations. The final doubt is whether these notions may be justifiably extended to the solution of physiopathological problems when the properties of pulmonary vessels and of the surrounding pulmonary tissue have been greatly altered.

Now, what of the future? Perhaps the only incontestable prophecy that can be made is that advances in methodology and advances in understanding will go hand in hand. Any attempt to define the limitations of our present methods of measuring pressure, flow, and volume in the pulmonary circulation points automatically to the directions in which improvements are at the moment being made. For pressure, our hope is for a reliable, pressure-sensitive head to the cardiac catheter. For flow, we look for a method of instantaneous measurement. For volume, we need some much more distinctive quantity than the central blood volume.

As progress is made, more results will pour in. Let us, then, beware of the danger of seeking security for our concepts in the accumulation of facts. As the poet has said:

> "Knowledge is proud that it has learned so much,
> Wisdom is humble that it knows no more."

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