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EFFECT OF LUNG VOLUME ON THE DISTRIBUTION OF PULMONARY BLOOD FLOW IN MAN[1]

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Abstract. The distribution of pulmonary blood flow was measured over a wide range of lung volumes in nine normal subjects in the seated erect position using radioactive xenon and a lung scanning technique. At functional residual capacity (FRC) blood flow decreased with distance down the lower third of the lung. This area of reduced basal blood flow was much less at higher lung volumes, but at volumes below FRC further reduction of blood flow in the dependent zone was seen. The reduction of pulmonary blood flow in a zone where vascular pressures because of gravity are highest is thought to be due to an increase in interstitial pressure affecting the vessels outside the influence of alveolar pressure. At normal lung volumes interstitial pressure is higher in the dependent zones of the lung in man mainly because of the reduced expansion of the lung parenchyma in these regions.

Extra-alveolar vessels
Interstitial pressure
Lung volume
Pulmonary blood flow
Regional differences in the lung

Measurements of regional pulmonary blood flow in erect man using radioactive gases have shown that flow decreases from the base to low values at the apex (WEST and DOLLERY, 1960; BALL *et al.*, 1962). This distribution of pulmonary blood flow can be explained by the relations between pulmonary arterial, alveolar and venous pressures (PERMUTT, BROMBERGER-BARNEA and BANE, 1962; WEST, DOLLERY and NAIMARK, 1964). At the top of the upright lung no flow occurs if alveolar pressure exceeds pulmonary arterial pressure. Flow begins approximately at the level where pulmonary arterial pressure exceeds alveolar and is determined by this pressure difference down to the height where venous pressure exceeds alveolar; over the remainder of the lung flow is governed by the arterial-venous pressure difference.

Most of the studies with radioactive gases have been made at fairly high lung volumes. Thus the measurements of WEST and DOLLERY (1960) were made at 1 litre above functional residual capacity and those of BALL *et al.* (1962) at the end of a deep breath. An exception was the study of ANTHONISEN and MILIC-EMILI (1966) who

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injected xenon-133 at different lung volumes. Their procedure which will be described more fully later takes account of the differences in regional expansion of the lung and allows blood flow per alveolus at different lung volumes to be directly compared. They reported that the whole lung at residual volume (RV) and the dependent one-third of the lung at functional residual capacity (FRC) had a uniform blood flow. They attributed this to the fact that venous pressure exceeded alveolar pressure in these situations and that the driving pressure for flow—the arterial-venous pressure difference—remained constant with distance down the lung.

In this paper we report the distribution of blood flow over the whole range of lung volumes using essentially the same method and calculations. However, we scanned the lungs with moving counters and we produced evidence of an important and hitherto unrecognized effect of interstitial pressure on lower zone blood flow in normal man.

Methods

SUBJECTS

Nine healthy volunteers were studied, of whom three were female. All subjects were laboratory personnel, familiar with respiratory procedures. None of the group had any respiratory symptoms. Three (L.L., R.S., G.K.) were cigarette smokers. No abnormalities were seen in recent chest X-rays. Thoracic gas volumes were measured at functional residual capacity on a constant volume body plethysmograph; results together with physical characteristics and ages are shown in table 1. Although in one subject (R.S.) the values for FRC/TLC and RV/TLC were higher than normally found in our laboratory, she had a normal chest X-ray and no respiratory symptoms.

PROCEDURE

The distribution of pulmonary blood flow was measured using radioactive xenon after

TABLE 1

Physical characteristics and lung volumes of subjects.

Subject	Sex	Age yrs	Wt. kg	Ht. cm	TLC litres BTPS	FRC/TLC (%)	RV/TLC (%)	Lung length; rib 2 to dome of diaphragm (cm) at TLC
NJ	M	35	100	188	6.75	41	20	19.0
JW	M	38	77	182	6.86	34	17	19.25
LL	F	28	55	164	4.43	38.5	19	16.0
HR	F	21	57	175	5.13	48.5	20	17.25
RE	M	28	68	175	6.94	42.5	20.7	19.75
EO	M	29	73	167	5.60	46.5	11	17.0
RS	F	26	49	168	4.70	72.5	38	16.5
GK	M	23	73	178	6.60	53	15	19.0
SG	M	28	82	178	7.40	54	21.6	18.0
Mean		28.4	70.5	174	6.05	47.9	20.3	17.9

the method of ANTHONISEN and MILIC-EMILI (1966) while subjects were sitting in the upright position. Xenon-133 in doses of 2–3 mc was dissolved in saline and injected through a 40 cm polythene catheter introduced under local anaesthesia into an antecubital vein so that its tip was beyond the shoulder. Xenon-133 was injected to reach the lung at different lung volumes in the following way. At the end of a normal breath the subject was switched into a spirometer containing air and continued to breathe normally. For measurements at functional residual capacity (FRC) his breathing was stopped at the end of the third or fourth tidal breath; for measurements at higher lung volumes he was then told to inspire until he was stopped at the appropriate volume, and for volumes less than FRC he exhaled until he was stopped or until he reached residual volume. Xenon was then injected in less than one second and immediately flushed in via a three-way tap with 3 ml of saline; during and for 5–7 sec after the injection the subject held his breath in a relaxed manner at the chosen lung volume. We have found that the time for injected xenon to reach a stable concentration in the lung as monitored by external counters is from 2–4 sec. During this time, at lung volumes below total lung capacity (TLC) subjects were holding their breath with an open glottis. During an injection at TLC the glottis may have been closed in some subjects but when one subject was asked to raise his intrathoracic pressure deliberately with a Valsalva manoeuvre no change in the distribution of blood flow was found.

Because of the low solubility of xenon most of it passed into the alveoli when it reached the lung. The subject then inspired to total lung capacity and held his breath while both lungs were scanned from base to apex over a distance of 30 cm. The time taken for the counters to scan the lungs was kept constant for any one subject and varied from 20–25 sec over the distance of 30 cm. In one subject duplicate injections were made at the same lung volume but the scanning speed was altered so that 12 sec were taken to scan the lung in one instance and 24 sec in the other; essentially the same regional distribution of blood flow was seen on both occasions. After breath-holding the subject exhaled over 4–6 sec to residual volume while expired xenon concentration at the mouth and expired volume were recorded. Up to four injections were made at different lung volumes and each was preceded by a background scan to ensure complete washout of radioactivity. Finally xenon gas in a concentration of about 1 mc/l was rebreathed for $1\frac{1}{2}$ min from a spirometer in closed circuit. Subjects hyperventilated during the rebreathing period to achieve complete equilibrium between xenon in the spirometer circuit and all parts of the lung. A scan of the lungs was then made during breath-holding at total lung capacity. Evidence for complete mixing came from the washout of radioactivity afterwards which was complete within 20 sec of similar hyperventilation on air, and the inspired and expired xenon concentrations at the mouthpiece which were equal before the scan was made.

COUNTING CONDITIONS

Chest counting rates were recorded from two pairs of scintillation counters ($1\frac{1}{2}$ inch diameter sodium iodide crystals) connected in parallel over the front and back of each lung. Focused collimators were used, six inches in length consisting of two horizontal

tapering slits. The resolution diameter (full width at half height) of a pair of these collimators was better than 2.5 cm in the vertical direction. The response of the counting field was substantially uniform across one lung but did not extend to the other lung. Count rates of the order of 500 counts per second were recorded over the middle of the lung for injections of 2 mc of xenon. Count rates from the front and back counters of a pair were combined in an adding unit and then energies below 50 keV were rejected by biasing. Counts per second over each lung were recorded by ratemeters whose time constant was 0.2 sec. A polythene tube (1.5 cm internal diameter) was attached to the mouth piece; 6 cm from the lips the tube passed through the base of a steel frame in which a scintillation counter was mounted vertically. The crystal ($1\frac{1}{2}$ inches diameter) was 2.5 cm above the tube; the time constant of the ratemeter was 0.2 sec. In this way the inspired and expired xenon concentrations at the mouth were measured. For gas concentrations of 1 mc per litre in the tube, counting rates of about 7500 counts per second were recorded. At the end of each scan following an injection of xenon, expired xenon concentration and expired volume were measured, thus allowing a plot of expired xenon concentration versus volume to be made. For the rebreathing procedure the spirometer circuit was primed with oxygen and contained a scintillation counter to record the xenon concentration, a fan to circulate the gas, and soda lime absorbers. The radioactivity of xenon in the syringe before each injection was measured in an ion chamber. Electrical signals from the spirometer, from the ratemeters from the right and left pairs of chest counters and mouthpiece counter, and from the scanning height marker in cm were displayed on an ultraviolet recorder. The radiation dosage to the lungs from the whole procedure was less than 200 millirads; to the rest of the body it was about 20 millirads (MATTHEWS, FOWLER and TURNER, 1963).

THEORY AND CALCULATIONS

ANTHONISEN and MILIC-EMILI (1966) pointed out that when xenon-133 is injected at volumes less than total lung capacity (TLC) and regional count rates are measured after inspiration of room air to TLC, the resulting regional concentration of xenon is proportional to blood flow per alveolus at the initial volume. The basic assumption is that at TLC all alveoli are approximately the same size; this was deduced by MILIC-EMILI *et al.* (1966) from the shape of the pressure volume curve of the lung and from measurements of pleural pressure at TLC. Confirmation of this has come from our laboratory where GLAZIER *et al.* (1967) have frozen intact dogs in the vertical position and shown that there is no significant difference between the volumes of basal and apical alveoli at high lung volumes, though at FRC the basal alveoli have only one quarter the volume of the apical alveoli.

Regional count rates in the lung scan after rebreathing are related to the alveolar volume at any level; since this scan is made at TLC the alveolar volume is related to the number of alveoli. In addition such factors as lung geometry, chest wall thickness and counter sensitivity are taken into account in this scan. The count rate will be affected by chest wall activity due to the solubility of xenon-133 in blood. This was kept to a minimum by having subjects hyperventilate during the wash-in period to

limit the rebreathing time to $1\frac{1}{2}$ min. An estimate of chest wall activity was made by making each subject hyperventilate with air at the end of the rebreathing period after the lung scan. After 15 sec less than 5 per cent of the scanning count rate recorded over the mid zone remained. This is of the order found by other workers (MATTHEWS and DOLLERY, 1965; MILIC-EMILI *et al.*, 1966).

By dividing regional count rates from the scan after an injection of xenon by the count rate recorded in the scan after rebreathing the fractional concentration of xenon for any lung level can be obtained in arbitrary units. For comparative purposes regional concentrations have been related to the concentration expected had the injected xenon-133 been wholly and evenly distributed to all alveoli in the lung. This ratio, expressed as a percentage, was introduced by BALL *et al.* (1962), and called the perfusion index. For the calculation it is necessary to know the amount of xenon-133 injected, the concentration of xenon-133 in the lung during the scan after rebreathing (equivalent to the spirometer concentration) and the lung volume at which scanning was done.

Regional perfusion per alveolus $\% = (Q/V) \cdot (X/Y) \cdot TLC \cdot 100$ where Q and V are the regional count rates after injection and rebreathing, X is the lung concentration of xenon-133 in mc/l after rebreathing, Y is the injected dose of xenon in mc, and TLC is the lung volume in litres for all scans.

For the study of the pattern of expired xenon, expired counting rate was plotted at each 500 ml of exhaled gas as a percentage of the maximum count rate during the expiration. After maximum count rate had been reached a straight line was drawn through the points and the slope determined.

POSITION

At the end of the procedures mentioned above a radioactive gallium marker was placed on the chest wall at the level of the second rib during a scan at TLC so that counting levels could be related to positions on the chest X-ray. Scanning started a few cm below the bottom of the lung and stopped just short of the apex.

Results

Fig. 1 shows the distribution of blood flow in the lung at high, intermediate and low lung volumes for all subjects. Mean values for blood flow per alveolus are plotted at cm intervals down the lung from the second rib. Above this level results were not sufficiently reproducible because of the small amount of lung tissue and relatively low flow in these areas, and have been discarded. After a maximal inspiration (TLC) blood flow increases down the lung in the expected manner over most of the vertical height; a small area of reduced blood flow is present at the base. At lower lung volumes such as at the end of a normal expiration (FRC) this zone of reduced blood flow becomes more marked; blood flow begins to decrease on the average 6 cm above the dome of the diaphragm or 10 cm above the actual bottom of the lung. Further reduction in the proportion of pulmonary blood flow to the base is seen after a maximal expiration to RV; apical flow now exceeds basal thus almost reversing the distribution at TLC.

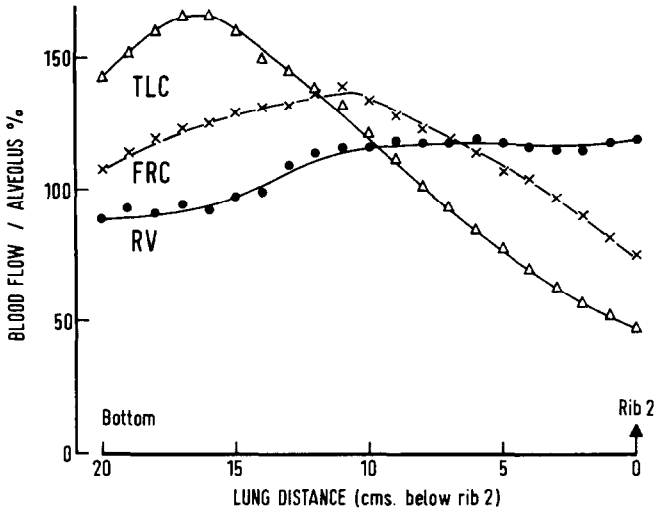

Fig. 1. Blood flow per alveolus as a percentage of that expected had all alveoli been perfused equally, plotted against lung distance at three lung volumes—total lung capacity (TLC), functional residual capacity (FRC) and residual volume (RV). Points represent the mean values of the right and left lungs of all subjects studied at that volume. Note the reduction of basal blood flow which is more marked at lower lung volumes.

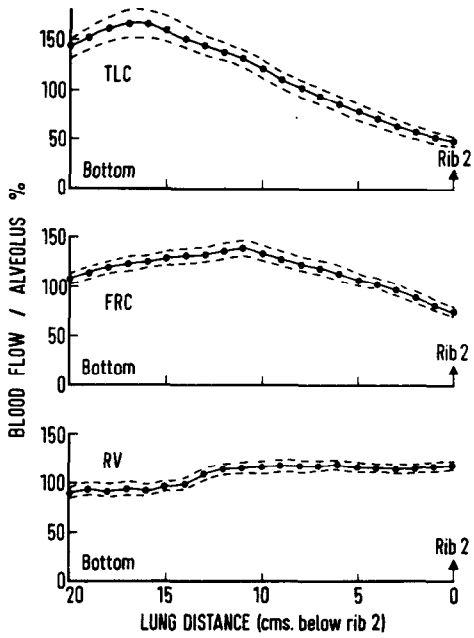

Fig. 2. Blood flow with confidence limits plotted against lung distance as for fig. 1. Results for the same lung volumes as fig. 1 but plotted separately. Interrupted lines indicate one standard error of the mean for each point.

Fig. 2 shows the results for each lung volume plotted individually with their confidence limits. At TLC each point represents the mean of 16 observations comprising measurements from the right and left lungs of 8 subjects. The figures for FRC and RV are the means of 18 observations (9 subjects) and 12 observations (6 subjects) respectively. Regional count rates were calculated at 1 cm intervals below the second rib over a distance of 20 cm and the perfusion index determined; the interrupted lines represent one standard error of the mean for each point. No significant differences were found between the right and left lungs of any one subject. Results were remarkably consistent and, as can be seen, the standard error of the mean is very small. The reduction in blood flow near the bottom of the lung (20 cm below the level of the second rib) was compared with the level of maximum blood flow with a t test to see whether the difference between the mean values was statistically significant. At functional residual capacity when compared with the mean value 11 cm below the second rib, and at residual volume when compared with the level of the second rib itself, the differences were highly significant ($P<0.001$). At total lung capacity, when compared with the mean value 16 cm below the second rib the difference was not statistically significant ($P>0.05$).

It was important to know whether an appreciable volume of lung tissue was in the counting field in the most dependent zone from which measurements were taken. X-rays showed that the level of the dome of the diaphragm was an average of 18 cm

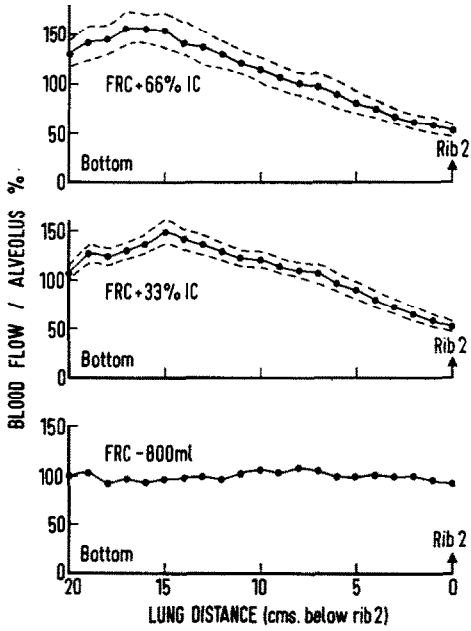

Fig. 3. Blood flow per alveolus plotted against lung distance at three lung volumes—66% and 33% of inspiratory capacity (IC) above FRC and 47% of expiratory reserve volume above residual volume (800 ml below FRC). Mean values shown with one standard error of the mean in the interrupted lines, except at FRC—800 ml where only one subject was studied.

below the second rib while the actual bottom of the lung was 4 cm lower. The base of the left lung was consistently 2 cm below that of the right; consequently the volume of lung seen by the counters was least at the right base. Even so, at the lowest point on the right side from which measurements were made the volume of lung was still substantial, as evidenced by an average count rate for all subjects of 125 counts per second above background count rate in the scan after a xenon injection at functional residual capacity. In the smallest subjects at that level the count rate was 70 counts per second—or about 7 times the background counting rate.

With lungs of different sizes and with different diaphragm levels it could be argued that the bottom of the lung rather than the second rib would be a better reference point from which to compare regional blood flow between two subjects and the two sides in a single subject. As a test of the reliability of the second rib level, mean values for blood flow distribution at functional residual capacity were plotted for the right and left lungs separately, and for male subjects only (omitting the shorter lungs of the female subjects) but no alteration in blood flow distribution was seen. Small differences, however, of up to 17 per cent in blood flow per alveolus between the right and left lungs were seen at total lung capacity over the lowermost 4 cm.

Four subjects were also studied at lung volumes between RV and FRC, and between FRC and TLC. The results with means and one standard error are shown in fig. 3. Three subjects were studied after inspiration from FRC to 66% of their inspiratory capacity (about 2 l in the males and 1 l in the female subject). Four subjects were studied at 33% inspiratory capacity (1.0 or 0.5 l above FRC respectively) and one

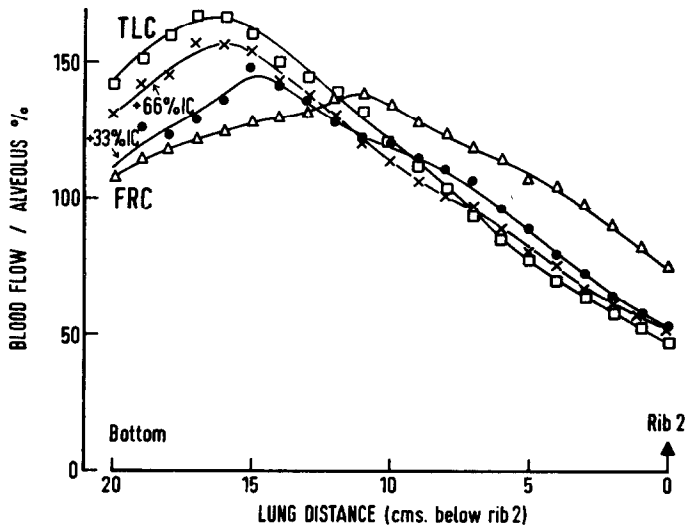

Fig. 4. Blood flow per alveolus plotted against lung distance at lung volumes higher than FRC. Mean values only: note the reduction in blood flow over the lower one-third of the lung at FRC which becomes much less at 33% of inspiratory capacity above FRC. It is still less at 66% of inspiratory capacity, though no further change occurs at TLC.

subject at 47% of his expiratory reserve volume above residual volume (800 ml below FRC).

When all the results are combined a consistent pattern emerges relating changes in distribution of regional blood flow to changes in lung volume. Over the range of low lung volumes, from residual volume (RV) to functional residual capacity (FRC) the pattern of blood flow changes from one where flow is increasing from base to apex (RV), to a uniform distribution (mid-way between RV and FRC) and finally at FRC to a decreasing flow from base to apex over the upper two-thirds of the lung with a large area of reduced basal blood flow. From FRC to total lung capacity (fig. 4) the slope of the decreasing flow from base to apex over the upper parts of the lung increases at higher lung volumes, but of particular interest is the decrease in the extent of the zone of reduced blood flow in the dependent part of the lung as lung volume increases. Most of the effect of an increase in lung volume on the distribution of flow at the base is seen at 33% of inspiratory capacity, and though a further change is seen at 66% of inspiratory capacity, by then the effect of lung volume has reached its maximum.

Valid measurements of the concentration of xenon in expired gas were obtained in three subjects. Maximum count rate was usually reached after expiration of 600–1200 ml but in two expirations only after 2000–2500 ml. In every case the expired alveolar concentration then fell almost linearly as expiration proceeded. The slope of the expired alveolar plateau increased as the lung volume at which the injection was made increased and an example of this in one subject is shown in fig. 5. Mean values for the three subjects for the slope plotted as percentage change of concentration per 500 ml

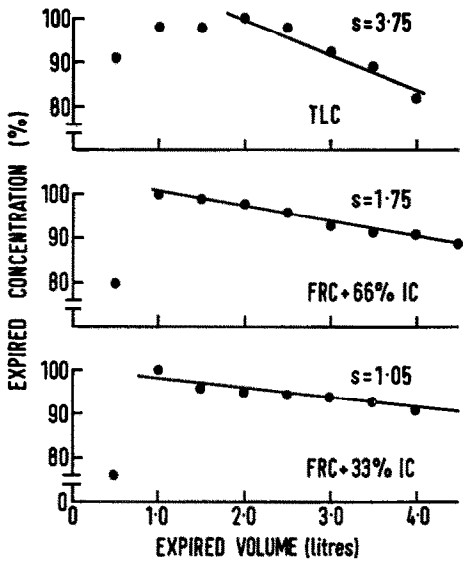

Fig. 5. Example of expired xenon concentration as a percentage of maximum expired count rate plotted against expired volume. The slope (s), representing percentage change of concentration per 500 ml expired volume, increases at higher lung volumes.

expired volume were:

FRC+33% inspiratory capacity	1.54
FRC+66% inspiratory capacity	2.54
TLC	4.85

Discussion

It is of considerable interest that in the dependent zones of the upright lung of normal man, blood flow decreases with distance down the lung while hydrostatic pressure is increasing. It is impossible to explain this pattern of blood flow on the basis of the relations between pulmonary arterial, alveolar and venous pressures. We believe that the added resistance to flow lies in the larger vessels of the lung outside the influence of alveolar pressure.

The concept of these two types of pulmonary vessels, "alveolar" and "extra-alveolar" (MEAD and WHITTENBERGER, 1964), is illustrated in fig. 6 which is a schematic representation of a pulmonary blood vessel. There is good reason to believe that the small pulmonary vessels and capillaries, shown in the centre of the diagram, are exposed to alveolar pressure, represented by the circle. It is known, for instance, that flow does not occur through those parts of the lung where alveolar pressure (modified by surface forces) exceeds arterial pressure (WEST *et al.*, 1964); microscopic examination of rapidly frozen lungs by FOWLER, PAIN and WEST (1966a) showed that under these conditions few vessels with diameters less than 30 microns were open. In view of the relatively small amounts of elastic tissue and the little if any muscle in vessels below 100 microns in diameter, these measurements strongly suggest that vessels up to about 30 microns are directly exposed to alveolar pressure (neglecting the small influence of surface forces).

At either end of the diagram in fig. 6 are illustrated vessels which lie beyond the confines of alveolar pressure. These are called, by definition, extra-alveolar vessels. These vessels, upwards of 100 microns in size, are surrounded by a thin sheath, and within this potential space—the perivascular space—run many of the lymphatics of the lung. The perivascular tissue is an important component of the interstitium of the lung and the pressure within the perivascular space is called the interstitial pressure.

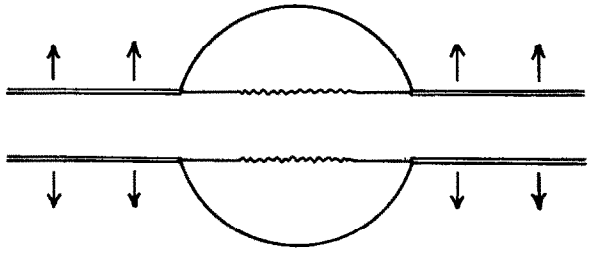

Fig. 6. Schematic representation of the pulmonary circulation to show the forces acting on extra-alveolar vessels. In the centre an alveolar vessel (including a pulmonary capillary) is shown surrounded by alveolar pressure. Beyond the confines of alveolar pressure, extra-alveolar vessels are illustrated surrounded by a thin perivascular space. Arrows indicate the outward pull on these vessels developed by the expansion of the lung.

Under what circumstances will the vascular resistance of these extra-alveolar vessels rise? There is accumulating evidence that the calibre of these vessels is determined by a balance of forces (PERMUTT, 1965). Using latex, MACKLIN (1946) showed that inflation of the lung increased the capacity of the larger pulmonary vessels. HOWELL *et al.* (1961) and PERMUTT (1965) produced evidence that lung inflation increased the capacity of those larger vessels outside the influence of alveolar pressure; they attributed this to the increasing negative pressure generated around them by the expansion of the lung. This pressure which we call interstitial pressure, may be considerably lower than alveolar or pleural pressures; in fig. 6 arrows mark the outward pull on these vessels developed by the expansion of the lung. Recently MEAD, TAKISHIMA and LEITH (1967) have argued that the effective distending pressure on the larger vessels depends on the extent to which these vessels do not follow the expansion of the lung. This implies that these vessels are exposed to expanding pressures considerably greater than transpulmonary pressure. Opposing the expanding action of lung inflation on the extra-alveolar vessels will be the tension in the wall of the vessels, tending to constrict them, or any rise of interstitial pressure either caused by a decrease in lung expansion or an accumulation of fluid in the perivascular space, as in oedema. The resultant of these forces will determine the calibre of these vessels and their vascular resistance.

MILIC-EMILI *et al.* (1966) have shown that at functional residual capacity (FRC) the air units at the base of the normal erect human lung are less well expanded (as a percentage of their expansion at total lung capacity) than those at the apex. In addition, direct measurements of alveolar size in dog lungs frozen in situ (GLAZIER *et al.*, 1967) have shown that alveoli at the apex in the erect position at FRC have a volume up to

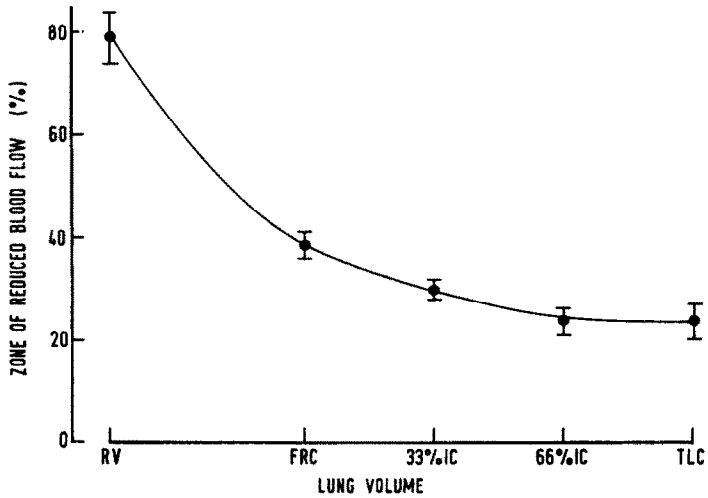

Fig. 7. The zone of reduced blood flow as a percentage of the vertical distance of the whole lung below the level of the second rib is plotted against lung volume. In this zone where blood flow is *decreasing* with distance down the vertical lung, interstitial pressure acting on the extra-alveolar vessels is believed to be affecting blood flow. Note the large increase in the effect of interstitial pressure at lung volumes below FRC.

four times that of alveoli at the base. After full expansion of the lung with 30 cm H_2O inflating pressure alveoli were equal in size throughout the lung.

Our results are consistent with these observations, and show that the contribution of extra-alveolar vessels to vascular resistance is related to the regional expansion of the lung. At residual volume the expansion of the lung parenchyma is so reduced that interstitial pressure affects the distribution of blood flow for most of the lung below the level of the second rib. As the lung expands to FRC interstitial pressure no longer influences the distribution of blood flow over the upper half of the lung, but the relatively poor expansion of the lower zones leaves vascular resistance higher in these areas. With further expansion of the lung to total lung capacity (TLC) the contribution of extra-alveolar vessels to pulmonary vascular resistance is seen over only a relatively small area at the bottom of the lung. Fig. 7 shows the extent of the zone of reduced blood flow as a percentage of lung distance below the second rib for any lung volume. The contribution of extra-alveolar vessels to vascular resistance rises markedly for lung volumes below FRC; at moderate expansion their influence is relatively small. There is comparatively little difference in this respect between FRC and TLC.

An additional reason why the resistance of extra-alveolar vessels may be higher at the bottom of the lung is that there may be a pressure gradient within the continuous perivascular space because of the column of lymph or tissue fluid in it. Evidence that this may occur comes from our work with an isolated lung preparation. We have invariably found a region of reduced blood flow over the lowermost 6 cm even though the lung is surrounded by a constant negative pressure so that all the parenchyma is uniformly expanded. We believe the reduction of blood flow at the base is due to raised interstitial pressure because it is eliminated when measurements of blood flow are made at high lung volumes. Other forces operating on the calibre of the extra-alveolar vessels can also be demonstrated in the isolated lung. Vasoconstrictor drugs such as serotonin increase and vasodilators such as isoprenaline isoproterenol decrease the extent of the zone of reduced blood flow at the base. Thus a higher interstitial pressure in the most dependent zones due to a column of tissue fluid may be an explanation for the surprising finding in the normal subjects of a small area of reduction of blood flow in the most dependent zone with full expansion of the lung. Although at TLC the mean value at the base is not statistically significantly different from that 4 cm higher up the lung, it can be seen that flow stops increasing with distance down the lung. On the other hand differences in blood flow at the right and left base at this lung volume may mean that the diaphragm is contributing in some way to the increase in vascular resistance at the bottom of the lung at TLC.

It is possible that at very low lung volumes, alveolar pressure in the dependent zones rises. At residual volume as a result of airways collapse such a mechanism may be contributing in part to the reduction of blood flow seen in the dependent zone. On the other hand this reduction of blood flow extends from the base up to virtually the level of the second rib, and MILIC-EMILI *et al.* (1966) have shown that in the upper zones at residual volume the airways are patent.

It appears that we must modify the original model (WEST *et al.*, 1964) explaining the

distribution of pulmonary blood flow to include the effects of interstitial pressure on the extra-alveolar vessels. Fig. 8 illustrates the model we propose. In zone 1 alveolar pressure exceeds arterial pressure; the collapsible vessels exposed to alveolar pressure close and no flow occurs. Flow begins in zone 2 because here arterial pressure exceeds

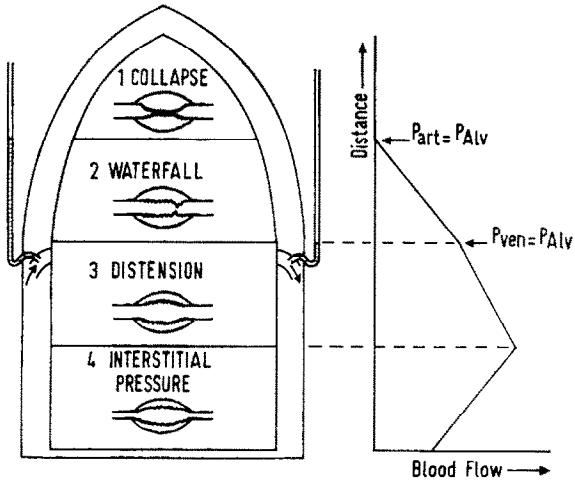

Fig. 8. Diagram to show the resistance vessels in different parts of the lung which are believed to determine the distribution of pulmonary blood flow. At the top of the lung the capillaries are collapsed if alveolar pressure exceeds arterial pressure, and no flow occurs (*zone 1*). In *zone 2*, arterial pressure exceeds alveolar pressure which in turn is greater than venous. Flow in this zone is under so-called waterfall conditions, and is governed by the arterial-alveolar pressure difference. Venous pressure exceeds alveolar pressure in *zone 3* and flow now depends on the arterial-venous difference. Flow increases down this zone because of distension and possibly recruitment of vessels. The results in this paper show that at the bottom of the lung, blood flow decreases with distance towards the base (*zone 4*). We believe the added resistance in this zone is due to interstitial pressure narrowing the calibre of the larger (extra-alveolar) pulmonary vessels.

alveolar; since alveolar pressure exceeds venous the amount of flow is determined by the arterial-alveolar pressure difference. The behaviour in this zone has been compared to that of a waterfall or Starling resistor (PERMUTT *et al.*, 1962). In zone 3 venous pressure exceeds alveolar so that flow is dependent on the arterial-venous pressure difference. Flow increases with distance down this zone due to distensibility and possibly recruitment of new vessels. In the dependent part of the lung we have added a new zone of interstitial pressure, zone 4. Flow is reduced in this zone in spite of higher intravascular pressures because the calibre of the extra-alveolar vessels is narrowed by the increased interstitial pressure, as a consequence of the reduced expansion of the dependent zones. Note that zone 4 cannot be so precisely defined in terms of vascular pressure as the other 3 zones, and it may be that interstitial pressure affects the distribution of blood flow to some extent in zones 2 and 3. In zone 4 the effects of interstitial pressure dominate.

We would predict that since the forces determining the calibre of the extra-alveolar vessels in man are delicately balanced especially in the dependent zones, any rise of

interstitial pressure would have a marked effect on the distribution of pulmonary blood flow and on pulmonary vascular resistance. A reduction in basal blood flow has been described in mitral stenosis (DOLLERY and WEST, 1960) and left ventricular failure (UEDA, IIO and KAIHARA, 1964) and it is likely that, in the early stages at least, this is due to a rise in interstitial pressure. In intact dogs we have found that a rise in interstitial pressure resulting from accumulation of fluid in the perivascular space (after rapid intravenous fluid-loading) reduces the proportion of blood flow to the dependent zones.

A scanning technique such as we have used allows measurements of regional pulmonary blood flow to be made over the greater part of the vertical lung, especially the dependent zones. A difference in technique probably explains the different interpretation of the similar measurements made by ANTHONISEN and MILIC-EMILI (1966). With fixed counters they did not make measurements from the most dependent zones. There is some scatter, however, in the results shown on their graphs and their data is compatible with a reduction of blood flow in the most dependent zones at residual volume and functional residual capacity. It is unlikely that their explanation of uniform blood flow with distance down the lung in terms of zone 3 is correct since FOWLER, WEST and PAIN (1966b) found that the pressure flow relations of the vascular units were such that the slope of increasing flow under zone 3 conditions was almost the same as that in zone 2.

The measurements we have made of the concentration of xenon in expired gas differ from those previously made with nitrogen (FOWLER, 1949) in that the tracer gas (xenon) is injected intravenously and labels only the perfused and probably most peripheral parts of the air units of the lung. The concentration of nitrogen in the latter part of an expiration following an inspirate of oxygen is not flat even in normal subjects but shows a gradual rise; an explanation for this is that different regions of the lung have slightly different nitrogen concentrations and empty at different rates. More recently CUMMING *et al.* (1966) proposed that a concentration gradient within the lung (stratified inhomogeneity) played a part in determining the rise in concentration of nitrogen during expiration. Our finding has been that invariably following an injection of xenon at lung volumes above FRC there was a fall in xenon concentration during most of expiration. These results cannot be explained on the basis of stratified inhomogeneity in alveoli and smaller air units, and are evidence that the pattern of emptying of the lung is dominated by regional factors rather than gaseous diffusion. In support of this, the slope of the decrease in concentration during expiration increased with lung volume, reflecting the increasing difference between apical and basal perfusion at higher lung volumes. During the last 50–70 per cent of a maximum expiration from total lung capacity the less perfused upper zones are apparently contributing an increasing proportion to the expired gas. At the very end of expiration the expired concentration sometimes fell more suddenly, presumably due to lower zone airways collapse, as suggested by DOLLFUSS, MILIC-EMILI and BATES (1967). Our measurements of expired xenon concentration support the conclusion that regional factors play the dominant part in the emptying pattern of the lung.

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