JOURNAL OF APPLIED PHYSIOLOGY
Vol. 25, No. 6, December 1968. *Printed in U.S.A.*

Effect of extra-alveolar vessels on distribution of blood flow in the dog lung

J. M. B. HUGHES, J. B. GLAZIER, J. E. MALONEY, AND J. B. WEST
Clinical Respiratory Physiology Research Group, Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London, England

HUGHES, J. M. B., J. B. GLAZIER, J. E. MALONEY, AND J. B. WEST. *Effect of extra-alveolar vessels on distribution of blood flow in the dog lung.* J. Appl. Physiol. 25(6): 701–712. 1968. — The distribution of blood flow in an isolated dog lung preparation and in the intact animal was measured with radioactive xenon. In the vertical isolated lung there was a reduction in blood flow to the most dependent zone which was eliminated at high lung volumes and transpulmonary pressures. The proportion of blood flow to the dependent zone decreased during infusions of vasoconstrictor drugs (serotonin) but increased with a vasodilator (isoproterenol). These changes were analyzed in terms of a balance of forces acting on the extra-alveolar vessels of the lung. The pressure in the perivascular space, interstitial pressure, falls as the lung parenchyma expands. As a result these vessels are held open and their resistance decreases. A rise in extra-alveolar vascular resistance occurs when increases in tension in the vessel wall, produced by vasoconstriction, oppose the low interstitial pressure. In intact dogs fluid loading of the circulation reduced the blood flow to the dependent zone as a result of the rise in interstitial pressure caused by edema.

interstitial pressure; vascular resistance; regional differences in the lung; pulmonary edema

MEASUREMENTS OF regional pulmonary blood flow in man with radioactive gases have shown that in the upright position blood flow is maximal at the base and decreases until it is virtually nil at the apex (2, 18). This pattern can be explained on the basis of the relations between pulmonary arterial, alveolar, and venous pressures as predicted from the pressure flow characteristics of the whole lung (15). The influence of a hydrostatic gradient of vascular pressure on regional pulmonary blood flow measured with xenon 133 was shown in an isolated lung preparation (20) where these three variables (arterial, alveolar, and venous pressures) could be controlled.

In certain conditions a very different pattern of regional blood flow is seen which cannot be explained by changes in the relation between vascular and alveolar pressures. A marked reduction in blood flow to the base of the lung has been described in an isolated lung preparation in the presence of a high venous pressure together with a low arterial-venous pressure difference (19). This increase in resistance in the dependent zone was attributed to perivascular edema although increasing the arterial-venous difference readily eliminated it. A large reduction in blood flow to the dependent zones occurs in patients with severe mitral stenosis (3), reversing the normal flow distribution. This striking pattern of regional pulmonary blood flow can be reproduced in normal subjects at low lung volumes (8). With xenon 133 we have shown that in normal subjects at residual volume apical flow is higher than basal flow. At functional residual capacity the point of maximal blood flow was 10 cm above the bottom of the lung, but the extent of this zone of reduced blood flow at the base of the lung diminished at higher lung volumes.

Recently a distinction has been made between the small vessels of the lung lying in and around the alveolar septa which are exposed to alveolar pressure and the larger pulmonary vessels with tone which are exposed to pressures lower than alveolar (7) called extra-alveolar vessels (11). With the radioactive xenon technique we have investigated the influence of extra-alveolar vessels on the distribution of blood flow in the isolated vertical dog lung especially in response to changes of lung volume and infusions of vasoactive drugs. In addition, we have deliberately raised the pressure surrounding these vessels—interstitial pressure—by intravenous fluid loading in the intact animal and have observed the change in the distribution of blood flow.

METHODS

Isolated lung. Details of the experimental preparation have been described previously (13, 20). The left lung of greyhound dogs was removed immediately after death of the anesthetized animal by exsanguination. The pulmonary artery, left main bronchus, and excised left atrium were cannulated and the isolated lung averaging

33 cm in height was suspended vertically in a Lucite box. The time from death of the animal to perfusion of the lung with blood in the experimental circuit varied from 20 to 51 min (average 31 min). The weight of the lung was supported by the bronchial cannula; spring clips attached to the upper and middle lobes prevented their falling over in expiration. The lung was ventilated by negative pressure and perfused with a steady flow of venous blood at 38 C from a mongrel dog (anesthetized with intravenous barbiturate). The blood was returned from the excised lung back to the mongrel dog who was ventilated with a constant volume pump set to maintain its arterial P_{CO_2} at 35–40 mm Hg. The P_{O_2}, P_{CO_2}, and pH of the circuit blood entering and leaving the isolated lung and the arterial blood of the donor dog were measured at intervals throughout the experiment. Five milliliters of blood were withdrawn into glass syringes and analyzed immediately with electrodes (Radiometer).

Blood flow through the isolated lung was controlled by a roller pump. Saline manometers measured the arterial and venous pressures. Arterial pressure readings were corrected for the small pressure drop across the cannula. Blood flow was measured by collecting timed samples in a measuring cylinder. Pulmonary arterial pressure could be varied by adjusting the output of the arterial pump, and venous pressure by varying the height of the venous reservoir.

Inflation of the lung was achieved by adjusting the ventilation pump to increase the negative pressure in the box. The pressure in the box was measured with a water manometer and since alveolar pressure was atmospheric this represented transpulmonary pressure. The collapsed lung was initially inflated with a transpulmonary pressure of 24 cm H_2O. Ventilation was maintained between measurements of blood flow distribution at transpulmonary pressure from 10 to 5 cm H_2O. Occasional deep breaths were given to discourage atelectasis and to assist in the equilibration and washout of radioactive gas.

The distribution of blood flow was measured with radioactive xenon by the method of Ball and others (2) and as previously described for the isolated lung (20). Before each measurement the lung was inflated with a large breath and ventilated with 10–5 cm H_2O transpulmonary pressure three or four times. About 2 mc of xenon 133 dissolved in saline was then injected into the arterial line while the lung was held in inspiration at a transpulmonary pressure of 10 cm H_2O. Because of its low solubility virtually all the xenon 133 passed into the alveoli on its passage through the lung. Arterial, venous, alveolar, and pleural pressures were recorded and flow was measured. The pair of scintillation counters for scanning the lung was initially placed over the lower, well-perfused part of the lung. When a steady count rate was recorded by these counters and usually also by an additional scintillation counter monitoring radioactivity in the venous blood leaving the lung, the flow through the lung was stopped, the lung counters were lowered to the bottom of the lung, and the lung was scanned from the base to apex over a distance of 30 cm. Afterward flow was restored and the lung was allowed to rebreathe for about 3 min from a rubber bag containing 500 ml of air until xenon was evenly distributed through the whole alveolar volume and the lung was scanned again to obtain a volume record. By dividing the ordinates of the first record by the ordinates of the second at 1- or 2-cm intervals up the lung, pulmonary blood flow per unit alveolar volume in arbitrary linear units at each level was obtained and plotted.

Measurements of pulmonary blood flow distribution were made under varying conditions of arterial, venous, and transpulmonary pressures. When the effects of changing lung volume were studied the injection and equilibration scans were always done at the same volume. Changes in lung volume and tidal volume were recorded on a 2-liter spirometer. Hypoxic conditions were induced by deflating the lung to a transpulmonary pressure of 3 cm H_2O and then inflating and rebreathing it from a bag containing pure nitrogen. Blood samples were taken from the pulmonary venous line for blood gas analysis just before the xenon injection usually after 7–15 min nitrogen rebreathing. Typical oxygen tensions were in the range 30–50 mm Hg. Isoproterenol, 5-hydroxytryptamine (serotonin), histamine, and acetylcholine were injected by a constant-infusion pump into the arterial line some distance from the lung so that adequate mixing occurred. Xenon injections were made after pulmonary arterial pressure was constant for 1–2 min (flow being constant) usually after 6–8 min.

At the end of the experiment the lung was weighed and pieces taken from the apex, middle, and lower lobes were put into formol saline. After embedding in paraffin wax, sections 8 μ in thickness were cut and stained with hematoxylin and eosin. At the end of four experiments the pleural surface of the lung was rapidly frozen by inundating the lung with liquid Freon (Arcton 12, Imperial Chemical Industries) cooled to -150 C with liquid nitrogen as previously described from this laboratory (19), and the freeze-dried sections were examined.

Counting conditions. The lung was scanned with a pair of scintillation counters which had multiholed focused collimators 2 inches long. Resolution of the multiholed collimators was such that the 50% response was 0.75 cm from the center of the counting field. Pulse energies below 50 kev were rejected. For injections of 2 mc xenon counting rates of 1,500–2,500 count/sec were available over the lower part of the lung where blood flow was high. The time constant of the counting and recording equipment was 1.0 sec for most experiments, in others it was 0.5 sec. The scanning speed varied between 0.17 and 0.25 cm/sec. This compares favorably with the xenon measurements of Maloney (10) on model lungs where for the most accurate recording the product of time constant and scanning speed should be less than 0.2.

Intact dogs. Greyhounds (22–29 kg in weight) were given a premedication of atropine 0.6 mg and diethylthiambutene (Themalon), a mild hypnotic and analgesic, 1 mg/kg. Anesthesia was induced with a

mixture of 1% chloralose and 5% urethan (8 ml/kg) and maintained regularly throughout the experiment with 1% chloralose (20 ml/hr). A tracheostomy was performed. Under fluoroscopic control a no. 8 cardiac catheter was passed into the left ventricle from the left carotid artery and a no. 9 catheter into the pulmonary artery from the right external jugular vein. Pressures were measured with transducers (Bell & Howell, England) and displayed on an ultraviolet recorder. Standard pressures from two saline-filled bottles at different heights were recorded and calibrations were repeated at intervals throughout the experiment.

The animal was positioned vertically (in a Pavlov stand) or supine (on a table) between a pair of scintillation counters which scanned both lungs together. In the vertical dogs the counters scanned a distance of 30 cm from below the level of the diaphragm to about 8 cm below the sternal notch. Some support was given to the diaphragm by an upper abdominal binder made from 2-inch bandage. In supine dogs the vertical distance of lung in the middle of the thorax available for scanning was on average 20 cm. Reference points for relating pressure measurements to position were the sternal notch in vertical dogs (equivalent to the lung apex on radiographs) and the highest part of the ventral surface of the chest in the horizontal dog. A catheter was inserted into the femoral artery and the pressure measured from a mercury manometer.

A muscle relaxant, gallamine triethiodide (Flaxedil), was injected intravenously in an initial dose of 40 mg and for the rest of the experiment the animal was ventilated from a Starling pump. Intracheal pressure was measured with a water manometer.

For a measurement of regional blood flow about 2 mc of xenon 133 was injected into a 50-cm polyethylene catheter placed in a foreleg vein with its tip beyond the shoulder. The xenon solution was immediately flushed in with saline. Measurements were made at different lung volumes in a manner similar to that used for normal subjects (8). For measurements at functional residual capacity (FRC) an injection was made shortly after the Starling pump was switched off and with the tracheal pressure atmospheric. Three or four seconds after the injection when the count rate recorded by the detectors over the middle of the lung was steady, the lung was inflated to a tracheal pressure of 20–30 cm H_2O with 1,000–1,500 ml of air from a 2-liter syringe to bring the lung volume as close to total lung capacity (TLC) as possible. (Terms such as TLC and FRC are strictly appropriate only for voluntarily achieved volumes, but we have used them for convenience and only after clearly describing how these volumes were achieved.) The counters were then lowered and the lung scanned from base to apex. After the scan about 20–30 large tidal breaths were given with the syringe for 1 min. At the end of this time the radioactive gas was distributed uniformly throughout the lung and a second scan was made after inflating the lung to the same tracheal pressure. In the scan after equilibration the count rate at any level reflected the volume of lung in the counting field, and by relating the first scan to the second, as in the isolated lung experiments, blood flow per unit of alveolar volume was obtained and plotted. Anthonisen and Milic-Emili (1) have pointed out that in man if xenon 133 is injected at volumes less than TLC and regional count rates are measured after inspiration of air to TLC, the resulting regional concentration of xenon is proportional to blood flow per alveolus. An advantage of this technique which has been used in normal subjects (1, 8) is that the distribution of blood flow at different lung volumes can be directly compared with the same lung geometry for all measurements. For measurements at volumes approximate to TLC, xenon was not injected until the lung had been inflated to the high volume from the syringe, and for measurements at low volumes air was withdrawn into the syringe from the resting volume (FRC); 500–700 ml were withdrawn until tracheal pressure was -10 to -15 cm H_2O. Xenon was injected at this volume and the lung was scanned after inflation to a high lung volume. The distribution of blood flow at intermediate lung volumes was studied in a similar fashion.

Fluid loading of the animal was achieved by rapid infusions of a 6% dextran solution in normal saline (average molecular weight 110,000) via a wide-bore catheter in the inferior vena cava. In the first 10 min, 500 ml were generally given followed by a further 1–2 liters at a slower rate. In four animals chest X-rays were taken in the anterior and lateral positions at the beginning and end of the experiment. The animals were sacrificed finally with an overdose of barbiturate or intravenous injection of potassium chloride. After clamping the trachea the chest was opened and the lungs inspected. The positions of the pulmonary artery and left ventricular catheters were confirmed. Sections of the upper, middle, and lower lobes of the left lung were taken for histological examination and processed as described above for the isolated lung.

Counting conditions were essentially the same as for the isolated lung experiments. For injections of 2 mc of xenon 133 a count rate of about 700 count/sec was available over the better perfused parts of the lung. The count rate represented the sum of counts coming from the right and left lungs at any level. The scanning speed was faster than in the isolated lung experiments, averaging 0.7 cm/sec, but the speed was kept slower than this over the dependent parts of the lung.

RESULTS

Isolated Lung Experiments

Thirty-seven separate lung preparations were studied. Lungs were perfused for up to 6 hr but about 4 hr was the usual time. The initial lung weight was 90–190 g and the gain in weight varied from 0 to 225 g with an average of 44 g (30% increase). Five preparations showed a weight gain of 5 g or less.

GAS EXCHANGE. Blood gas measurements were obtained

in 34 lungs. In the venous blood from the donor dog which was used for perfusion of the isolated lung, average values were P_{O_2} 42 mm Hg (range 31–54), P_{CO_2} 48 mm Hg (range 38–60), and pH 7.36 (range 7.21–7.42). It was found that in spite of positive-pressure ventilation the arterial blood lactate concentration in the donor dog rose throughout the experiment, from values less than 1 mEq/liter initially to about 1.75 mEq/liter at the end. In order to determine whether this affected the preparation, the concentration of lactate in the venous blood from the donor dog which was used in perfusion of the isolated lung was increased to 3.25 mEq/liter by a constant infusion of lactic acid. This lowered pH by 0.18 units on average, but did not affect the distribution of pulmonary blood flow or overall vascular resistance. The P_{O_2} of the arterialized blood leaving the lung preparation measured during tidal breathing averaged 110 mm Hg at the beginning of the experiments and 95.6 mm Hg at the end. In only 10 out of 30 lungs was the P_{O_2} of the pulmonary venous blood less than 90 mm Hg at the end of the perfusion. P_{CO_2} tended to be low (average 21 mm Hg).

VASCULAR RESISTANCE AND EDEMA. Changes in vascular resistance during the course of the experiments were not specifically looked for, but in 13 preparations where the measurements were available the average rise in pulmonary artery pressure under conditions of constant flow between the beginning and end of the experiment was 2.7 cm of saline. In these preparations the initial average pulmonary arterial pressure and overall blood flow were 16.5 cm saline referred to the bottom of the lung and 116 ml/min respectively. On only two occasions was foam found in the large airways at the conclusion of the experiment and in only two others was any significant alveolar edema found on histological examination. In order to see whether a possible immunological rejection process was taking place within the isolated lung and affecting its behavior, one of the mongrel donors was treated for 5 days beforehand with 20 mg of alkeran (Melphalan), an immunosuppressive drug. No difference was seen in the distribution of blood flow, overall pulmonary vascular resistance or histological appearances.

Distribution of blood flow in the dependent zone. The distribution of blood flow in similar preparations has been reported previously from this laboratory (20) and its relation to vascular and alveolar pressures characterized. Below the level at which pulmonary arterial pressure equals alveolar pressure, flow increases with distance down the vertical lung because of increasing vascular pressures due to gravity. A new finding in this series of experiments was a reduction in blood flow per unit volume over the most dependent zone at the usual transpulmonary pressure (10 cm H_2O) at which our measurements were being made. This marked reduction in blood flow was seen consistently over the lower 4–6 cm of the lung in 33 out of 37 preparations, irrespective of time of perfusion or whether the lung gained in weight. Because there did not seem to be any obvious explanation for this we set out to study systematically the various factors determining the proportion of blood flow to the dependent zone.

1) TRANSPULMONARY PRESSURE. Figure 1 shows the effect of increasing transpulmonary pressure (TPP) on the distribution of blood flow in the most dependent zone. It can be seen that the reduction of blood flow became less as transpulmonary pressure was raised until it was finally abolished. In all of the 14 preparations where measurements were made at transpulmonary pressures of 10 and 20 cm H_2O the distribution of blood flow changed in this manner. Figure 2 shows the distribution of blood flow at abnormally low transpulmonary pressure (3 cm H_2O) contrasted with that at a higher volume and transpulmonary pressure. Besides a decrease in the proportion of flow to the most dependent zone, a trough representing an area of increased vascular resistance can be seen in the blood flow distribution over the midzone of the lung. By shielding the lower lobe with a lead glove in one preparation this reduction in blood flow was shown to be located in the dependent parts of the middle and upper lobes.

We attempted to determine the relative importance of transpulmonary pressure and lung volume as factors influencing flow through the dependent zone. We exploited the hysteresis in the pressure-volume curve of the isolated lung to make paired measurements of the distribution of blood flow at the same transpulmonary pressure but at different volumes and vice versa. Isopressure and isovolume measurements were made in five lung preparations; differences of volume at the same transpulmonary pressure and difference of transpulmonary pressure at the same volume averaged 220 ml and 5.3 cm H_2O respectively. In 10 paired isovolume

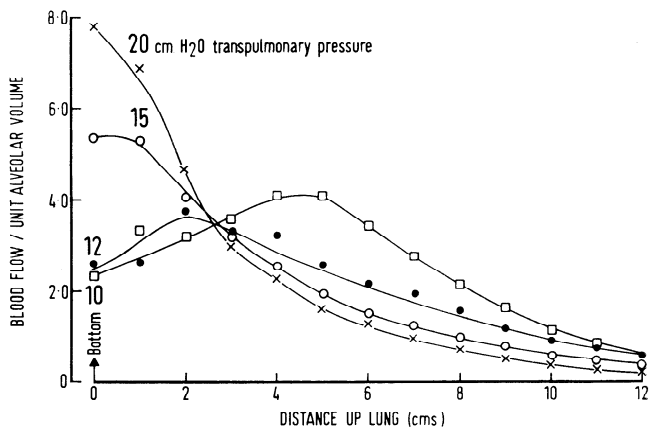

FIG. 1. Distribution of blood flow per unit alveolar volume (in arbitrary units) plotted against distance over the dependent 12 cm in the isolated lung. Four measurements are shown at gradual increments of lung volume represented by transpulmonary pressures (TPP) of 10, 12, 15, and 20 cm H_2O. Pulmonary arterial pressure referred to the bottom of the lung was 17.2 cm of saline at TPP 10 cm, 18 cm at TPP 12 cm, 16.5 cm at TPP 15 cm, and 13 cm at TPP 20 cm. Flow was constant at 120 ml/min; the level of the venous reservoir was below the bottom of the lung on all occasions. Note the reduction of blood flow over the most dependent part of the lung at 10 cm H_2O TPP and its gradual elimination at higher lung volumes.

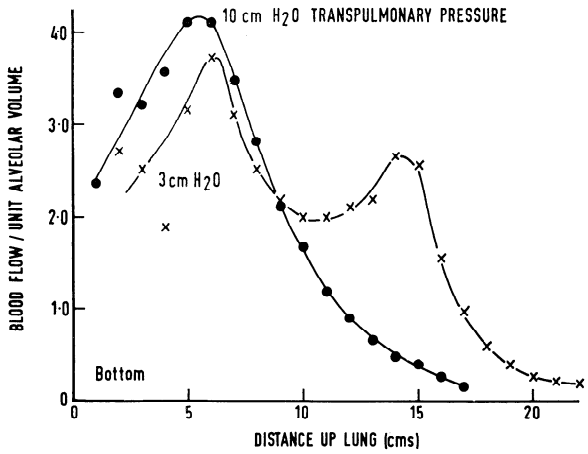

FIG. 2. Distribution of blood flow per unit alveolar volume plotted against distance in the isolated lung at intermediate (TPP 10 cm H_2O) and low (TPP 3 cm H_2O) lung volumes. Total height of the lung was 30 cm. Pulmonary arterial pressure referred to the bottom of the lung was 17.2 cm of saline at TPP 10 cm and 21.8 cm at TPP 3 cm. The level of the venous reservoir was below the bottom of the lung on both occasions and flow was 120 ml/min. At the lower lung volume (TPP 3 cm H_2O) there is a further reduction in the proportion of blood flow to the base compared with that at a TPP of 10 cm H_2O, and an additional reduction in blood flow about half-way up the vertical distance of the lung; this "trough" corresponds in height with the dependent part of the middle and upper lobes.

measurements the point of maximal blood flow moved on average 1.2 cm toward the base of the lung at the higher transpulmonary pressure. In five paired isopressure measurements the point of maximal blood flow moved a similar distance (1.0 cm) toward the lung base at the higher volume. Because we were limited by the pressure-volume hysteresis curve the changes we observed were not large; however, it seemed that lung volume and transpulmonary pressure were of approximately equal importance in altering the vascular resistance of the lower zone.

2) VASOCONSTRICTOR DRUGS. 5-Hydroxytryptamine (serotonin) in doses up to 150 μg/min (usually 75 μg/min) and histamine in doses up to 250 μg/min caused a marked rise in pulmonary vascular resistance. Pulmonary artery pressure rose on average 8 cm of saline under conditions of constant flow (equivalent to 150% increase in vascular resistance at constant pressure). The changes in dependent zone blood flow were similar for both drugs. Figures 3 and 4 show how serotonin selectively reduces lower zone blood flow at high and medium transpulmonary pressures in a fashion similar to a reduction in lung volume. Serotonin was a powerful vasoconstrictor drug in this preparation and its effects were consistent. A reduction in dependent zone blood flow similar to that in Figs. 3 and 4 accompanied by a marked rise in pulmonary vascular resistance was seen on 16 out of 19 occasions in which the drug was used. A trough or double-humped appearance was seen on seven occasions.

3) VASODILATOR DRUGS. Isoproterenol (isoprenaline) in doses up to 30 μg/min caused a moderate reduction of vascular resistance. Under conditions of constant flow pulmonary artery pressure fell on average by 1.9 cm of saline representing a 15% fall in vascular resistance at constant pressure. Six measurements were made in a total of three lung preparations; on three occasions a

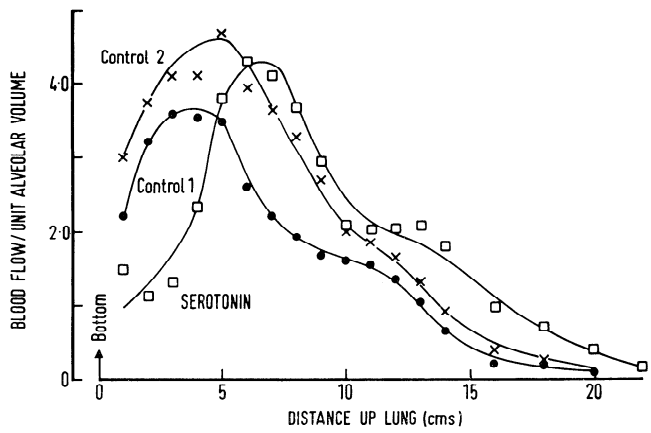

FIG. 3. Distribution of blood flow at an intermediate lung volume (TPP 10 cm H_2O) plotted against distance up the isolated lung to show the effect of a vasoconstrictor drug (serotonin). Serotonin was infused at a rate of 3 ml/min for 6 min in a dosage of 90 μg/min. Pulmonary arterial pressure, referred to the bottom of the lung was 18.2 cm of saline for *control 1*, 24.5 cm during serotonin infusion, and 19.3 cm for *control 2*. The level of the venous reservoir was below the lung; flow was 92 ml/min for *control 1* and 112 ml/min for the other two measurements. Note the further reduction in dependent zone blood flow during the serotonin infusion in spite of the higher intravascular pressure.

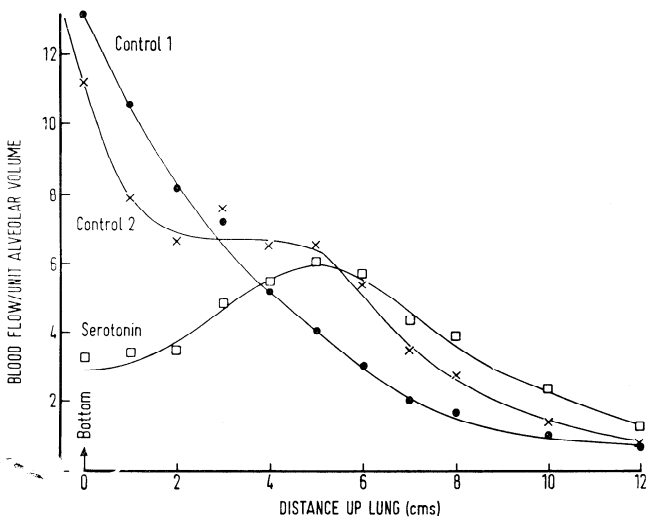

FIG. 4. Distribution of blood flow in an isolated lung plotted against distance over the lower 12 cm of the lung showing the effect of serotonin at a high lung volume. All measurements were made at a TPP of 20 cm H_2O with the level of the venous reservoir below the bottom of the lung. Serotonin was infused at a rate of 2.5 ml/min for 7 min in a dosage of 70 μg/min. Pulmonary arterial pressure referred to the bottom of the lung was 16.0 cm of saline for *control 1*, 22.0 cm of saline during serotonin infusion, and 18.8 cm for *control 2*. Flow varied slightly from 100 to 112 ml/min. Serotonin caused a marked reduction in blood flow to the dependent zone; note that no reduction of blood flow at the base is present in the control measurements because of the high lung volume.

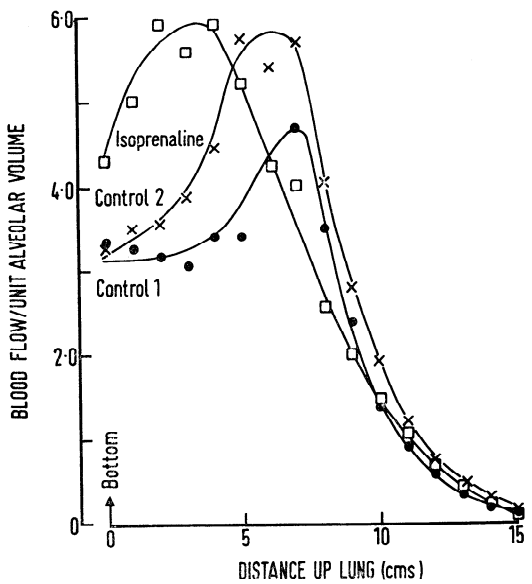

FIG. 5. Distribution of blood flow plotted against distance over the lower half of the vertical isolated lung to show the effect of a vasodilator drug (isoproterenol) on dependent zone blood flow. Isoproterenol was infused at a rate of 15 ml/min for 6 min in a dosage of 9 μg/min. All measurements were made at an intermediate lung volume (TPP 10 cm H_2O) with the venous reservoir level with the bottom of the lung. Pulmonary arterial pressure referred to the bottom of the lung was 14.2 cm of saline for *control 1*, 12.9 cm during isoproterenol infusion, and 14.1 cm for *control 2*. Flow was 116 ml/min for the control measurements and 128 ml/min for isoproterenol. Note that the level of maximum blood flow moves toward the base of the lung after isoproterenol in the opposite direction to that after a vasoconstrictor.

small but definite increase in dependent zone blood flow occurred as illustrated in Fig. 5. Acetylcholine was infused on four occasions in doses up to 1.5 mg/min. On one occasion (when the drug was infused into the lung close to the pulmonary artery) flow to the dependent zone was significantly increased. There were no marked changes in overall vascular resistance.

4) HYPOXIA. Lowering the alveolar oxygen tension so that the P_{O_2} of the pulmonary venous blood leaving the lung fell to below 50 mm Hg caused a rise of pulmonary artery pressure though this was variable in degree (average 3.2 cm saline at constant flow), representing a 20–130% rise in vascular resistance. The effect on the distribution of blood flow was inconsistent and on nine out of 23 occasions there was no change. In eight measurements, compared with the control, the proportion of blood flow to the lower zone decreased and the level of maximal blood flow moved up the lung away from the base, but on six occasions the opposite change was seen. There was no correlation between the distribution of blood flow to the lower zone and the rise in vascular resistance.

5) VASCULAR PRESSURES. In general, changing arterial and venous pressures did not by themselves have any effect on the reduction of blood flow in the dependent zone. Arterial pressure was changed by varying the flow rate while venous and transpulmonary pressures remained constant. In one experiment, for example, arterial pressure was increased by 12 cm saline, from 26 cm saline referred to the bottom of the lung, to 4 cm above the apex, by increasing the flow rate from 110 ml/min to 820 ml/min; the level of the venous reservoir was 22 cm above the bottom of the lung for both measurements. There was no change in the pattern of blood flow but there was an increase in the proportion of flow to the upper zone consistent with the increase of arterial pressure. There were similar findings in two other preparations. The effect of raising venous pressure on dependent zone blood flow was studied at constant flow rates (altering arterial pressure) and at constant arterial pressure (altering flow); sometimes both flow and arterial pressure were changed. The level of the venous reservoir was moved from below the bottom of the lung to 4 cm below the apex. This range of approximately 30 cm overestimates the true change because the large veins near the hilum in this preparation collapse at low levels of venous pressure and are exposed to the negative box pressure (21). Under these circumstances venous pressure equals pleural (box) pressure at the level of the hilum; the operative venous pressure cannot fall below this even if the level of the venous reservoir were lowered below the lung. Therefore, at TPP 10 cm H_2O in this preparation venous pressure equals alveolar pressure 10 cm below the hilum and the effective level of venous pressure, referred to the bottom of the lung, would be about 8 cm saline. To give an example, effective venous pressure (all pressures will be referred to the bottom of the lung) was raised from 1 cm saline (TPP = 20 cm H_2O) to 24 cm saline, arterial pressure increased from 25 to 32 cm saline, and flow remained fairly constant (196 and 212 ml/min). There was no change in the pattern of blood flow but there was an increase in the proportion of flow to the upper zone consistent with the increase of arterial pressure. Similar results were obtained in three other preparations at transpulmonary pressures of 5 and 10 cm H_2O. In two other preparations arterial pressure was kept constant at about 30 cm saline. Effective venous pressure on one occasion (TPP 10 cm H_2O) was increased from 10 cm to 24 cm saline; flow decreased from 800 ml/min to 400 ml/min. There was no effect on the distribution of blood flow either in the dependent zone or over the rest of the lung. Similar results were obtained on other occasions. In none of these experiments was the arterial-venous pressure difference less than 6 cm saline.

In addition, there was one set of conditions, previously described (19), of a low arterial-venous pressure difference with a high pulmonary venous pressure and a low overall blood flow, in which a very marked reduction in dependent zone blood flow occurred. Figure 6 shows how a gradual reduction of arterial-venous pressure difference and flow reduces dependent zone blood flow, initially in the bottom of the lower, middle, and upper lobes, and finally throughout the whole of the lower lobe and the dependent parts of the middle and upper lobes. Similar effects were seen at higher and lower transpulmonary pressures (20 and 5 cm H_2O) except that in

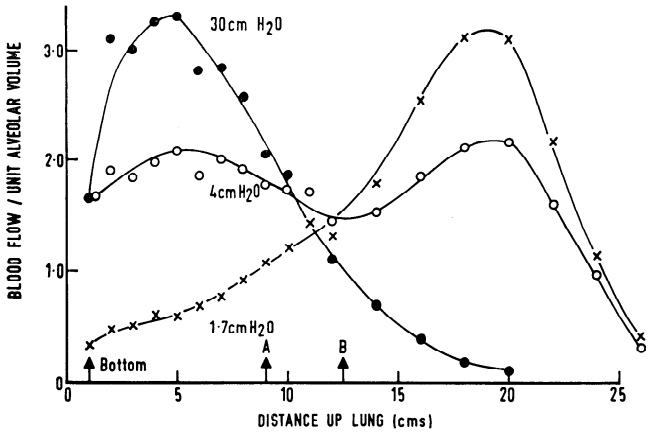

FIG. 6. Distribution of blood flow in an isolated lung plotted against distance up the lung to illustrate the effect of a narrow arterial-venous pressure difference. All measurements were made at TPP 10 cm H_2O. Vascular pressures are referred to the bottom of the lung. In A-V = 30, pulmonary arterial pressure was +22.3 cm and venous pressure was −7.5 cm of saline; flow was 348 ml/min. In A-V = 4, arterial pressure was +32 cm, venous +28 cm, and flow 108 ml/min. In A-V = 1.7, arterial pressure was +29.7, venous +28 cm, and flow 24 ml/min. The height of the lung was 28.5 cm. Note that as A-V difference narrows and flow diminishes there is a progressive reduction in the proportion of blood flow to the dependent parts of each lobe involving finally the whole of the lower lobe.

the former there was no reduction of dependent zone blood flow at all until the arterial-venous pressure difference was reduced to about 7 cm saline.

6) EDEMA. We did not make a systematic study of the effects of edema and in fact handled the preparation in such a way as to minimize its formation. As already mentioned gross edema as judged by the appearance of foam, large gain in weight, and histological alveolar edema was an infrequent occurrence. Nevertheless, as will be seen in the presentation of the histological appearances, at the end of a 4-hr perfusion the perivascular space surrounding the vessels in the dependent part of the lower lobe was usually more distended with fluid compared with the rest of the lung. In spite of this and the fact that the lower lobe often ventilated poorly toward the end of the experiment no dramatic changes in the distribution of blood flow were seen. In four out of 22 preparations where comparable measurements were made at the same transpulmonary pressure at the beginning and end of the experiment there was a definite reduction in the proportion of flow to the dependent zone; a further six preparations showed changes that were less marked. There was no correlation with percentage gain of lung weight or histological appearances.

No-flow point. In the lung, flow ceases at about the level at which alveolar pressure equals arterial pressure. This means that after an injection of xenon 133 into the pulmonary artery no radioactivity will be detected over the lung above that level, once background and scattered radiation have been accounted for. In calculating the no-flow point the width of the detector field, the time constant of the recording apparatus and the scanning speed must also be taken into consideration (10). For the ordinate of Fig. 7 the appropriate corrections have been made and the observed no-flow point is plotted in centimeters above or below the level at which alveolar pressure equals arterial pressure (measured at the arterial cannula). All measurements were made at the same transpulmonary pressure (10 cm H_2O) and with the level of the venous reservoir below the bottom of the lung; flow varied from 100 to 160 ml/min. Volume history was the same in all cases; the lung was given a large inflation to a transpulmonary pressure of 21 cm H_2O and then ventilated for 3–4 breaths from 10 to 5 cm H_2O transpulmonary pressure. The difference in the no-flow point induced by serotonin, hypoxia, and isoprenaline correspond well with the changes in pulmonary artery pressure (under constant flow conditions). At higher flow rates, up to 800 ml/min, the observed no-flow point under control conditions was considerably lower (average of −5.0 cm saline for 10 observations). Corrections were made for the resistance of the arterial cannula so this may represent a pressure drop within the arterial tree. If the lung was inflated from a transpulmonary pressure of 5 cm H_2O to 15–18 cm H_2O, the no-flow point rose an average 2.7 cm above the control value (at 10 cm H_2O) and after deflation from TPP 10 cm to 3 cm H_2O it was 2.0 cm lower than the control, presumably reflecting the influence of surface forces (13).

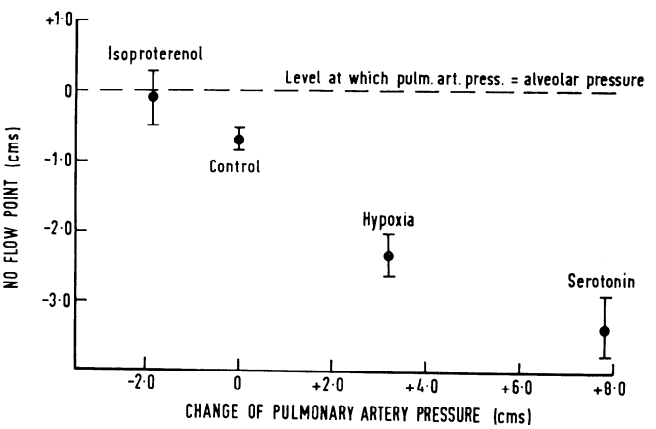

FIG. 7. The vertical level in the lung at which flow stops, referred to the level at which pulmonary arterial pressure is equal to alveolar pressure, is plotted for control measurements of the distribution of blood flow (81 observations), during hypoxia (24 observations), and during infusions of serotonin (13 observations) and isoproterenol (7 observations) against the change in pulmonary artery pressure in centimeters of saline (under conditions of constant flow). Vertical bars indicate one standard error of the mean. All measurements were made at TPP 10 cm H_2O with the same volume history and with the level of the venous reservoir below the bottom of the lung. Flow was within the range 100–160 ml/min. With a vasoconstrictor such as serotonin the level at which flow ceases is 3.25 cm of saline lower than that predicted from the measurement of pulmonary artery pressure, and 2.5 cm lower than the control measurement. Hypoxia causes less vasoconstriction, as judged by the change in pulmonary artery pressure, and less change in the no-flow point. The no-flow point changed in the reverse direction compared with the control measurements after a vasodilator (isoproterenol).

Pressure flow relations. Previous work has shown that below the level at which pulmonary arterial pressure equals alveolar pressure flow increases with distance down the vertical lung in accordance with the relations between pulmonary arterial, alveolar, and venous pressures. Permutt and his colleagues (15) have shown that when pulmonary arterial pressure exceeds alveolar pressure which in turn exceeds venous pressure, the pressure governing flow is the arterial pressure minus alveolar pressure. Under these conditions, called zone 2 (20), the driving pressure increases by approximately 1 cm/cm of distance down the lung because of gravity. In that part of the lung where venous pressure exceeds alveolar pressure (zone 3) flow depends on the arterial-venous pressure difference. Earlier work (20) indicated that flow continued to increase down the lung in zone 3 though at a slower rate than in zone 2.

We compared the rate of increase of blood flow down the vertical lung under zone 2 and zone 3 conditions. The most accurate comparison of these slopes is possible when venous pressure equals alveolar pressure about halfway up the vertical lung so that the lower half of the lung is in zone 3 and the upper half or third in zone 2. Calculations of the slopes in arbitrary units per centimeter were made over 5–10 cm in the lower two-thirds of each zone where the increase of blood flow was most nearly linear. Six comparisons were made at a transpulmonary pressure of 10 cm H_2O and three comparisons at TPP 20 cm H_2O; the results were similar at the two pressures. The mean increase in blood flow in zone 2 was 1.58 ($\pm$.17 SE) units per centimeter of distance and 2.1 ($\pm$0.23 SE) units in zone 3. The difference between the means was not significant. Changes in the slope of increasing blood flow when they did occur were not closely related to the junction between the zones (point at which venous pressure equals alveolar pressure) and tended to remain unchanged after lowering the venous reservoir below the bottom of the lung. In the upper part of zone 2, approaching the no-flow point, the slope was invariably much less, as previous workers have observed (4, 13).

Intact Dog

Eleven dogs were studied in the vertical position and seven dogs in the horizontal supine posture. The average weight of the dogs in both groups was similar (25 kg). Mean pulmonary artery pressure in the vertical dogs averaged 6.5 cm H_2O below the level of the sternal notch (equivalent to the lung apex); in supine dogs it averaged 2.0 cm H_2O above the top point of the ventral surface of the chest. Left ventricular end-diastolic pressure, measured with the catheter in the left ventricle, averaged 26 cm H_2O below the sternal notch in the vertical dogs and 17 cm H_2O below the top of the chest in the supine dogs. Chest X-rays were taken in four of the dogs in the vertical position and the lower border of the left ventricle averaged 24 cm and the main pulmonary artery 15 cm below the sternal notch. The dogs were ventilated from a Starling pump set to maintain an arterial P_{CO_2} of 40 mm Hg. This required a higher tidal volume (550 ml average as against 520 ml) and a higher maximal intratracheal pressure (14.5 cm to 11 cm H_2O) because the level of mean pulmonary artery pressure was lower in the vertical dogs. The arterial P_{O_2} in both groups averaged 80 mm Hg. Cardiac output as determined by the direct Fick method in one of the vertical dogs was 2.73 and 2.65 liters/min. Foam was seen in the trachea at the end of one experiment.

Distribution of blood flow in the dependent zone. 1) EFFECT OF DEXTRAN INFUSION. From 500 to 2,000 ml of 6% dextran was rapidly infused into five of the vertical and five of the supine dogs. Pulmonary artery pressure rose on average 15 cm H_2O in the vertical and 23 cm H_2O in the supine dogs. Left ventricular end-diastolic pressure rose on average 13.5 cm H_2O in both positions. Ventilation was kept constant. In the vertical dogs arterial P_{O_2} increased from 80 to 92 mm Hg and arterial P_{CO_2} decreased from 40 to 36 mm Hg. There were no significant changes of P_{O_2} or P_{CO_2} in the supine animals. Figure 8 shows the reduction in lower zone blood flow in one dog in the vertical position which occurred after a 1,500-ml infusion of dextran. Very similar changes were seen in the other four vertical dogs. The supine dogs showed little alteration in the distribution of flow.

2) EFFECT OF LUNG VOLUME. The effect of lung volume on the distribution of blood flow was studied in all preparations. At functional residual capacity we found that blood flow was usually least at the apex and increased

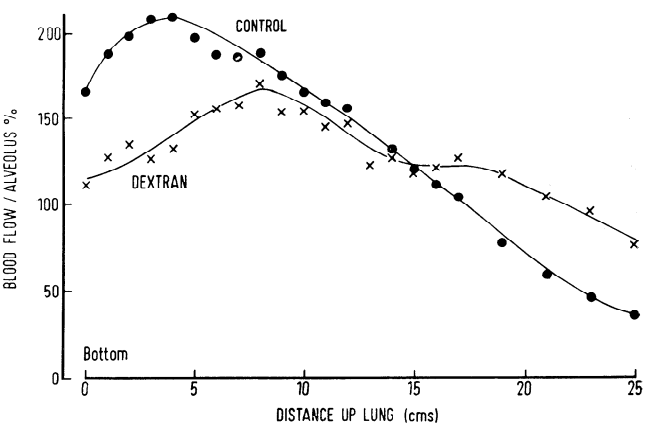

FIG. 8. The distribution of blood flow per alveolus as a percentage of that expected had all alveoli been perfused equally, plotted against distance up the lung in an intact greyhound in the vertical position. In both cases the injection of xenon was made at functional residual capacity and the chest scanned after a 1-liter inflation with air. Allowances were made in the calculations for differences in the amounts of xenon 133 injected. In the control injection pulmonary arterial pressure was 6 cm H_2O and left ventricular end-diastolic pressure (EDP) was 29 cm below the level of the sternal notch. Infused intravenously were 1,900 ml of 6% dextran and the distribution of flow was measured 32 min later; pulmonary arterial pressure had risen by 16 cm and left ventricular EDP by 16.5 cm. There is marked reduction in blood flow to the dependent zone after the dextran infusion with the suggestion of a further reduction of flow in the midzone; there is an increase in flow to the apex of the lung after dextran because of the higher pulmonary arterial pressure.

with vertical distance down the lung, but that a significant area of reduced blood flow was present in the most dependent region. Animals in the supine position showed a similar pattern of blood flow from dorsal to ventral. In the supine position as the lung volume at which the distribution of flow was measured decreased, so the proportion of blood flow to the dependent (i.e. dorsal) zone became less until at a lung volume approaching residual volume (500 ml below FRC) there was more blood flow to the ventral than the dorsal zone. A similar pattern of regional blood flow, including the reversal of the predominant gradient of blood flow with distance down the lung, has been found in normal erect human subjects (8) when the lungs are scanned from bottom to top (base to apex). However, we were not able to show similar changes of blood flow at different lung volumes in greyhound dogs suspended in the vertical position in which it was found that the zone of reduced blood flow at the bottom of the lung shown at FRC in Fig. 8 was little affected by changes in lung volume. In the vertical dog the explanation for the lack of change in dependent zone blood flow with lung volume changes may lie in the preparation itself. Five out of the 11 dogs anesthetized and suspended vertically died during the course of the experiment; this did not occur in the animals in the horizontal position. Another factor is that the abdominal binder possibly was not effective enough to prevent distortions of the thoracic cage.

Histological Appearances

PERIVASCULAR EDEMA. The amount of fluid in the perivascular sheath, as judged by the width of the cuff of fluid surrounding arteries and veins (from 50 to about 1,000 μ diameter) was assessed in two ways. In all lungs, sections from the top of the upper lobe, the middle lobe, and the bottom of the lower lobe were graded by eye 1–5 according to the width of the perivascular cuff in relation to the diameter of the vessel. Grade 1 was the barely detectable perivascular space in the lungs of greyhounds examined soon after death. Grade 5 was characterized by an extensive cuff of fluid around all arteries and veins. In addition, measurements of the width of the perivascular spaces were made in a representative selection of slides. Vessels of approximately spherical or oval shape were selected and their internal diameters measured in two planes at right angles; the width of the perivascular cuff at each end of each diameter was measured and the mean of the two measurements was determined. The width of the perivascular cuff as a percentage of the internal diameter was thus obtained for the vessel in two planes at right angles; the average of the two was taken as the cuff-to-lumen ratio for that vessel. Two to four vessels were examined in each section (a total of 83 vessels) and the results when compared with the grading system showed good agreement in that a difference of two grades out of five on subjective assessment was accompanied by a substantial difference in cuff-lumen ratio.

Intact dog. Figure 9, *A* and *B*, illustrates the accumulation of perivascular fluid in the dependent zones (lower lobes) of the lung after two intact greyhound experiments. The animal from which Fig. 9*B* was taken had been killed after the rapid infusion of 2 liters of 6% dextran solution. The effect on the distribution of blood flow is shown in Fig. 8. Perivascular edema was distributed uniformly throughout the lungs in the vertical dogs. In 12 animals there was no significant difference between the perivascular edema grading for the apex (3.4 ± 0.35 SE) compared with the base (3.25 ± 0.24 SE); the mean ratio of perivascular cuff-to-vessel lumen in four animals was not significantly different (19% for the base and 24% for the apex).

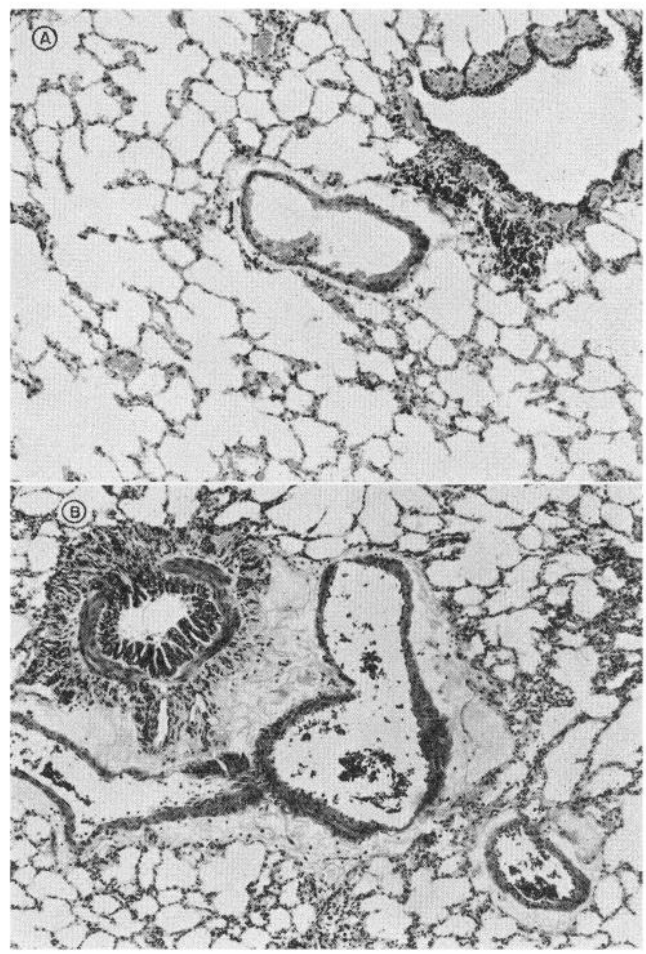

FIG. 9. *A:* photomicrograph of a section from the lower lobe of the lung taken after an experiment with an intact greyhound. A thin cuff of perivascular tissue surrounds the small artery in the center of the picture; the perivascular space is small. Hematoxylin and eosin. × 70. *B:* section from the lower lobe of another dog with intact chest after fluid loading with 1,900 ml of 6% dextran in saline. The section is from the same animal whose distribution of pulmonary blood flow and change of left ventricular diastolic pressure after dextran infusion are shown in Fig. 8. Note the effect of fluid loading in distending the perivascular space surrounding the vessels. Lakes of fluid can be seen in dilated lymphatics. Hematoxylin and eosin. × 70.

Isolated lung. In these vertical lungs perivascular edema was always more marked at the bottom of the lower lobe than at the apex. The mean grading for the base in 37 experiments was 4.0 compared with 2.5 for the apex, and the perivascular cuff-vessel lumen ratio in eight isolated lungs was 56% for the base and 22% for the apex. In 15 preparations the dependent part of the middle lobe had on average more perivascular edema (grade 3.25 ± 0.26 SE) than the upper part of the lower lobe at the same vertical level (grade 2.75 ± 0.3 SE), and in seven lungs the average cuff-lumen ratio was 42% for the middle lobe and 23% for the lower. On one occasion a small amount of Evans blue dye was injected with a fine needle subpleurally at the apex of the lung; 2 hr later the dye was seen scattered over the surface of the middle and lower lobes. This was taken as evidence that there was communication between the interstitium in different parts of the lung through the perivascular space. Regional differences in perivascular edema were not seen in horizontal lungs perfused for 4 hr; the average cuff-to-lumen ratio in two cases was 16% for the apex and 14% for the base.

Alveolar Size

From the freeze-dried sections of the four isolated lung preparations in which the pleural surface had been rapidly frozen, measurements of alveolar size were made in the same manner as previously described from this laboratory (6). A measurement of blood flow was made just prior to freezing and the surfaces selected for freezing included the area of increased vascular resistance in the dependent zone near the bottom of the lung where blood flow was decreasing with distance down the lung, and an area about 10 cm above it. In the four preparations the volume-to-surface ratio, proportional to the radius of the alveoli, was .0165 near the base and .0161 10 cm higher up the lung. These results confirm those of Glazier et al. (6).

DISCUSSION

The decrease in blood flow in the most dependent zone of the vertical isolated lung was a surprising finding because in this region intravascular pressures are highest due to gravity. We believe the explanation lies in the extra-alveolar rather than the alveolar vessels. It is useful to distinguish between two types of vessels in the expanded lung depending on the pressures to which they are exposed. Macklin (9) showed that if the pulmonary arterial and venous systems in an isolated lung were connected to burettes filled with a latex suspension which did not penetrate the smaller vessels, the level in the burettes fell when the lung was inflated. However, the levels rose if continuity between the large and small vessels was established with saline. Similar studies were carried out by Howell and his colleagues (7) with kerosene instead of latex. They showed that the portion of the vascular bed whose volume decreased with inflation of the lung ("compressed compartment") lay in the smaller vessels, which include the pulmonary capillaries, in and around the alveolar septa. These have been called alveolar vessels (11) to distinguish them from the extra-alveolar vessels, whose volume expands with lung inflation. By lowering the level of the vascular reservoirs below the bottom of the lobe to make vascular pressure less than alveolar pressure, they showed that when the lobe was inflated blood was drawn up into the lung from the burettes attached to the artery and veins. Permutt (14) has measured the extent to which the burettes had to be moved down to keep the vascular volumes constant. This is a measure, under isovolume conditions in the vascular compartment, of the negative pressure developed around these vessels as the lung expands. For an inflation to a transpulmonary pressure of 30 cm H_2O he estimated that the interstitial pressure, the pressure in the perivascular space surrounding the extra-alveolar vessels, may be as much as 20 cm H_2O below pleural pressure. The anatomic boundary between alveolar and extra-alveolar vessels has not been defined precisely. Microscopic examination of rapidly frozen lungs (5) showed that in parts of the lung where alveolar pressure exceeded arterial pressure few vessels with diameters less than 30 μ were open. Larger vessels, however, remain patent even when the pressure inside them is considerably less than atmospheric, presumably chiefly due to the low interstitial pressure surrounding them.

The fall in vascular resistance in the dependent zone of the lung as the parenchyma is expanded (Fig. 1) can be explained by a decrease in resistance of the extra-alveolar vessels as a result of the fall in interstitial pressure in the perivascular space surrounding them. The present study suggests that the caliber of the extra-alveolar vessels is determined by a balance of forces. The pressure around the vessels becomes lower as the parenchyma is expanded; as a result the vessels are held open and offer less resistance to flow. At a transpulmonary pressure of 20 cm H_2O we were unable to detect a decrease of blood flow at the bottom of the lung and the increasing flow from apex to base could be explained entirely on the basis of the relations between vascular and alveolar pressures. However, at lower lung volumes and transpulmonary pressures the pull of the parenchyma on the extra-alveolar vessels is less, interstitial pressure rises, and extra-alveolar resistance, as judged by a decrease of flow to the dependent zones (Figs. 1 and 2), increases.

Several factors alter the low interstitial pressure and raise extra-alveolar vascular resistance. Perivascular edema raises interstitial pressure and isolates the vessel wall from the expanding pull of the parenchyma. A rise in interstitial pressure in the intact dog lung as a result of fluid loading (Fig. 9*B*) increased extra-alveolar vascular resistance (Fig. 8). Tension in the walls of the extra-alveolar vessels will also oppose the action of the low interstitial pressure, for example, when vasomotor tone is increased during an infusion of a vasocon-

strictor drug. A marked increase in the resistance of the extra-alveolar vessels occurred with the vasoconstrictor drug, serotonin (Figs. 3 and 4), but the opposite effect was seen with a vasodilator (Fig. 5).

Do the alveolar vessels contribute to the increase in flow to the dependent zone which occurs with inflation of the lung? In a similar isolated lung preparation, Pain and West (13) showed that blood flow rose 4 cm higher up the lung when in its inflation state than in its deflation state at the same volume. They attributed this difference to changes in surface tension which during inflation lowered the pericapillary pressure and held the alveolar vessels open. However, there are several reasons why an increase in surface tension acting on alveolar vessels will not explain the changes of vascular resistance at the bottom of the lung which occur at different lung volumes. First, in measurements of blood flow made at the same transpulmonary pressure but at different volumes, we found less blood flow to the dependent zone on inflation than at the same pressure on deflation. Second, a change in pericapillary pressure of 4 cm H_2O is small when compared with our estimate from Permutt's data of a change in interstitial pressure of 18 cm H_2O with respect to alveolar pressure during inflation from a transpulmonary pressure of 10 cm H_2O. Third, J. B. Glazier from our laboratory (manuscript in preparation) has measured capillary red cell volume from histological sections of rapidly frozen strips of lung and has found that it decreases over a comparable range of capillary pressures as transpulmonary pressure is raised from 10 to 30 cm H_2O.

In the upper part of the lung at the point where flow ceases another effect of extra-alveolar vascular resistance can be seen (Fig. 7). In these measurements we prevented changes in surface forces by maintaining a constant volume history. The measurements made during infusion of the vasodilator, isoproterenol, show that a pressure drop occurs in the arterial extra-alveolar vessels due to tone in the vessel walls. During infusion of a vasoconstrictor, serotonin, the pressure drop from pulmonary artery to capillaries increased by 2.7 cm compared with the control. If the driving pressure for flow through the extra-alveolar vessels on the arterial side, and particularly the muscular arterioles, is inflow pressure minus critical closing pressure as suggested by Permutt and Riley (17), then the change in no-flow point reflects the critical closing pressure of the arterial extra-alveolar vessels. However, if alveolar vessels are able to constrict in response to serotonin or hypoxia, changes in no-flow point may additionally reflect the critical closing pressure of these vessels.

In previous work (20), the effect of extra-alveolar vascular resistance on the distribution of blood flow in this preparation was not seen clearly and the distribution was explained entirely in terms of the pressures acting across the walls of the small vessels exposed to alveolar pressure—namely, zones 1, 2, and 3. It is clear that a rise of resistance in extra-alveolar vessels, if great enough, will dominate over the forces operating around small vessels in zones 2 and 3 and produce a decrease in blood flow, as seen in the most dependent zone. A lesser rise of extra-alveolar vascular resistance may modify (i.e., reduce) the slope of increasing flow with distance down the lung in zones 2 and 3. In contrast to our findings of almost identical slopes in zones 2 and 3, West et al. (20) under similar experimental conditions reported that flow increased with distance down the lung in zone 3 but less rapidly than in zone 2; however, these authors commented in their paper (p. 719), "Because the slope of the line relating blood flow to distance was so steep (. . . fig. 8B) it was often impossible to see a change in slope below the level at which venous pressure equaled alveolar pressure. It was only clearly seen when arterial pressure was only a little higher than the venous pressure . . . ." Our findings are basically similar but we now separate the factors which may affect the slope in zone 3. It is therefore understandable that there are various reports showing the different behavior of blood flow in zone 3. Anthonisen and Milic-Emili (1) reported that flow in man was uniform but their measurements were made at a low lung volume (residual volume). West and Dollery (21) measured in an isolated lung the changes in pulmonary blood flow as Pv was raised above the lung (all the lung in zone 3) keeping Pa-Pv constant. The increase in flow as venous pressure increased agreed fairly well with increases in regional blood flow in zone 3 (20) measured with radioactive gases. On the other hand, Fowler et al. (4) in a similar preparation found that for the same capillary pressures conductance was approximately the same in zone 2 as in zone 3, which is in agreement with our present results. In addition, our measurements of the slopes of zone 2 and zone 3 were made over a range of transpulmonary pressures. At TPP 20 cm H_2O, for instance, we feel that any extra-alveolar vascular resistance which might affect the zone 3 slope must be negligible.

An important effect occurs in zone 3 in the dependent zones when the arterial-venous pressure difference is small as shown in Fig. 6. We believe that under these conditions interstitial pressure (representing the sum of the forces in the interstitial space and in the vessel wall) exceeds downstream pressure. Consequently a Starling resistor mechanism develops around the extra-alveolar vessels and the driving pressure for flow becomes the arterial-interstitial pressure difference rather than the arterial-venous difference. This notion presupposes two things: first, that interstitial pressure rises when vascular pressures are increased. In support of this is the finding that moderate rises of venous and arterial pressure do not overcome the effects of interstitial pressure on dependent zone blood flow. Second, that interstitial pressure is inherently higher in the more dependent zones. We have shown that extra-alveolar vascular resistance is higher in the dependent zone of the vertical isolated lung when moderately inflated to a transpulmonary pressure of 10 cm H_2O. Interstitial pressure also appears to be higher in the de-

pendent parts of the middle and upper lobes giving a double-humped appearance at low lung volumes (Fig. 2) and during serotonin infusions. The reason for this is not clear. Histological measurements at the end of the experiment showed that interstitial edema was more severe in the dependent parts of the lobes of the lung. However, this is not a complete explanation because an increase in extra-alveolar vascular resistance in the most dependent zone was seen in the first measurements of blood flow made after setting up the preparation, and in lungs which had not gained any weight throughout the experiment. Often the perivascular space on histological examination showed no abnormality or else the appearances in the most dependent zone compared with other regions were identical. In addition, there was a relatively poor correlation between edema as judged by increases in lung weight and extra-alveolar vascular resistance.

A second possibility which would result in a local rise in interstitial pressure would be a reduction in lung expansion in the dependent zone, for although the lung was surrounded by a uniform pleural pressure the way it was supported in the box by the bronchial cannula could have resulted in the parenchyma at the base being less well expanded. This notion is not supported by the measurements of alveolar size made in this paper and by Glazier et al. (6) and by measurements of the distribution of ventilation in the isolated lung (22); both methods suggest that the parenchyma is fairly uniformly expanded. Last, the pressure in the interstitial perivascular space may be inherently higher at the bottom of the lung than the top. Injection of Evans blue dye subpleurally suggested that there was communication between different parts of the lung through the interstitium. Since this space contains lymph vessels, a column of lymph or tissue fluid which produces a hydrostatic pressure gradient may exist. To affect the distribution of blood flow a gradient of interstitial pressure which increased at more than 1 cm H_2O/cm distance would be needed to offset the normal vascular pressure gradient.

A previous study (8) showed a reduction of pulmonary blood flow in the dependent zone in normal human subjects at functional residual capacity. At this lung volume the parenchyma at the base of the lung is less well expanded (as a percentage of its expansion at total lung capacity) than that at the apex (12). This reduction in expansion probably accounts for the rise in interstitial pressure.

We should like to thank Dr. J. S. Calnan for assistance with the injections of Evans blue dye, Miss L. Iliff for all the blood gas measurements and Mrs. R. Stevenson, Mr. G. Kingaby, and Mr. D. Woodland for valuable technical help.

This work was supported by the Medical Research Council.

J. B. Glazier: Postdoctoral Research Fellow of the National Heart Institute.

Received for publication 11 March 1968.

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