Distribution of blood flow in isolated lung; relation to vascular and alveolar pressures

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West, J. B., C. T. Dollery, and A. Naimark. Distribution of blood flow in isolated lung; relation to vascular and alveolar pressures. J. Appl. Physiol. 19 (4): 713-724. 1964.—The left lung from a dog was removed, ventilated with negative pressure, and perfused with venous blood. Pulmonary arterial, venous, and alveolar pressures could be varied over a large range. The distribution of blood flow in the lung was measured with Xe133. Under these conditions, there was no blood flow above the level at which alveolar equalled arterial pressure (measured at the arterial cannula). Below this level there was a linear increase in blood flow down the lung when the venous pressure was kept low. Raising the venous pressure made the distribution of flow more uniform below the level at which venous and alveolar pressures were equal although flow still increased down this zone. The flow distribution could be completely accounted for by the mechanical effects of the pressure inside and outside the blood vessels which each behaved like a Starling resistance. It was possible to simulate the flow distributions found in man in various physiological and diseased states.

pulmonary hydrostatic effect Starling resistance

The lung is a unique organ in that it separates liquid and gas by a thin membrane. Because of the very different densities of these two substances, the pressure difference across this membrane varies depending on the vertical level in the lung so that small vessels at different levels are subjected to different transmural pressures. If these vessels are collapsible and/or distensible, their caliber will depend on their vertical level and thus regional differences in blood flow will be expected.

In man the pulmonary blood flow increases some ninefold from the apex to the base of the upright lung. Various physiological and pathological states alter this observed flow distribution; posture for example affects it in that the apical and basal blood flows become equal when the subject is supine. Exercise and other conditions such as intracardiac shunts which increase the pulmonary blood flow result in a more even distribution of blood flow in the lung, presumably because the pulmonary artery pressure is raised (24). There is evidence that the pulmonary venous pressure affects the distribution of blood flow; for example, patients with moderate mitral stenosis and therefore a raised venous pressure have a more even distribution of flow than normal subjects (10). Changes in alveolar pressure are also thought to affect the distribution of flow in man (13) and in the dog (3). However no direct measurements of the various pressures which presumably determine flow in the lung together with the corresponding flow distributions have been reported as yet.

This paper describes studies made using radioactive gases to measure the regional blood flow at various levels of an isolated perfused dog lung. In this preparation, arterial, venous, and alveolar pressures could be altered at will and the resulting effect on the distribution of pulmonary blood flow measured.

METHODS

Experimental preparation. Mongrel dogs weighing 20–35 kg were premeditated with 0.3 mg atropine sulphate and anaesthetized with intravenous thiopentone sodium (0.4–0.6 g). Anesthesia was maintained with pentobarbitone sodium (60–120 mg at intervals when necessary). An endotracheal tube was inserted, intravenous heparin given (2,000 IU/kg; Paines and Byrne, Ltd.) and 500 ml of venous blood removed to prime the perfusing circuit. The animal was then quickly bled to death and the left lung removed via a large intercostal incision. First the left pulmonary artery was isolated and divided between ties close to its origin from the main trunk. Next the left main bronchus was divided at the main carina. Finally the left atrium was incised along the atrioventricular junction, the right atrium was cut away, and the pulmonary veins entering from the right lung were divided. The left lung could then be removed together with the left atrium. A clip was placed on the pulmonary artery to prevent air entering it and a glass cannula tied in. Another glass cannula was tied into the bronchus, this cannula having an angle so that the bronchus entered the suspended lung at the correct attitude. The pulmonary veins entering the left atrium from the right...
The lung was then placed in a Lucite box with the three cannulas projecting through the front through rubber seals in the front of the box. Air in the box was kept warm and moist by circulating it over hot water. Venous blood was removed from a second dog through femoral vein cannulas and passed via a finger pump to an air reservoir to damp out pulsations, then to a wire-mesh filter and a glass heat exchanger. Blood entered the lung through the pulmonary artery cannula which was provided with a thermometer, a saline manometer, and a needle for injecting radioactive xenon solution. Blood left the lung via the venous cannula, which also had an attached manometer, and flowed to a constant-volume reservoir which could be raised or lowered to vary the venous pressure. A float-actuated switch controlled another finger pump which returned the blood to the dog via an external jugular vein. Scintillation counters on both sides of the box could be moved by a hydraulic pump and they scanned the lung from bottom to top following an injection of radioactive xenon solution. Combined outputs from the two counters were connected to a pen recorder. A contactor attached to the counters gave a signal on another pen every half inch of vertical movement (see Fig. 3).

The perfusing circuit is shown in Fig. 1. A second dog was anesthetized in the same way and intravenous heparin was given (2,000 IU/kg). Blood was taken via two femoral vein catheters and passed through a finger pump (Sigmamotor model T6S) the output of which was continuously variable up to about 1,200 ml/min. Pulsa-
tions in the pump output were damped out by an air reservoir; thus all the measurements reported here were done under steady-flow conditions. The blood then passed through a fine stainless steel mesh filter and a glass heat exchanger so that it entered the lung at about 38°C. The venous cannula and line were of wide-bore tubing (10 mm i.d.) and led to a venous reservoir with a float-actuated mercury switch which controlled another finger pump. This returned the blood to an external jugular vein of the dog. The circuit as described ensured that relatively normal venous blood entered the perfused lung but when attempts were made to increase the flow above about 250 ml/min, blood could not be removed sufficiently rapidly from the femoral veins. For flows in excess of this therefore, a wide-bore shunt was temporarily connected between the outlet side of the venous reservoir and the inlet side of the arterial pump. With this ar-
angement, flows through the lung of up to 1,200 ml/min were achieved.

Saline manometers (3-mm-bore glass tubing) were connected close to the arterial, venous, and bronchial cannulas, and to the inside of the box which ventilated the lung. Blood flow through the whole lung was measured by collecting timed samples in a measuring cylinder. The circuit allowed the important pressures affecting the distribution of blood in the lung to be varied at will. Pulmonary artery pressure was varied by adjusting the arterial flow; venous pressure by adjusting the height of the reservoir; alveolar pressure by obstructing the outlet of the bronchial cannula at one box pressure and then resetting the ventilation pump.

The lung was generally perfused for about 4.5 hr and in some preparations it gained only about 10 g weight during that time. On other occasions, increases of 30 or more grams were found and histological examination carried out by Dr. Monica Bishop showed various degrees of interstitial or intra-alveolar edema. These large increases in weight were usually found when the lung had been exposed to prolonged high venous pressures and a few experiments were terminated by the appear-
ance of pink frothy fluid in the bronchi. Pulmonary edema is prone to occur in this type of preparation unless the circuit is scrupulously cleaned between experiments and because of this a cleaning procedure suggested by Professor M. de B. Daly was carefully followed.

The pulmonary vascular resistance of the preparation was measured on three occasions with the lung on its
side and the venous equal to alveolar pressure at the highest point in the lung. With a flow rate of 1 liter/min through the lung, the pulmonary arterial-venous pressure difference averaged 25 cm saline. Using a formula which takes into account the surface area of the donor dog and the proportion of the total lung volume represented by the left lung (6), the pulmonary vascular resistance averaged 7.0 mm Hg liter⁻¹ min⁻¹ m⁻² which is just within the range for normal resting dogs (6).

Evidence that this type of preparation has a relatively normal physiology is that its over-all gas exchange is good. In a separate series of measurements on eight similar preparations the average alveolar-arterial O₂ and CO₂ differences were about 11 and 2 mm Hg, respectively, values comparable with those reported for the intact anesthetized dog (18, 20). The present preparation was also capable of striking changes in vasomotor tone. For example, there was a marked rise in pulmonary vascular resistance when the lung was allowed to re-breathe its own alveolar gas. The responses to hypoxia and hypercarbia in similar preparations have been studied by others (8).

Radioactive gas measurements. In 30 lungs measurements of the distribution of blood flow were made with Xe133. This gas was introduced for measuring pulmonary blood flow by Ball et al. (1) and the present technique was developed by Dollery and Gillam (8). A solution of Xe133 was prepared by dissolving a carbon dioxide dilution of the highly radioactive gas (as received from the Radiochemical Centre, Amersham, Bucks., England) in 20 ml of physiologically normal saline. About 2 ml of this solution containing about 1.5 mc of Xe133 were injected into the arterial line just proximal to the cannula through a spray-tipped needle to ensure good mixing with the blood. The lung was held in inspiration and the arterial, venous, alveolar, and pleural pressures noted as the radioactive gas reached the lung and was evolved into the alveolar gas.

The arrival of Xe133 was monitored by a pair of scintillation counters aligned with the lung (Fig. 1) and when all the radioactive gas had reached the lung, the lung was scanned from bottom to top by raising the counters with an electrically driven hydraulic pump. The combined output of the two counters was fed to a pen recorder. A second pen was actuated by contacts on the counter gantry which closed each half inch of movement of the counters and so indicated their vertical position relative to the lung. The resulting scan (see Fig. 3 for an example) depended on the relative amounts of Xe133 which had reached different parts of the lung (and therefore on their blood flow), and also on the distance from the counters and absorption characteristics of the lung at different levels. In order to allow for these differences in geometry, a rubber bag was attached to the bronchial cannula and the lung allowed to re-breathe for about 2 min until the Xe133 was evenly distributed throughout the whole alveolar volume. The lung was then scanned again and the resulting record gave the counting rates at each level which would have been found if all the lung had been evenly perfused according to its alveolar volume. By dividing the ordinate of the first record by the ordinate of the second at various lung levels, the blood flow per unit alveolar volume in arbitrary units could be plotted. In all, several hundred separate measurements of flow distribution were made.

The counters had NaI crystals 1.5 in. diameter and four-holed focused collimators 6 in. long giving a counting field in which 90% of the counts came from a cylindrical core of lung 3 cm in diameter. Xe133 emits 80- and 90 kev-gamma rays and pulses having energies below 47 kev were excluded by biasing. Injections of 1.5 mc gave counting rates of about 300 counts/sec over the thickest and best perfused parts of the lung. Scanning speed was about 0.5 in/sec and the 90% response time of the counting plus recording equipment to a stepwise change in counting rate was 0.5 sec. In order to determine the resolution of the scanning system, a 0.5 cm i.d. glass sphere filled with Xe133 was placed against the lung inside the Lucite box and scanned in the usual way. Figure 2 shows that when the counter centers had moved 1.3 cm from the center of the source, the counting rate had fallen to 90% of the maximum counting rate.

In some experiments, an additional scintillation counter monitored the xenon radioactivity in pulmonary venous line between the venous cannula and the reservoir. The Tygon tubing (10-mm bore) was led through a groove in a lead brick which was then placed against a 1.5 in. diameter NaI crystal scintillation counter. Counting rates of 4,000 counts/sec were available when the tubing was filled with Xe133 in a concentration of 7 mc/liter. When the output of the counter was fed to a pen recorder, indicator-dilution curves were available following each xenon injection.

In seven lungs, regional blood flow was measured from the clearance rate of O₂¹⁵-labeled CO₂ using the technique previously described (24). Cyclotron-produced O₂¹⁵ was converted into CO₂ and pumped to the labora-
FIG. 3. A: actual record obtained as the counters scanned from bottom to top of a lung following an injection of Xe133 dissolved in saline. Left lung from a 26-kg mongrel dog. Lung suspended vertically as in Fig. 1, and held in inspiration by negative box pressure of -10 cm saline. Alveolar pressure (PA) was atmospheric. Pulmonary arterial pressure (Pa) was 32 cm saline referred to the bottom of the lung and the lung height was 27 cm, so that arterial equaled alveolar pressure 5 cm above top of lung (neglecting the resistive pressure drop along the pulmonary artery). Venous reservoir was below the bottom of the lung so the venous pressure was less than atmospheric throughout the lung. Blood flow rate approximately 500 ml/min. Pen at top of tracing marked each 0.5 in. of vertical movement of counters. Scanning speed about 1 cm/sec. Full-scale deflection 300 counts/sec. Record shows a rapid rise in counting rate and then a steady fall as the counters moved up the lung; this reflected both the blood flow distribution and the volume of the lung at different levels. B: Record obtained after 1 min rebreathing when the Xe133 had been evenly distributed throughout the whole alveolar volume. This scan took into account the volume and absorption characteristics of the lung at different levels and shows the tracing which would have been obtained if the lung had been evenly perfused per unit alveolar volume. C: Plot of blood flow per unit alveolar volume (in arbitrary units) against distance up the lung made by dividing the ordinates of A by the ordinates of B at 0.5 in. intervals after subtracting appropriate backgrounds. There was an approximately linear change in flow up the lung and virtually no flow at the top.

FIG. 4. Effect of reducing the pulmonary artery pressure on the flow distribution. Same conditions as in Fig. 3 except that the blood flow rate was reduced to about 200 ml/min so that the pulmonary arterial pressure (Pa) was only 16 cm saline referred to the bottom of the lung. Thus arterial equaled alveolar pressure (PA) 16 cm above the bottom (subtracting the hydrostatic component). A shows that the counting rate following the injection had fallen to background level by the time the counters had moved about 16 cm from the bottom of the lung and this is shown graphically in C.

In three lungs, measurements were made using cyclotron-produced N13 (half-life 10 min). The isotope was produced by bombarding carbon with 15 Mev deuterons, the gas being flushed out of the target by a stream of methane. This was converted into CO2 by passing it over a hot copper oxide furnace, and shaking the gas with normal saline gave a solution containing 0.5 mc N13 in 10 ml saline. This solution was injected as for Xe133 and and the lung scanned. The technique of producing a solution of N13 was developed by John C. Clarke. N13 has the advantages that coincidence counting can be used with its very low background counting rate, and that nitrogen is some 14 times less soluble in blood than xenon.

Other measurements. Two other techniques for examining the distribution of blood flow in the lung were used. In the first, 10 ml of 80% Hypaque, a radiographic contrast material, were injected into the arterial line and serial radiographs taken. In the second, 10 ml of 1% Evans blue solution were injected in the same way and the coloration produced on the pleural surface of the lung was photographed as the blood passed through the lung.
RESULTS

To introduce the results, a typical measurement of blood flow distribution will be described in some detail (Fig. 3). This left lung from a 26-kg mongrel dog weighed 142 g before and 98 g after 5 hr perfusion. It was suspended in the upright position and perfused with blood at a flow rate of approximately 500 ml/min. The venous reservoir was placed below the level of the bottom of the lung. With the lung held inflated by a negative pressure in the box of -10 cm water (bronchus open to air), the level of the saline in the arterial cannula manometer was 5 cm above the top of the lung. Three milliliters of saline containing Xe133 were injected into the arterial line and after waiting 15 sec for all the xenon to reach the alveoli, the lung was scanned twice from bottom to top by raising the counters. The scans were good repeats and the second is shown in Fig. 3A. Marks made by the second pen indicating the vertical height of the counters can also be seen. The tracing shows a high counting rate near the bottom of the lung which decreased as the counters approached the top. A small rubber bag was then attached to the bronchial cannula and the lung was allowed to rebreathe and another two scans recorded, one of which is shown in Fig. 3B. This tracing gives the distribution of counting rates which would have been found if the lung had been evenly perfused per unit alveolar volume. The actual blood flow distribution was found by dividing the ordinates of Fig. 3A by the corresponding ordinates of Fig. 3B after smoothing out the random fluctuations. The result is shown in Fig. 3C.

It can be seen that the blood flow per unit lung volume decreased fairly steadily from the bottom to the top of the lung. There is some unevenness because of the somewhat low counting rates obtained with the high resolution collimators (Fig. 2) but the results of many similar scans show a generally linear fall in blood flow per unit lung volume under these conditions.

The separate effects of varying the pulmonary arterial, alveolar, and pulmonary venous pressures on the distribution of flow will now be considered in turn. All these measurements were made with the lung suspended in the upright position and the effect of changing lung position was subsequently studied. Although single illustrative examples are shown in the figures, the conclusions are based on a large number of separate measurements.

Effect of varying the pulmonary arterial pressure. Arterial pressure was altered by varying the output of the arterial pump, and the pressure was measured on a saline manometer attached to the arterial cannula. Figure 4 shows the flow distribution obtained with the same lung shown in Fig. 3 but perfused at the abnormally low flow rate of about 200 ml/min with the result that the arterial pressure was 14 cm saline below that used for Fig. 3. The level of the saline in the arterial manometer was then 9 cm below the top of the lung which was therefore the level at which the hydrostatic component of arterial pressure equaled atmospheric pressure and therefore alveolar pressure, since the lung was held in inspiration by negative pressure and the bronchus was open to air. Note that the actual arterial pressure at any level of the lung will be a little less than the hydrostatic component derived from the arterial manometer because of the flow-resistive pressure drop along the artery, but this discrepancy becomes progressively less toward the top of the lung where the flow becomes smaller.

Figure 4 shows that where arterial pressure was less than alveolar pressure, no flow could be detected, but there was an approximately linear increase in blood flow with distance down the lung below the point where arterial and alveolar pressure were equal.

A more extreme example of the concentration of flow at the base of the lung in the presence of a low perfusing pressure is shown in Fig. 5. Here with a flow of 52 ml/min through the lung, the level at which arterial equaled both atmospheric and alveolar pressures was less than one-third of the way up the lung and radioactive xenon was confined to this region. An interesting feature of this lung was that the hilum where blood entered the lung was considerably higher than the flow cutoff point so that although there was pulmonary arterial flow up to the hilar level, pulmonary capillary flow was confined to a much smaller region. (The radioactive xenon was measured after it had been evolved into alveolar gas, not while it was in the blood.) This concentration of xenon in the most basal parts of the lung below the hilum when the perfusing pressure was very low was confirmed on many occasions.

The relation between the level up the lung at which
flow ceased and that at which arterial equaled alveolar pressure was generally good with two exceptions. In some lungs in which perfusing pressure was reduced below the hilum, some radioactivity could be detected up to the hilum. The probable reason was that xenon-labeled blood had not been completely washed out of the larger arteries and evidence for this was that on some occasions, a definite hump in the counting rate tracing was observed at the hilar level. Probably an aggravating factor in these instances was the very low flows necessary to provide the unusually low perfusing pressures.

The other exception to the generally excellent correlation between the level at which flow ceased and that at which arterial equaled alveolar pressure was an anemic area in the top 3-4 cm of the upper lobe was often seen in the earlier preparations. The cause of this was not certain but it was possibly due to air in the smaller arteries. This unperfused area was not found in later preparations.

The relation between the level at which arterial equaled alveolar pressure (as measured on the arterial manometer) and the level in the lung at which flow fell to zero was measured on 32 separate scans in 14 different preparations. The plot of blood flow per unit lung volume often had a rounded end point over the last 1-2 cm because of the fringe of the counting field and in these cases, a line was drawn through the approximately linear portion of the plot and extrapolated to the baseline to determine the no-flow level (see Figs. 5 and 7A for example). The measurements were only made on lungs in the upright position. Scans in which there was clear evidence of a constant anemic area at the apex, or in which a local increase in counting rate was observed at the hilum with a low perfusing pressure, were discarded.

The mean difference by which the no-flow level exceeded the level at which arterial equaled alveolar pressure was 0.5 cm (± 0.1 cm). This figure includes a systematic overestimate of the no-flow level because of the finite extent of the counting field and it can be concluded that the difference between the two levels under the conditions studied was less than 1 cm.

The distribution of pulmonary blood flow when the arterial pressure was abnormally high was also measured and an example is shown in Fig. 6. Here the level at which arterial equaled alveolar pressure was 13 cm above the top of the lung and it can be seen that there was still ample flow at the apex which increased linearly with distance down the lung. The pulmonary venous pressure was also raised for this measurement.

**Effect of varying the alveolar pressure.** Alveolar pressure was altered by obstructing the bronchial cannula at an appropriate pleural (box) pressure and then resetting the pleural pressure. A saline U tube manometer attached to the cannula gave the alveolar pressure while the lung was held in inspiration. The flow distributions were compared at the same lung volume by always obstructing the bronchial cannula at the same pleural pressure and then resetting the pleural pressure to give the desired alveolar pressure. The arterial pressure was then adjusted by varying the flow through the lung or the venous pressure. Inevitably these maneuvers meant that comparisons were made at different pleural pressures since it was impossible to change the alveolar pressure but maintain the same pleural pressure and lung volume. However varying the pleural pressure has itself little effect on the distribution of flow.

Figure 7 shows the effect on the flow distribution of raising and lowering the alveolar pressure while keeping the pulmonary arterial pressure constant. The same lung preparation and the same pulmonary artery pressures were used for Figs. 4 and 7 but whereas the alveolar pressure was atmospheric for Fig. 4, it was 6 cm saline above and 5 cm below atmospheric in Fig. 7A and B, respectively. Thus Fig. 4, 7A and B should be compared. It can be seen that the result of increasing the alveolar pressure by 6 cm saline was to reduce the flow at the top of the lung so that the level at which flow ceased was depressed by about 6 cm (Fig. 7A). Thus again this level corresponded to that at which arterial and alveolar pressure were equal. Similarly the effect of reducing the alveolar pressure by 5 cm saline was to raise the level at which flow ceased by about 5 cm (Fig. 7B). This pattern was confirmed in several separate experiments.

**Effect of varying the pulmonary venous pressure.** Pulmonary venous pressure was altered by changing the level of the reservoir in the venous line; it was measured by a saline manometer attached to the venous cannula. Fig. 8A shows the blood flow distribution obtained in a lung in which the venous pressure was raised so that the arterial-venous difference was only 6.5 cm saline. If this diagram is compared with Fig. 3 where the venous pressure was very low, it can be seen that the result of raising the venous pressure was to make the flow distribution more even in the lower part of the lung. The flow still de-
creases with distance up the lung but the slope of the line is less steep. In the example shown the transition appears to be at about the level where alveolar and venous pressures are equal, and this would be expected on theoretical grounds (see Discussion).

In order to study the distribution of flow when the venous pressure was raised, measurements were also made with the level of the venous reservoir just above the top of the lung and an example is shown in Fig. 8B. In ten such measurements on six separate lungs the relation between blood flow and distance up the lung was generally linear. The slope of the line was such that the blood flow per unit lung volume decreased by an average of 62% over 20 cm of distance from the bottom of the lung (SEM 4.7%). This method of expressing the slope is used because blood flow cannot be calculated in absolute units. For comparison, the line relating blood flow per unit lung volume to distance up the lung in man decreases by 89% in 20 cm of distance (24).

Because the slope of the line relating blood flow to distance was so steep (as shown in Fig. 8B), it was often impossible to see a change in slope below the level at which venous equaled alveolar pressure. It was only clearly seen when the arterial pressure was only a little higher than the venous pressure as in Fig. 8A, because under these conditions, the slope of the line above the level at which venous equaled alveolar pressure was much steeper than the slope below this level.

A number of tracings showed a marked reduction in blood flow in the lowest part of the lung when the venous pressure was raised high and these records were omitted from the series from which the slope referred to above was calculated. There is no obvious mechanical explanation for this finding which is being studied further.

Effect of changing the position of the lung. Although the bulk of measurements were made with the lung in the upright position in order to exaggerate the hydrostatic pressure gradient, studies were also carried out with the lung on its side with the hilum uppermost, and in the inverted position. For the latter measurements, a clip was attached to the extreme edge of the lower lobe for additional support.

Figure 9 is an example of the distribution of blood flow obtained with the lung on its side with the flow rate adjusted so that pulmonary artery and alveolar pressures were equal (both atmospheric pressure) about 3 cm above the top of the lung. The venous reservoir was below the bottom of the lung. There was again an approximately linear increase in flow down the lung although because of the shape of the organ, measurements were only possible over about 10 cm of vertical distance.

In three lungs, the effect of inverting the lung on the flow distribution was studied and an example is shown in Fig. 9B. Here there was some irregularity in the slope of the flow distribution but a generally linear increase in blood flow with distance down the lung can be seen.

Effect of perfusing the lung from pulmonary vein to artery. Measurements were also made with the upright lung back perfused by reversing the arterial and venous connections. Under these conditions the pulmonary vascular resistance is approximately the same as for forward perfusion and the lung effectively oxygenates the blood as judged by the difference in color between inflow and outflow blood. The distribution of blood flow was also similar and Fig. 9C shows an example.

Results obtained with CO₂₁₅, N₂₁₃, and other techniques. The results presented so far were obtained using Xe₁₃³, this technique being both informative and convenient. In several preparations, additional evidence was gained by measuring the clearance rates of oxygen-labeled carbon dioxide during breath holding from defined areas of lung using stationary counters. This technique has the disadvantage that only one region of the lung can be examined with a pair of counters at each breath, but it has the advantage that blood flow in any particular region can be directly compared when the perfusing pressures are altered. This is not the case with xenon because the blood flow per unit lung volume (the ordinate on Figs. 3-9) is in arbitrary units which change when the distribution of flow changes.

Figure 10 shows the results in one lung of plotting the clearance rate of CO₂₁₅ against pulmonary artery minus venous pressure or artery minus alveolar pressure, whichever is the smaller. This abscissa was chosen because of the evidence on other grounds that these are the significant pressure gradients determining pulmonary capillary flow (see Discussion). The graph shows a good linear relation which passes close to the origin and is confirmatory evidence that flow ceases at the level where pulmonary arterial and alveolar pressures are equal.

The N₂₁₃ measurements were chiefly used to test whether the level at which blood ceased was that at which pulmonary arterial equaled alveolar pressure. Because coincidence counting could be used for this isotope, the background counting rate was virtually nil so that a sharp cutoff was seen when the counters moved above the zone containing radioactivity. The results confirmed those obtained with xenon and both sets were pooled to obtain the figures cited earlier for the relation between the two levels.
and it was important to wait for sufficient time for this inflowing blood. The radioactivity took appreciably longer to reach alveoli far from the hilum at low flows.

The saline solution of xenon was injected through a needle with a spray nozzle to ensure good mixing with the inflowing blood. The radioactivity took appreciably longer to reach alveoli far from the hilum at low flows and it was important to wait for sufficient time for this to occur before starting to scan. Up to 30 sec was necessary when the flow rates were very low and the lung blood volume increased (as was the case when the venous pressure was raised). In practice, the arrival of the xenon in a distal part of the lung was monitored with stationary counters and the scan only begun when the counting rate had reached a steady level. Duplicate runs were always done, the second about 30 sec after the first.

Xenon is slightly soluble in blood (blood/gas partition coefficient is 0.18 at 37°C) so that small amounts of radioactivity were lost during the breath-holding period. The effect was measured by scanning the lung at intervals following the injection. At low blood flow rates, the xenon loss rate was not measurable, but at higher flows it was appreciable. For example, in a typical lung in which the flow rate was 540 ml/min, the counting rate near the bottom of the lung fell at the rate of 21%/min. Since it was only necessary to wait for 5–10 sec after the injection before scanning with these higher flow rates, the resulting fall in counting rate was about 3%. The fall in counting rate would be proportionally smaller where the blood flow was less so that the blood flow of well-perfused areas would be systematically underestimated by up to 3%. For N₂¹⁸ which is 14 times less soluble than xenon, the error would be correspondingly smaller and, in practice, a fall in counting rate during the breath-holding period could not be detected. The rate of removal of xenon from the whole lung could also be measured from the counter which monitored the radioactivity in the pulmonary venous line. This showed the expected accumulation indicator-dilution curve for an injectate of very low solubility. The peak activity declined at a rate up to 20%/min depending on the blood flow through the lung and its size.

During the breath-holding period, xenon was free to diffuse in the gas phase to adjacent alveoli, so that, in theory, regional differences could become blurred by this means. In fact, however, it was possible to show that this error was very small. In lungs in which the perfusing pressure was very low, the xenon was evolved into the lowermost part of the lung (for example, Fig. 5) and by repeated scanning, the rate at which the xenon front moved up the lung during a long breath-holding period could be measured. In fact, there was no measurable broadening of the xenon front over a period of 1.5 min.

It is not possible to give a single figure for the repeatability of the blood flow distribution as measured here with radioactive xenon because of the difficulty of describing a pattern of flow by one number. However the studies of the relation between the level at which arterial pressure equaled alveolar, and the level in the lung at which flow fell to zero give a measure of the repeatability of the slope of the flow distribution under one set of conditions. In 32 separate measurements in 14 different preparations, the SD of a single observation was 0.7 cm. Converting this figure to the slope of the line giving the flow distribution (as for example in Figs. 4, 5, and 7), the SD of a single measurement was about 4% of the slope.

The errors discussed above are small and apply only...
FIG. 9. A and B: effect on flow distribution of changing the position of the lung. In A lung was suspended on its side; in B, lung was suspended upside down. In both instances, Pa was atmospheric, and Pv was less than Pa throughout the lung which was scanned vertically. Note the generally linear increase in blood flow down the lung. C: effect of reversing perfusing a lung from pulmonary vein to pulmonary artery. Lung was suspended vertically and the perfusing pressure (in this instance Pv) equaled Pa (atmospheric) 25 cm above the top of the lung. Pa was less than Pa to the scan following the injection. Equilibration of xenon throughout the lung by rebreathing occurred so rapidly that minor effects such as the removal of xenon from well-perfused areas were completely smothered. Various possible errors in relating CO215 clearance rates to blood flow have been discussed elsewhere (9, 25) and will not be re-examined here since the bulk of the measurements in the present investigation were made with Xe133.

Cause of the observed distribution of blood in the lung. Knowing the separate effects of varying the pulmonary arterial, venous, and alveolar pressures on the distribution of flow in the lung, it is now possible to build up an integrated picture relating the mechanical forces to the pattern of distribution of blood flow. Much of this has been predicted from the pressure flow characteristics of the whole lung by other investigators particularly Permutt and Riley and their colleagues (17, 19) but the present study is the first in which has been possible actually to measure regional blood flow under rigorously controlled conditions.

The lung can be conveniently divided into three zones according to the heights of the pulmonary arterial (Pa), alveolar (Pa), and venous (Pv) pressures (Fig. 11).

Zone 1 is that part of the lung above the level at which arterial and alveolar pressure are equal. In Fig. 11, the alveolar pressure has been shown as atmospheric as it is in man at the end of inspiration or expiration, and the Pa - Pa level is therefore nearly the height of the blood in the open-ended manometer in the pulmonary artery. (In fact, because of the pressure drop along the artery and its branches caused by flow, Pa falls off a little more rapidly with height inside the lung compared with the manometer.) The present study shows that there is no pulmonary blood flow in zone 1 and this is presumably because the vessels are directly exposed to alveolar pressure. They apparently behave as the resistance in a Starling heart-lung preparation in which a thin collapsible tube (made, for example, of thin rubber) is surrounded by a chamber in which the pressure can be varied. There is no flow through such a device when the chamber pressure (Pa in Fig. 11) is higher than the perfusing pressure Pa because the tube is then completely collapsed; similarly in the lung, the small vessels are closed by the alveolar pressure in zone 1.

Zone 2 is that part of the lung between the levels at which arterial and alveolar pressure are equal, and venous and alveolar pressure are equal. The present study shows a linear increase in flow with distance down this zone and a similar pattern would be found with a Starling resistance in which there was laminar flow. The reason is that because the thin tube offers no resistance to the collapsing pressure, the pressure inside the tube is the same as the pressure outside, so that the pressure gradient responsible for flow is the perfusing minus chamber pressure (Pa - Pa in Fig. 11; not Pa - Pv). This behavior has been variously compared with that of a sluice (2) or waterfall (17). The collapsible tube actually develops a constriction in its downstream end (where the pressure is least) and the constriction becomes less marked as Pa - Pa increases, until a point is reached when the downstream pressure Pv exceeds Pa. When this occurs, the collapsible tube is no longer flaccid because the pressure inside exceeds the pressure outside at every point in its length. Under laminar flow conditions, there will be a linear relation between volume flow rate and the pressure gradient Pa - Pa. In the lung, Pa is the same at every level while Pa steadily increases down the lung. Thus the linear increase of flow with distance down zone 2 is satisfactorily explained.

Zone 3 is that part of the lung below the level at which venous and alveolar pressures are equal. The present study shows an increase of flow with distance down this zone though the rate of increase may be less than in zone 2 (Fig. 8). The increase in flow appears to be approximately linear with distance down the lung. Again the distribution of flow in this zone can be explained by analogy with a Starling resistance. Because venous pressure is higher than alveolar pressure throughout this zone, the pressure inside the collapsible vessels will be everywhere higher than the pressure outside so that the vessels will not be flaccid but expanded. Now the pressure difference controlling flow is not Pa - Pa but Pa - Pv. At first sight, it appears that there would be no change in blood flow down zone 3 because Pa - Pv is the same at all levels. However, if the vessels are not only collapsible but also distensible, their degree of distension will depend on their transmural pressure difference. This will increase down the zone, since the pressure inside will lie between Pa and Pv both of which increase through the hydrostatic effect, while the pressure outside will be constant. Thus if part of the vessel
which resists flow is distensible, the resistance to flow will
decrease down the zone. However it is not surprising
that the slopes of zone 2 and zone 3 may be very dissimi-
lar since they are governed by entirely different factors.

All the xenon scans show a definite slope in zone 3 and
it is therefore somewhat misleading to plot the zone 3
clearance rates in Fig. 10 against Pa - Pv without allow-
ing for whether they are measured near the top or
bottom of the zone. The consequent systematic error is
apparently concealed by the generally poor repeatability
of the clearance rate measurements. The zone 2 clear-
ance rates are correctly plotted against Pa - PA.

The slope of zone 3 was further studied to determine
whether the pressure outside the distensible resistive
vessels was the alveolar or the pleural pressure or a mix-
ture of both. This was done by turning the preparation
over so that the lung was on its side to reduce hydro-
static differences within it, and raising the outlet of the
venous line above the top of the lung. Pv was then raised
in steps and Pa - Pv kept constant by altering the out-
put of the pump. When volume flow rate was then
plotted against Pv, the slope of the line was virtually a
measure of the slope of zone 3 (since Pa and Pw were
kept constant).

Similar measurements were then made varying Pa but
holding Pa - Pv and lung volume constant, and varying
Pw and lung volume but holding Pa - Pv and Pa con-
stant. The results which will be reported elsewhere in
more detail show that the pressure outside the distensible resistive vessels of zone 3 is almost entirely alveolar.

In the experiments reported here, it was possible to
reduce the pressure inside the pulmonary veins below
the box pressure by sufficiently lowering the venous
reservoir. There was evidence that under these condi-
tions, the operative venous pressure in the lower part of
the lower lobe approached the pleural pressure rather
than the pressure shown by the venous manometer
(which was attached to the venous cannula outside the
box). The large veins themselves were then apparently
behaving as Starling resistors. However, no effect of this
complication on the distribution of blood flow was de-
tectable. It was only when extremely low flows were
studied that the evidence for this second Starling resistor
became apparent and these results will be reported
celsewhere.

In the above analysis, care has been taken not to im-
licate any one part of the pulmonary vessels, for example
the capillary, as the cause of the observed flow differ-
ences. At first sight, the capillaries might be expected to
be the first vessels to close as alveolar exceeds arterial
pressure since they lie unsupported in the alveolar walls.
However it has been suggested that the surface tension
in the alveolar wall would have a component tending to
hold the capillaries open (4, 16). The pressure inside
the adjacent small veins is less than in the capillaries be-
cause they are downstream, and if these veins are sub-
jected to alveolar pressure, they would be the first to
be closed. By the same argument these vessels would be the ones which
would partially close in zone 2. On the other hand, the
flow-resistant vessels which distend and cause the flow
differences in zone 3 may be arterioles since the increase
in transmural pressure down zone 3 has such a large effect
on flow. The vessels are presumably near the alveoli
because the pressure outside them is alveolar rather than
pleural.

The finding that blood rose up the lung only to the
level at which Pa = PA contrasts with the work of Lloyd
and Wright (16) who showed that dog lobes perfused at
very low flows at room temperature with an electrolyte
solution containing Evans blue dye showed blue stain-
ing in the cut sections up to 5 cm above the Pa = PA
level. However because of so many differences in tech-
nique, the two studies are not easily compared.

In the present experiments no attempt was made to
study the effect of varying the surface tension in the
alveoli, the volume history of the lung being the same
for all the measurements of flow distribution. The lung
was continually cycled at 12 breaths/min between about
-2 and -10 cm water pressure (with respect to at-
mosphere) and was then expanded by about 10 cm saline
pressure and held in inspiration while the measurement
was made. The xenon was injected a few seconds later.
There is no reason to suspect that the surface tension of
the preparation was abnormal; its tidal volume for a
7-cm saline pressure swing was about 250 ml giving a
compliance of about 0.04 liter/cm H2O which is about
normal for one lung of a dog of this size (22).

Again, no systematic measurements were made of the
effect on the distribution of blood flow of varying the
pleural (box) pressure over a wide range. Most of the
studies reported here were made with a pleural pressure
of about \(-10 \text{ cm } H_2O\) with respect to atmosphere, but
a few measurements made with pressures above and
below this suggested that changes in pleural pressure
and lung volume had no marked effect on the distribu-
tion of flow.

No mention has yet been made of the contribution
made by vasomotor tone to the distribution of blood
flow. There was no doubt that the vasomotor tone in this
preparation could change dramatically, for example, when
it was allowed to rebreathe into a rubber bag. In
a typical experiment, the pulmonary artery pressure rose
by 14 cm saline during a 5-min rebreathing period, and
in order to return the arterial pressure to its original level,
it was necessary to reduce the blood flow to a third. Thus
the pulmonary vascular resistance had trebled as a
response to the low oxygen—high carbon dioxide gas
mixture.

However the findings presented here show that the
role of vasomotor tone is in determining the pulmonary
artery pressure and that when this is set, the distribution
of blood flow can be predicted on purely mechanical
grounds. There is no evidence that regional variations in
vasomotor tone modify the distribution of flow since the
observed distribution could be completely accounted for
by the mechanical effects of pressures inside and outside
the vessels at different levels in the lung.

**Distribution of blood flow in the lung in man.** The findings
presented here are entirely consistent with previous ob-
servations on the distribution of flow in man made with
radioactive gases. A complication is that pulmonary
artery pressure in man is pulsatile as is pulmonary capil-
larly flow (15) and mean flow is presumably related to
mean pressure. In the normal upright lung there is
almost no flow at the top where pulmonary artery
pressure is close to alveolar pressure (7), and there is an
approximately linear increase in flow with distance down
the lung (23). In the supine lung when the hydrostatic
differences between apex and base is removed, flow in
these two regions is the same (24). On exercise, the pul-
monary artery pressure increases thus decreasing the rela-
tive hydrostatic difference between any two levels in the
lung so that the relative flow difference between upper
and lower zones becomes less (24). In addition, during
exercise, the blood in the pulmonary artery probably has
considerable kinetic energy which is not reflected in the
pressure measured lateral to flow, and this energy will be
available to move the blood up the lung. Calculations show
that this effect is negligible under the conditions
described in this paper. The same result is seen in pa-
ients with left-to-right shunts and increased pulmonary
blood flow and also in patients with pulmonary hyper-
tension but a normal pulmonary blood flow (11). Pa-
ients with mitral stenosis (10) and left ventricular failure
have a more complicated picture. In moderate disease,
the difference in flow between upper and lower parts of
the lung becomes less and there are two reasons for this.
One is that the pulmonary venous pressure is raised so
that more and more of the lung is in zone 3 where, as
Fig 8 shows, blood flow is more evenly distributed. An
additional reason is that the pulmonary artery pressure is
passively raised. In avcvc mitral stenosis (10) and left
ventricular failure, the blood flow at the top of the lung
may far exceed the flow at the bottom and this reversal
of the normal distribution cannot be explained on the
basis of the findings presented here.

Studies by other investigators provide indirect evi-
dence that increasing the alveolar pressure affects the
distribution of blood flow in the lung. For example
Folkow and Pappenheimer (13) showed that in two
normal subjects who breathed against a constant positive
pressure of 20 cm H_2O, there was an increase in the
number of alveoli which were poorly perfused but well
ventilated. The effect was equivalent to complete ob-
struction of the circulation to 10% of the ventilated
alveoli. To explain these changes as the result of a more
uneven distribution of flow down the lung, it would be
necessary to know that the rise in pulmonary arterial
pressure as a result of the pressure breathing was less
than the rise in alveolar pressure. This information was
not available in the human experiments, but was the

**FIG. 11. Diagram to show the supposed behaviour of the small
vessels in different parts of the lung, and the resulting regional
differences in blood flow. The lung is divided into three zones ac-
according to the relative magnitudes of the pulmonary arterial,
venous, and alveolar pressures. In zone 1, alveolar exceeds arterial
pressure so that the collapsible vessels are held closed and there is no
flow. In zone 2, arterial pressure exceeds alveolar, but alveolar
exceeds venous. Under these conditions, there is a constriction at
the downstream end of each collapsible vessel and the pressure in-
side the vessel at this point is equal to alveolar pressure, so that the
pressure gradient causing flow is arterial — alveolar. This gradient
increases linearly with distance down the lung, and therefore so
does blood flow. In zone 3, venous exceeds alveolar pressure and
the collapsible vessels are held open. Now the pressure gradient
causmg flow is arterial — venous and this is constant down the
zone. However the transmural pressure difference steadily increases
down the zone, and part of the vessel dilates. Blood flow therefore
also increases down this zone, though measurements show that the
change is less rapid than in zone 2. (Note that a slight curvature has
been shown on the right hand graph in both zones 2 and 3. This
is because the relation between caliber and flow is probably
alinear.)
case in a separate study by Bitter and Rahn on anesthetized dogs in which breathing against a sustained pressure of 40 cm H₂O resulted in the equivalent of 45% of the alveolar tidal volume going to unperfused alveoli (3).

REFERENCES


WEST, DOLLERY, AND NAIRNARK

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