Influence of Pulmonary Arterial and Left Atrial Pressures on Pulmonary Vascular Resistance

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A method has been developed by which flow to each lung, as well as pulmonary artery and left atrial pressures can be measured and varied at will. Vascular resistances were determined over a wide range of these variables. Both pressures have a marked effect on vascular resistances; the higher either pressure, the lower the resistances. This effect is most marked at low levels of pressure and flow. The absolute levels of the pressures, by affecting vascular distension, are major determinants of pulmonary vascular resistance.

The existence of vasomotor activity in the pulmonary vascular bed is well established, though the degree and significance of such activity have been much debated. Recent interest has focused on the influence of hypoxia and drugs on pulmonary vascular reactions, and on changes of pulmonary vascular resistance associated with mitral stenosis and certain types of congenital heart disease. Confusion exists in this subject because of insufficient knowledge of the mechanical factors which influence resistance. Changes of vasomotor tone can be inferred only if the background of mechanical factors is sufficiently known. Since the pulmonary vascular bed is a highly distensible system, one would expect that changes of luminal pressure might have a large effect on resistance through changes of caliber of the system. Some information on this effect has been provided by the work of Edwards, Haddy and Campbell, Hall and Williams. To obtain more information about these factors, a preparation was developed in which a detailed analysis could be made of mechanical as well as vasomotor changes which affect blood flow through the lungs.

Methods

The experimental approach involved direct continuous measurement of the blood flow to each lung, together with measurement of the pressures in right and left pulmonary artery, left atrium, femoral artery and airway in the anesthetized, thoracotomized dog. Mongrel dogs weighing from 13.6 to 29 Kg. were anesthetized by intravenous injection of either chloralose (48 mg./Kg.) and urethane (480 mg./Kg.) or Nembutal (30 mg./Kg.). The chest was opened by sagittal sternotomy while ventilation was maintained with a fixed stroke pump connected to a tracheal cannula. The end-expiratory pressure was maintained at 5 cm. H2O in order to maintain a satisfactory end-expiratory volume of the lungs.

The pericardium was opened and ties were placed around the main pulmonary artery at the valve level and around the left main branch just outside of the pericardium. Mepesulfate was given as an anticoagulant. The clamped outflow tube (fig. 1) was inserted through the right atrium into the right ventricle. The obturated large cannula R (fig. 1) was inserted through the right atrium into the right ventricle. The obturated large cannula R (fig. 1) was inserted through a small incision in the right ventricular conus. The obturator was withdrawn and the outflow tube was opened to the reservoir, while the pump, previously primed with donor blood, was started. The cannula R was then advanced into the main pulmonary artery where it was tied. The pump output was adjusted to maintain left atrial and femoral artery pressures in the preoperative range. Subsequently the smaller unpatulous cannula L was inserted into the main pulmonary artery where it was tied.
Fig. 1. Diagram of the experimental preparation. RV = right ventricle, RA = right atrium, F = flowmeters, R = main pulmonary artery cannula, L = left pulmonary artery cannula, RT - PA and LT. PA = right and left pulmonary arteries. The two pressure catheters are seen entering the system just distal to the flowmeters; the ties are seen in position around the pulmonary arteries.

through the lumen of R into the left pulmonary artery and tied in place. In this manner an extracorporeal pump system was established without interruption of the circulation, and essentially without blood loss. During the experiment circulating blood volume was controlled by addition of donor blood and/or Dextran.

Blood flows were measured with Shipley-Wilson rotameters. Vascular pressures were obtained from catheters in each pulmonary artery, PA, and the left atrium, LA, and from a cannula in one femoral artery. They were measured with Sanborn Co. electrical capacitance manometers, and electrically integrated while the airway pressure was measured with an inductance manometer. All the values were recorded on Sanborn Co. multi-channel, direct-writing oscillographs.

Blood temperature was maintained between 35 and 38 °C by heating the reservoir and by infrared irradiation of the blood in the rest of the extracorporeal circuit.

In the presentation of results, mean vascular pressures are employed throughout. Pulmonary vascular resistance was calculated by dividing the PA - LA pressure gradient by flow, and was expressed in mm. Hg/ml./min.

Results

The results were derived from three different types of experiment. In the first type the relationship of resistance to increased perfusion pressure was examined by progressively increasing the pump output in steps which were maintained until flows and pressures were stable. The right lung always accepted more blood flow than the left, the proportion ranging from 55 to 70 per cent of total flow. For any given dog, flow distribution was essentially constant through the whole range of flow rates.

Figure 2 is a characteristic example of the results and represents the changes in flow, left atrial pressure and left lung resistance plotted against the simultaneous changes in PA pressure. The shape of the curve relating PA pressure to resistance was characteristic. There was a rapid reduction of resistance as PA pressure increased up to a range of 19 to 23 mm. Hg, after which further increments of PA pressure resulted in relatively slight changes.
of resistance. Such curves or segments thereof were obtained on numerous occasions in 20 dogs. They all showed a similar shape, though their location in respect to pressure and resistance varied somewhat.

A defect in the above type of procedure was the unavoidable elevation in left atrial pressure which occurred at the high flow rates. In order to assess the effect of changes in left atrial pressure alone, an approach was employed in which the resistance of only one lung at a time was observed. Left atrial pressure was elevated in steps by tightening a tourniquet around the ascending aorta. Pulmonary artery pressure in the lung under study was kept at a constant level by the adjustment of clamps on the right or left pulmonary inflow channels. Table 1 shows in successive columns a series of tests in which pulmonary arterial pressure (PA) was kept constant while left atrial pressure (LA) was altered. It also shows the pulmonary-atrial pressure difference (ΔP) and flows. From these, changes in resistance (Res) were calculated. It was found that left atrial pressure elevation, at a constant level of PA pressure, produced a significant decrease of pulmonary resistance.

Finally, a procedure was employed in which the relationship of resistance to changing pulmonary artery pressure could be observed at constant levels of left atrial pressure. At a fixed pump output (thus ensuring a constant LA pressure) flow was deflected in progressive steps first into one lung and then the other by adjusting clamps on the pulmonary inflow tubes. The resistance in each lung could then be examined throughout wide ranges of flow and PA pressure at any selected left atrial pressure. The desired levels of LA pressure were secured by suitable adjustments of the aortic tourniquet and pump output. Experiments of this type were performed in 5 dogs. Figure 3 is an example of the pressure-resistance curves obtained in one dog at three different left atrial pressures.

The curves in figure 3A and 3B were obtained simultaneously, the high PA pressure range in one lung being examined at the same time as the low pressure range in the opposite lung. As might be expected, resistance was lower in the right (larger) lung. The curves are essentially similar in shape to the curve illustrated in figure 2, though of necessity only relatively

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<th>Table 1.—The Influence of Left Atrial Pressure on Pulmonary Vascular Resistance Measured at Constant Levels of Pulmonary Arterial Pressure*</th>
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*Pressures in mm. Hg, flow in ml./min., and resistance in mm. Hg/ml./min.
small ranges of PA pressure could be explored at any one level of LA pressure. It was again apparent that in the low ranges, small variations of PA pressure produced large changes in resistance while in the higher ranges, alterations in PA pressure produced only slight changes of resistance. It is also evident however that at any given PA pressure, resistance was lowered by increments of LA pressure. As with PA pressure, changes in LA pressure had a greater influence on resistance in the lower ranges than in the high, e.g., there was a difference of approximately 5 mm Hg in LA pressure between the lower and middle curves in Fig. 3, and of only 2 mm Hg between the middle and upper curves.

Data indicating the level of "critical closing pressure" in the pulmonary vascular bed were also obtained in these experiments. When flow through one lung was arrested, PA and LA pressures became equal only when the LA pressure was above 7 mm Hg. At LA pressures below this, cessation of flow was associated with a significant pressure difference between the pulmonary artery and the left atrium. This indicated closure of the vascular pathway between these points.

**DISCUSSION**

The resistance-PA pressure data obtained in this study are substantially similar to the resistance-flow data obtained by Williams for one lobe of the dog lung. Williams found that denervation of the bronchus and absence of ventilation of the perfused lobe had no effect on the resistance curves obtained and since the pulmonary artery branch was dissected and a cannula tied in, it is probable that the lobe was effectively denervated.

A similar relation between pulmonary vascular pressures and resistance was also obtained in a different preparation, in which no surgical interference with pulmonary innervation was made. The blood flow was measured with an aortic flowmeter and was varied by infusions of blood and dextran. Total spinal block and vagotomy did not significantly alter the shape of the curve.

The principal features of the resistance-transmural pressure plots are the large changes of resistance with small changes of PA or LA pressure in the low ranges, and the small changes of resistance with large changes of PA or LA pressures in the high ranges. These characteristics of the resistance curve may be
explained on the basis of several contributing factors. If the pulmonary vascular bed behaved like a system of rigid tubes and if flow were laminar, the resistance curve would be a horizontal straight line, i.e., each increment of flow would be accompanied by a proportional increment of pressure drop across the system and it would make no difference whether this was accomplished by a rise of PA pressure or a fall of LA pressure. In a complex distensible system, however, at low transmural pressures, the caliber of vessels is minimal and some are probably closed completely. As the transmural pressures rise, caliber increases and resistance to flow decreases in proportion to the fourth power of the radius. When caliber increases further, as determined by the volume-pressure characteristics of the vessels, equal increments of radius have progressively less influence on resistance, and the system behaves more and more as if it were rigid.

Most of the factors which determine resistance in a vascular bed cannot be actually measured because of their complexity, inaccessibility, and distortion by experimental attempts at measurement. The contribution of pulmonary arteries, capillaries and veins to resistance cannot be quantified separately. However, two factors which have a large measure of control over the caliber of the whole system can be measured with relative ease, at least in the experimental animal; these are the pulmonary artery and left atrial pressures, which determine both the distention of the intervening system and, by their difference, the pressure head available for flow. Although difficult to accomplish in the intact organism, both should be measured as transmural pressures, especially in the low ranges at which resistance is so sensitive to change of pressure.

Although it was technically impossible to secure a larger overlap of the curves in figure 3A and 3B, some conclusions can be drawn. If resistances are compared where equal PA ranges overlap, it is clear that (at a given PA pressure) a change of LA pressure from 6 to 8 mm. Hg makes a large difference in resistance. As LA pressure becomes higher, however, its influence is progressively less. The curve for an LA pressure of 11.1 mm. Hg (not shown) was almost the same as that for an LA pressure of 14.8 mm. Hg (fig. 3).

Similar relationships are found when different levels of PA pressure are compared at equal LA pressures. Resistance is most sensitive to change of LA or PA pressure when both PA and LA pressures are low, and changes of PA pressure have a diminishing effect on resistance as LA pressure becomes higher. When LA and PA pressures exceed about 15 mm. Hg, resistance ceases to be greatly influenced by further changes of either.

It is of interest that, at a LA pressure of less than 7 mm. Hg, there was a persistent pressure difference at zero flow; this phenomenon was not present at higher LA pressures (fig. 3), and indicates that the “critical closing pressure” in this preparation was in the vicinity of 7 mm. Hg.

The importance of taking account of these factors in the interpretation of observations on pulmonary vascular resistance is further illustrated by the experiments with drugs. Figure 4 shows the effect when serotonin was injected into the RPA cannula over a period of 20 sec. Recirculation was prevented up to point R by diverting right ventricular outflow into a separate reservoir. PA, LA and FA denote mean pressures in the pulmonary arteries, left atrium and femoral artery.
injected into the right pulmonary artery cannula while total flow was kept constant. The drug had a strong vasoconstrictor effect on the right lung as evidenced by a reduction of flow to that lung, an increase in PA pressure and a rise of right pulmonary resistance. Of special interest, however, is the fall in the resistance in the opposite lung. This is readily understood when the influence of an elevation of PA pressure is taken into account. The elevation of PA pressure in the left lung was caused by increased flow through it due to the vasoconstriction in the other lung.

By contrast, figure 5 shows the effect when an injection of epinephrine was made into the right lung of the same animal. Again a vasoconstrictor effect was obtained, as evidenced by a reduction in the right flow. The contralateral lung resistance, after an initial fall, became elevated. The initial fall was presumably the result of the elevation of left PA pressure. However, as the drug reached the coronary vessels, left atrial pressure fell due to the positive inotropic effect of epinephrine. The left resistance increase was due to the lower LA pressure and more than counteracted the decrease due to the continued elevation of the left PA pressure. Thus, in this experiment, two mechanical factors tended to change resistance in opposite directions; elevation of PA pressure causing a fall, and lowering of LA pressure causing a rise in resistance. These factors also influenced resistance in the right lung into which the drug was injected. The changes in right resistance are a poor index of the change in vasomotor tone which occurred.

Although mechanical factors satisfactorily explain the events, it must be stated that passage of the drug through the bronchial circulation was not excluded. The dose reaching the contralateral lung this way is probably minimal, and further recirculation was prevented for some time after the injections (figs. 4 and 5).

The changes in vascular resistance in the “control” lung illustrated here have been repeatedly observed following drug injection into a pulmonary artery, and can always be accounted for when changes in PA and LA pressures are known. They illustrate clearly the difficulties in the interpretation of changes in calculated resistance. In experiments in the intact animal, or man, designed to elicit changes in vascular tone following interventions such as drug injection or exercise, there are usually changes in output and consequently PA pressure, and/or LA pressure. The mechanical effects of these pressure changes, working in the same or opposite directions, may greatly modify or even outweigh the primary effects looked for. Conclusions about changes in pulmonary resistance should therefore be made cautiously, unless the measurements are made at comparable distending pressures. When this cannot be achieved, only those resistance changes opposite in direction from those to be expected on mechanical grounds may be considered due to intrinsic tone change.

Some applications to clinical data deserve comment. When comparing values of pulmonary vascular resistance in various diseases, the absolute levels of PA and LA pressure should be considered. It is not surprising that patients with large pulmonary blood flows and elevated PA pressures due to congenital shunts...
show low, "subnormal," values of pulmonary vascular resistance as long as complicating pulmonary vascular disease has not occurred. There are, however, relatively few patients with mitral stenosis in which this has been recorded. This may indicate that most mitral patients at the time of catheterization already have pulmonary vascular constriction or disease. This is further supported by the finding that the pulmonary vascular resistance is below normal in dogs with experimental mitral stenosis of up to 10 months' duration. Haddy and associates, in the same study, also observed that the PA pressure was a poor index of the degree of LA pressure elevation. This emphasizes the need for measurements of left atrial or "pulmonary capillary" pressures when studying mitral stenosis.

**Summary**

A preparation for the study of pulmonary vascular resistance has been described in which right and left lung blood flow were measured, together with pulmonary arterial and left atrial pressures. The flows and/or pressures could be varied at will. Elevation of either left atrial or pulmonary artery pressure resulted in lowered resistance. At low pulmonary artery and left atrial pressure levels small changes in PA or LA pressure had a marked influence on resistance; the influence of either pressure on resistance was progressively less in the higher ranges.

"Critical closing" was demonstrated in the pulmonary vascular bed, but was found to occur only at low levels of left atrial pressure.

The manner in which altered distending pressures might confuse the interpretation of resistance data was illustrated and it was concluded that the significance of changes in pulmonary vascular resistance should be treated with reserve unless the measurements are made at comparable distending pressures.

The importance of measuring pulmonary "capillary" or left atrial pressures, when studying mitral disease or drug effects, is emphasized.

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**References**

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