Distribution of Extravascular Fluid Volumes in Isolated Perfused Lungs Measured with $H_2{}^{15}O$

T. JONES, HAZEL A. JONES, C. G. RHODES, P. D. BUCKINGHAM, and J. M. B. HUGHES

From the Medical Research Council Cyclotron Unit and Department of Medicine, Hammersmith Hospital, London, W12 OHS

ABSTRACT The distributions per unit volume of extravascular water (EVLW), blood volume, and blood flow were measured in isolated perfused vertical dog lungs. A steady-state tracer technique was employed using oxygen-15, carbon-11, and nitrogen-13 isotopes and external scintillation counting of the 511-KeV annihilation radiation common to all three radionuclides. EVLW, and blood volume and flow increased from apex to base in all preparations, but the gradient of increasing flow exceeded that for blood and EVLW volumes. The regional distributions of EVLW and blood volume were almost identical. With increasing edema, lower-zone EVLW increased slightly relative to that in the upper zone. There was no change in the distribution of blood volume or flow until gross edema (100% wt gain) occurred when lower zone values were reduced. In four lungs the distribution of EVLW was compared with wet-to-dry ratios from lung biopsies taken immediately afterwards. Whereas the isotopically measured EVLW increased from apex to base, the wet-to-dry weight ratios remained essentially uniform. We concluded that isotopic methods measure only an "exchangeable" water pool whose volume is dependent on regional blood flow and capillary recruitment. Second, the isolated perfused lung can accommodate up to 60% wt gain without much change in the regional distribution of EVLW, volume, or flow.

INTRODUCTION

Large differences in blood flow and pulmonary capillary pressures exist between the top and bottom of the upright lung (1, 2). Variation in the amount of interstitial fluid per unit lung volume between apex and base might occur as a consequence. Hence it would be of interest to measure its distribution, particularly in the case of pulmonary edema in man.

To date, measurements of extravascular lung water (EVLW) [1] in vivo have been limited to determinations for the lungs as a whole (3, 4), although some regional determinations have been made post mortem from lung biopsies (5). Measurements of total EVLW have used the double-indicator dilution technic (6). By using appropriate γ-emitting tracers, detectable by external counting, regional measurements of EVLW could be made in vivo. However, tracer dilution technics are subject to extrapolation errors, and are perfusion-dependent; consequently the EVLW pool tends to be underestimated (7, 8). An additional difficulty in using the indicator dilution techniques for a lung region is the need to determine the absolute blood flow through that zone.

This paper presents a steady-state technique for obtaining the distribution of EVLW in the intact, isolated, perfused lung. The method rests on subtracting the steady-state distribution of blood volume, by using ^{11}CO-labeled red cells, from that for water by using $H_2{}^{15}O$ (9). The advantage of an equilibrium technique is that more time is available for the tracer to mix with the total exchangeable water pool; data analysis is simpler and less subjective than transit-time determination by extrapolation. Furthermore, by using an additional isotope, nitrogen-13, the distribution of regional blood flow can be obtained by arterial injection of $^{13}N_2$ in solution, and regional alveolar gas volume by rebreathing the lung with $^{13}N_2$ gas. Thus, with these isotopic procedures it is possible to compare the distribution of EVLW directly with that of regional blood flow, blood volume, and alveolar

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[1] *Abbreviations used in this paper:* EVLW, extravascular lung water; PBV, pulmonary blood volume; PVR, pulmonary vascular resistance.

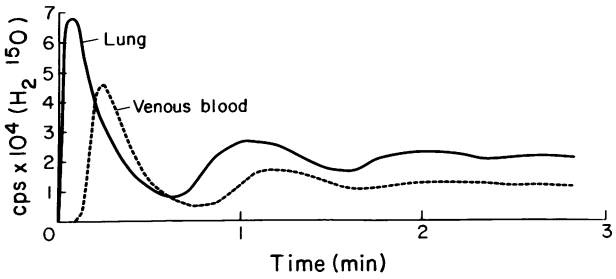

FIGURE 1 Time-activity curve recorded from mid-zone of isolated, perfused lung and venous effluent after pulmonary artery injection of $H_2{}^{15}O$. Note steady count rates, indicating equilibration is achieved 2–3 min after injection.

gas volume. The steady-state technique has been examined in the isolated, perfused lung with different degrees of weight gain. In some instances the distribution of EVLW has been compared with the direct measurement of regional wet-to-dry weight ratios from lung biopsies.

METHODS

Greyhound dogs were anesthetized with intravenous thiopetone (25 mg/kg) and given heparin (20,000 U). The left lung was excised immediately after death by exsanguination. After cannulation of the left main pulmonary artery, bronchus, and left atrium, the lung was weighed and suspended vertically in a Lucite box with its weight supported by the bronchial cannula. The preparations were 30–35 cm in height with the hilum 17–20 cm above the lung base. An isolated lung perfusion circuit (without donor dogs), similar to that described by West et al. (1), was used. The lung was perfused with autologous whole blood (at 34–48°C) at steady flow of 450–1,050 ml/min in closed circuit. Pulmonary arterial and venous pressures were measured with saline manometers, and blood flow by collecting timed samples in a graduated cylinder. The lung was expanded with air or oxygen to which 7% CO_2 had been added by lowering the pressure in the Lucite box, and ventilated with -10 to -5-cm H_2O box pressure changes. Before each isotope, scan the lung was expanded fully by lowering box pressure to -24 cm H_2O for 20 s before returning to and being held at -10 cm H_2O for the measurement.

Lung total water distribution was measured by introducing oxygen-labeled water ($H_2{}^{15}O$) (10), usually as a bolus, into the perfusion circuit. Radioactivity within the lung was monitored by two scintillation detectors on either side of the lung connected in parallel to an analyzer and data logger. The detectors had 1½-inch sodium iodide crystals and focused slit collimators with 3-inch lead shielding (11). Activity in the perfusion circuit was monitored by a similar scintillation detector over the pulmonary venous line. The time-course for $H_2{}^{15}O$ equilibration between the lung and venous blood is shown in Fig. 1. This illustrates time-activity curves over the lung mid-zone and pulmonary venous line after a bolus injection of 40 mCi of $H_2{}^{15}O$. A period of 4 min was allowed for equilibration; the counters were then lowered and the lung scanned from bottom to top at a rate of 0.5–1 cm/s, the total scanning time being between 1 and 2 min.

The distribution of water in the lung was then obtained by dividing the regional lung count rates by the corresponding count rates recorded simultaneously over the venous blood line. This processing corrects for the decay of the isotope during the scan and any slow changes in concentration of tracer in the perfusion circuit. The validity of this method rests on the assumption that at any time during the scan, the concentration of $H_2{}^{15}O$ in the lung tissue equals that of the venous blood. After decay of the oxygen-15 ($t_{\frac{1}{2}}$, 2.1 min), the distribution of blood volume in the lung was similarly measured, by scanning the lung after equilibration with 5–10 ml of the dog's blood labeled with carbon-11 monoxide (10). Both oxygen-15 and carbon-11 emit 511-KeV annihilation γ rays from the positron emission common to both radionuclides. By using the same γ ray energy for detection of lung and blood activities, the water and blood pools were measured with equal geometrical efficiency. The suitability of ^{11}CO as a red cell marker for this procedure was assessed by determining the rate of evolution of ^{11}CO from the blood. The blood concentration was found to fall at a rate of approximately 10%/h. This corresponds closely to the data obtained by Glass et al. (12). Since the total duration of the regional blood volume measurement was on average 7 min, the loss of ^{11}CO into the alveoli and lung tissue was neglected in the calculations.

The distribution of blood flow in the lung was obtained by injecting a saline solution of nitrogen-13 of about 1 mCi into the pulmonary artery during breath holding; because of its low solubility, more than 95% of the injected label is evolved into the alveolar gas. As expected, the venous blood counts downstream from the alveoli were close to background levels after injections of ^{13}N solutions. A more accurate measure of the solubility of ^{13}N in the lung has been obtained in our laboratory by measuring the effective pulmonary arterial venous shunt for ^{13}N. In the anesthetized, supine, intact dog, values of about 4% were obtained (unpublished observations). Since this figure includes shunts through non-gas-exchanging vessels, the fractional uptake of ^{13}N by the blood from the alveoli will be somewhat less. Finally, regional alveolar gas volumes were measured by rebreathing the lung from a bag for 3–5 min to which 2–4 mCi of ^{13}N gas had been added; several large inflations were given to promote gas mixing and equilibration in all regions. Nitrogen-13, like ^{15}O and ^{11}C, also decays with positron emission, giving rise to the same 511-KeV γ ray. Thus, the ^{13}N perfusion and lung volume scans can be directly related to those of water ($H_2{}^{15}O$) and blood volume (^{11}CO-red cells), by the common detection geometrical efficiency.

Before the end of the experiment, 2–5 ml of red cells labeled with about 200 μCi of chromium-51 (13) were added to the perfusion circuit. The lung was removed from the circuit and weighed after blood had drained from the large vessels. In some cases, 1–3-g samples were taken of the peripheral lung tissues from 10 sites equally distributed from apex to base. The water content of the samples was determined by drying them at 80°C to a constant weight and correcting for "trapped blood". The trapped blood volume of the samples was determined from their ^{51}Cr activity, compared with that in a weighed blood sample taken from the perfusion circuit. After the final weighing, the dried biopsy samples were dissolved in 30% sodium hydroxide solution, so that ^{51}Cr activity in the biopsy and blood samples could be measured with equal geometrical efficiency in a well counter. The contribution by blood to the wet and dry weight of the lung biopsies was determined from the wet-to-dry weight ratio of the blood sample and the total blood con-

TABLE I

Initial Weight, Weight Gain, Pulmonary Artery (Pap) and Venous (Pv) Pressures, and Blood Flow ($\dot{Q}$)

Lung no.	Wt	Wt gain	Pap	Pv*	$\dot{Q}$	Pap/$\dot{Q}$
	g	*%*	*cm H_2O*	*cm H_2O*	*min^{-1}*	
1	134‡	8	37	+5	0.87	43
2	165	28	35	+2	0.81	43
3	150	30	32	−6	1.05	30
4	158‡	46	34	+2	0.61	56
5	92	52	40	−5	0.58	69
6	119	58	36	0	0.54	67
7	151	103	64	−2	0.47	136
Mean	139	46	40	−0.6	0.70	57

* Pressures measured relative to bottom of lung.

‡ Estimated from body weight (SD ±15 g). Lung weight (g) = bodyweight (kg)·6.1 − 32.1 (r = 0.81).

tent of the lung biopsy. For this correction the hematocrit in the lung was assumed to be the same as that of the peripheral blood. Lung samples were also examined histologically after staining with hemotoxylin and eosin.

RESULTS

Seven lungs were studied in the vertical position. The period over which measurements were made varied between 43 and 85 min (average 68 min). Vascular pressures, blood flow, and weight gain of the preparations are shown in Table I. In two preparations the initial weight was estimated from body weight, from our own data for dogs of the same species. Iliff (14) found in excised dog lungs that a weight gain exceeding 35% of the lung weight at excision was required before significant alveolar edema could be identified. On this criterion, lungs 1–3 were relatively normal and lungs 4–7 edematous. This was confirmed on microscopic examination. Airway foam was seen in the main bronchi in lungs 5–7, but the distribution of gas volume (measured with ^{13}N) showed little change from that in less edematous lungs.

As regards pulmonary vascular resistance (PVR) and flow, West et al. (1), from whom this preparation was derived, found the PVR, calculated according to the formula of Daly (15), was 7.0 mm Hg liters^{-1} min m^{-2} with the lung on its side. This is just within the normal range (1.7–7.5) for resting dogs (15). Comparison of the vertical lung with a low venous pressure with a horizontal dog is hardly justified, but if the pulmonary artery pressure in Table I is referred to the level of the hilum rather than the base of the lung, the PVR of the lungs 1–3 averages 6.5 and that of 4–7, which were more edematous, 12 mm Hg^{-1} min m^{-2}. Thus, the vascular resistance of this preparation was at the upper limit of normal, becoming elevated as edema accumulated. Flow rates for the whole lung were nevertheless rather low compared with conscious animals, about 0.10 ml g^{-1} s^{-1} in lungs 1–3

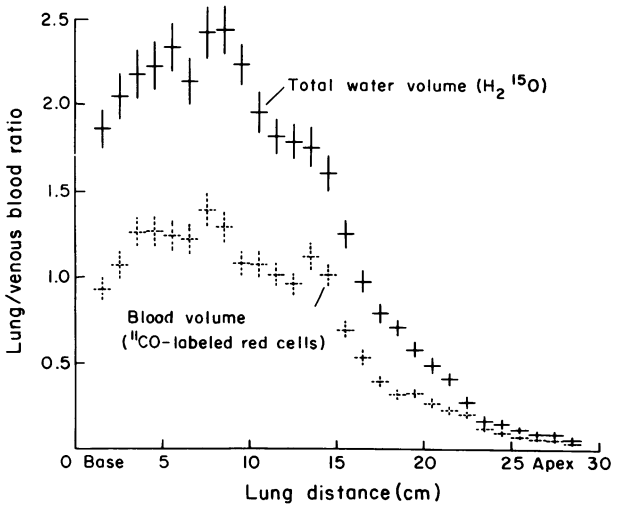

FIGURE 2 Steady-state distribution of water ($H_2{}^{15}O$) and PVB (^{11}CO-labeled red cells) in one vertical isolated lung. Vertical bars are SE of the lung-to-venous blood count rate ratio, horizontal lines indicate distance over which lung counts are accumulated.

and 0.07 ml g^{-1} s^{-1} for lungs 4–7, compared with 0.30 ml g^{-1} s^{-1} found by Goresky et al. (8). In addition the preparations differ from intact lungs in showing an inevitable increase in weight with time, and having no bronchial arterial or lymphatic flow.

To illustrate the data and analysis, the distribution of total exchangeable water ($H_2{}^{15}O$) and blood volume (^{11}CO) in lung 3 is shown in Fig. 2. These volume distributions have been obtained by dividing the count rates for the individual points on the scans by the corresponding count rates of the simultaneously measured venous blood activity, and by assuming this has equilibrated with the lung tissues (Fig. 1). This data processing provides indices of the regional volumes of exchangeable water

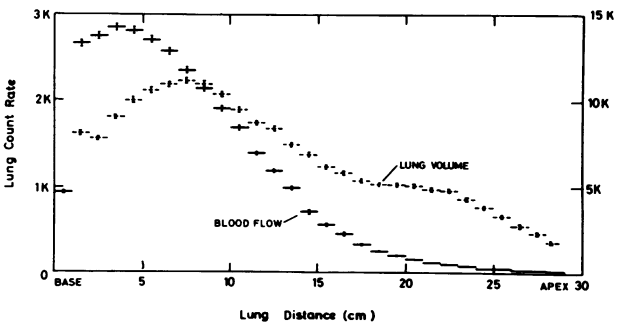

FIGURE 3 Distribution of lung blood flow (after injection of $^{13}N_2$ solution) and lung gas volume (after equilibration with $^{13}N_2$ gas) in one vertical isolated lung. The count rate on the left ordinate refers to the blood flow distribution and the right to lung volume.

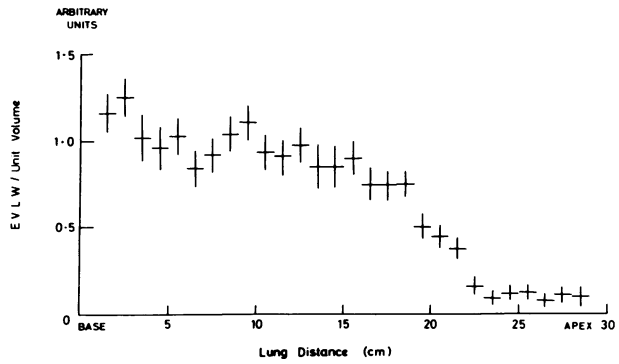

FIGURE 4 EVLW per unit volume plotted against distance for one vertical isolated lung. Bars as in Fig. 2.

and blood. Fig. 3 shows the distribution of (*a*) pulmonary gas volume after rebreathing ^{13}N gas and (*b*) pulmonary blood flow after injection of ^{13}N solution into the pulmonary artery. Note the effect of gravity on the distribution of perfusion, as previously shown (1), with a low blood flow at the apex that increases with distance down the lung.

EVLW distribution was obtained from Fig. 2 by subtracting the blood volume scan from the total water scan. This procedure for extracting EVLW is valid because the units of the indices of the lung water and blood volume are identical, since both these spaces are determined with equal geometrical efficiency. The ^{11}CO red cell distribution establishes the relationship between the venous counter and the activity contained within the lung's vasculature, if the labeled red cells are as uniformly mixed within the blood in the lungs as in the venous line. This procedure also assumes that the hematocrit is the same in the venous blood as that in the lung. This is reasonable since the pulmonary capillary blood volume (16), where the hematocrit will be slightly different, represents only 25–30% of the total pulmonary blood volume (PBV) (17, 18). If the absolute sensitivities of the lung and venous blood counters are known, the indices of water and blood volume can be converted into absolute volumes. It is difficult to determine the correct detector sensitivities and hence the distribution of EVLW and PBV was measured in relative terms. The distribution of EVLW after subtraction of the vascular volume was divided by the regional pulmonary gas volume. Thus regional EVLW per unit lung volume in arbitrary units was obtained as shown in Fig. 4. Note the low value of exchangeable EVLW at the lung apex. The blood volume and blood flow distribution were similarly expressed per unit of gas volume.

For normalization, we divided each lung distribution into three zones of equal height. The EVLW, PBV, blood flow, and gas volume for each zone were expressed as a fraction of the corresponding total distribution. The zone fractions were then divided by the corresponding fractional gas volume content. Thus EVLW, PBV, and blood flow data were normalized per unit volume so that all distributions could be related to each other. The mean results of this analysis for the seven vertical preparations are shown in Fig. 5.

The increase of EVLW, blood volume, and flow from apex to base is very similar except over the lower half of the lung, where the gradient of increasing flow exceeds that for blood and EVLW volumes. Without the gas volume scan, the activities for the upper, mid, and lower zones for the EVLW and blood volume measurements were expressed as a percentage of the total lung activity and plotted against each other as in Fig. 6. The relationship between extravascular and blood volume in any zone fell close to the line of identity.

Since we were studying preparations with varying degrees of edema (Table I), we have related the distribution in individual experiments to the percentage of weight gain. This is not a strictly accurate measurement of edema formation, since no estimation was made of trapped blood initially. Fig. 7 plots the values for the distribution of EVLW per unit volume. Between 30 and 60% weight gain, the EVLW in the lower zone tends to

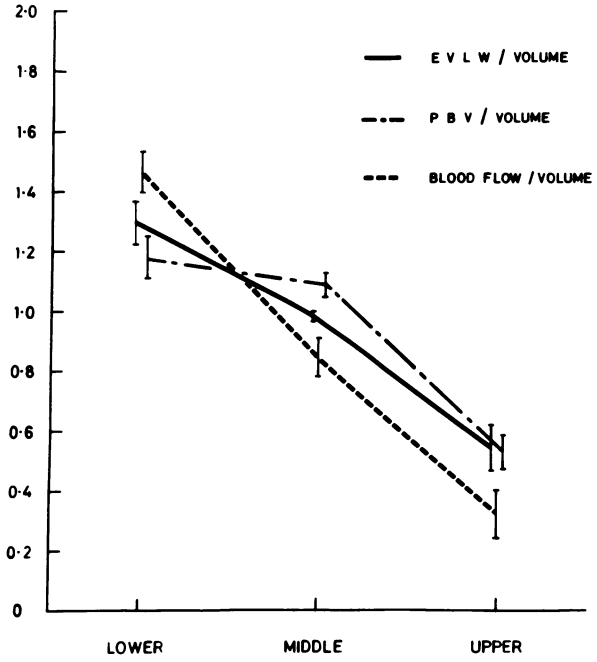

FIGURE 5 The average distribution of EVLW, PBV, and blood flow per unit volume in seven vertical isolated lungs. Each lung was divided into three zones (upper, middle, and lower) and the values in each zone expressed as percentage of the total. The lung volume scan was treated similarly and used for normalization. The bars are the standard errors of the means.

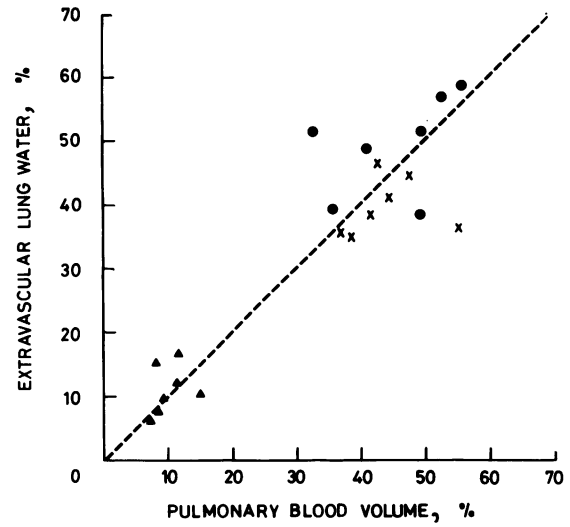

FIGURE 6 EVLW as percent of total for upper (▲), middle (×), and lower (●) zones plotted against PBV as a percentage of the total, in seven vertical isolated lungs. Interrupted line gives line of identity.

increase relative to that in the upper zone, leaving the mid-zone unchanged. (The distribution of ventilated pulmonary gas volume after equilibration with ^{13}N gas was similar in all preparations and independent of weight gain). Fig. 8 plots the distribution of blood volume against percent weight gain. There is no change in distribution except for the lung with 100% weight gain with gross edema, where mid-zone blood volume exceeds that in the lower zone. There was also change in the distribution of pulmonary blood flow, as shown in Fig. 9, except in the most edematous preparation where blood flow distribution was significantly more uniform. In Fig. 10 the distributions of the EVLW in lungs 2 and 5 are compared with wet-to-dry ratios from lung biopsies taken immediately afterwards. It is clear that the exchangeable water pool (EVLW) differs from the direct determination of lung water, especially at the apex of the lungs where blood flow was low. A similar uniform distribution of wet-to-dry weight ratios was also noted in the two other lungs, 1 and 3, in which it was measured.

DISCUSSION

Use of external counting. For measuring pulmonary edema in man, short-lived γ-emitting tracers detectable by external counting offer several advantages. They are noninvasive and can be repeated as the clinical situation demands. In additions, these radioisotopes offer the only practical method of measuring EVLW in different regions of the lung. Nevertheless, indicator-dilution measurements of volume are subject to several constraints, the most important of which are adequate mixing and representative sampling. Previous measurements of total EVLW with tracer techniques have shown that the use of mean transit time to measure volume underestimates the actual water pool (7, 8). This is attributed to areas of poor or absent blood flow, resulting in inadequate equilibration of the tracer within these regions. Another defect of the transit time method is that undue weight is given to regions of high flow in the extrapolation of the arterial curve. Thus, the low-flow regions in the tail of the curve are unresolved. By adopting the steady-state technique (Fig. 1), we hoped to overcome some of these problems. The analysis is attractively simple, but in practice certain problems remain. In vivo, the contribution of the chest wall will have to be taken into account. Secondly, comparison of the distribution of EVLW with wet-to-dry weight ratios (Fig. 10) indicates that complete mixing had not been achieved and that exchangeable rather than total EVLW is being measured. Thirdly, successive but not simultaneous measurements of lung water, blood volume, gas volume, and blood flow can be carried out, since the tracers involved all emit the same γ ray energy.

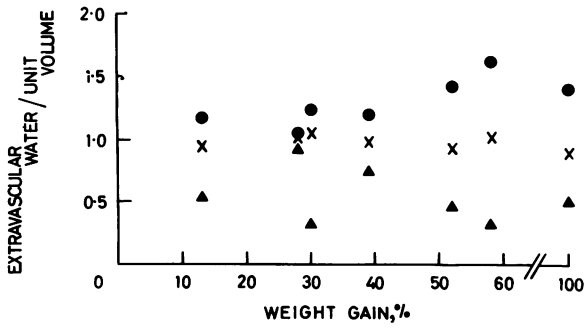

FIGURE 7 EVLW per unit volume for upper (▲), middle (×), and lower (●) zones, plotted against percentage of weight gain in seven vertical isolated lungs.

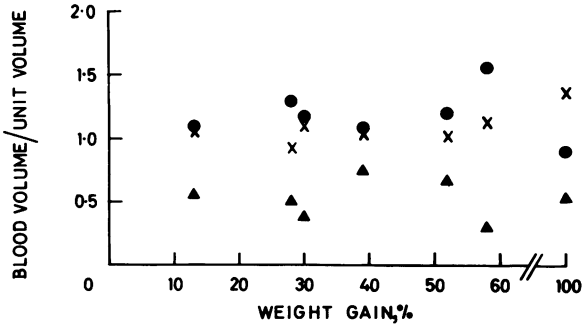

FIGURE 8 PBV for upper (▲), middle (×), and lower (●) zones plotted against percentage weight gain in seven vertical isolated lungs.

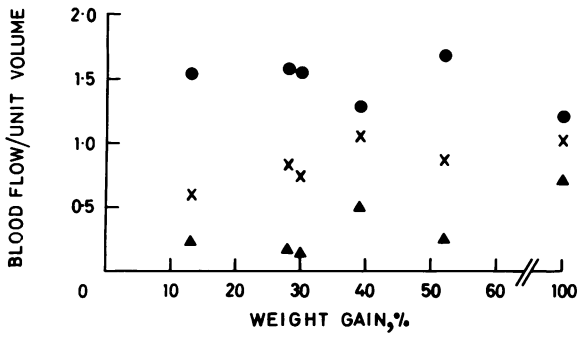

FIGURE 9 Blood flow for upper (▲), middle (×), and lower (●) zones plotted against percentage weight gain in seven vertical isolated lungs.

Dependence of EVLW on perfusion and capillary recruitment. Fig. 5 suggests that the ability to measure EVLW with a tracer method depends upon regional pulmonary blood flow, which in turn is related to the level of pulmonary arterial pressure. For the whole lung Permutt et al. (19) found that increases of pulmonary arterial pressure at constant venous pressure were accompanied by increases in PBV and in carbon monoxide diffusing capacity (D_{LCO}); the increase in D_{LCO} was independent of the level of left atrial pressure, suggesting that most of the increase in blood volume was caused by recruitment of the capillary bed by the higher levels of upstream pressure.

In a dog lung preparation identical to ours, Glazier et al. (20) made direct histologic measurements of capillary dimensions and blood volume at different levels. With the venous pressure low (zone II conditions) capillary blood volume per unit length of alveolar septum increased by about 7%/cm of distance down the lung. The increase in capillary filling was caused equally by recruitment of new vessels and capillary distension. Our regional measurements of EVLW and blood volume are consistent with this interpretation because increasing recruitment of capillaries in the dependent zones, where arterial pressures were highest, would have promoted better mixing and equilibration of the tracer with the total water pool.

There is also a suggestion in Fig. 5 that the measurement of regional EVLW is less perfusion-dependent over the lower half of the lung at high values of relative blood flow. This finding is similar to that of Goresky et al. (4), who measured total EVLW in dogs at different levels of cardiac output. Presumably at high flows or pressures, maximal recruitment has been achieved. The majority of capillary recruitment in zone II conditions in vertical perfused lungs occurs in the first 10 cm of distance below the no-flow point (21), as suggested in Fig. 10.

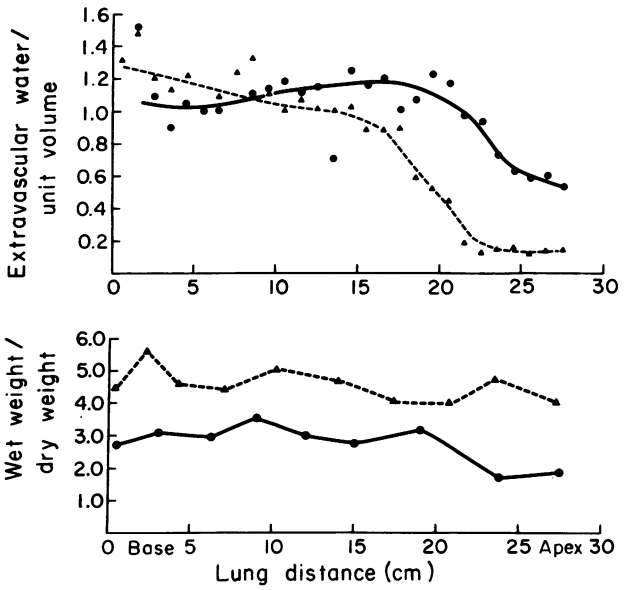

FIGURE 10 Distribution of EVLW per unit lung volume and wet-to-dry weight ratios plotted against lung distance in two vertical isolated lungs. Note the uniform distribution of wet-to-dry weight ratio even in the more edematous lung (----), in contrast to the uneven distribution of EVLW as measured with $H_2{}^{15}O$.

The close correlation between regional blood volume and EVLW volume in Fig. 6 is of considerable interest. Increases in blood volume reflect dilatation or recruitment of arteries, capillaries, and veins. There is direct and indirect evidence to suggest that in this preparation recruitment and distension of capillaries play the most important role. Venous dilatation can be excluded because venous pressures were low and less than alveolar pressures (zone II conditions). There may be some increase of arterial diameter from apex to base on the basis of the increase in intravascular pressure; nevertheless, there will not be any regional differences in vessel length, since parenchymal expansion, upon which length depends, is uniform in the isolated lung (22). This will restrict changes of arterial blood volume. Finally, the increase in EVLW from apex to base without an increase in wet-to-dry weight ratio supports the notion that capillary recruitment is mainly responsible for the regional differences in EVLW.

Edema. In this preparation the distribution of EVLW, blood volume, and blood flow was relatively independent of modest amounts of edema. For perfusion, Muir et al. (23) found that gross alveolar edema was required for a reduction in local blood flow. Except at extremely low flows and arterial-venous differences (24), the distribution of blood flow in the isolated lung preparation is relatively insensitive to edema (22), though reductions in basal blood flow are seen if measurements

are made at lower transpulmonary pressures (5 cm H_2O) and lung volumes (25). In the one preparation (lung 7) with severe edema, lower zone blood volume and flow was reduced relative to that in the middle and upper zones. Otherwise, the distributions of EVLW, blood volume, and wet-to-dry weight ratios stayed remarkably constant for lung weight gains from 18 to 55%. These findings, similar to those of Naimark et al. (5), require further explanation.

Conclusions. This study provides further evidence that tracer dilution methods measure a lung water pool whose volume is dependent upon regional blood flow and capillary recruitment. Second, the isolated perfused lung can accommodate up to 60% weight gain without significant changes in the distribution of EVLW, blood volume, or blood flow between zones. Although the isolated lung lacks normal lymphatic and neural connections, similar results in mild to moderate edema have been reported in anesthetized dogs (5). These findings must be set against the clinical and radiologic observation that edema in man accumulates preferentially in the dependent zones of the lungs. Further development of this technique for in vivo application will have to include an assessment of the chest wall contribution and the use of imaging devices such as the positron camera (26) to define lung regions and correct accurately for regional differential γ ray absorption. With such endeavours it may be possible to measure the distribution of extravascular lung water in man.

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