Regional lung hematocrit in humans using positron emission tomography

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BRUDIN, L. H., S. O. VALIND, C. G. RHODES, D. R. TURTON, AND J. M. B. HUGHES. *Regional lung hematocrit in humans using positron emission tomography.* J. Appl. Physiol. 60(4): 1155–1163, 1986.—Regional lung hematocrit ratio (R) was measured in five normal subjects and five patients (2 with pneumonia, 2 with nephrotic syndrome with anemia, and 1 with pancreatitis) using positron emission tomography, a red cell marker ^{11}CO, and a plasma marker [*methyl*-^{11}C]albumin). The measurements were made in a transaxial thoracic section at midheart level with the subject in supine posture and with a spatial resolution of 1.7 cm. The normal regional hematocrit ratio (means ± SE) calculated for the lung was 0.90 ± 0.014, 0.94 ± 0.023 for the thoracic wall, and 1.00 ± 0.003 for the heart chambers. The regional lung hematocrit ratio in the patients ranged between 0.81 and 0.86. No correlation was found among the regional lung hematocrit ratio and regional blood volume, lung extravascular density, and the peripheral hematocrit (obtained from venous blood samples). To the extent that 70% of the pulmonary blood in the field of view is in larger vessels with normal hematocrit, the hematocrit in the capillary bed is approximately two-thirds that of the peripheral venous value. Blood volume measurements on the basis of single vascular tracers need to take account of these results.

regional hematocrit; pulmonary blood volume

MORE THAN FIFTY YEARS AGO Fåhreus (4) showed that erythrocytes and plasma, streaming through a glass capillary, had different velocities, and that this difference was a function of the diameter of the vessel. As a direct consequence of this, the erythrocyte volume fraction of whole blood (hematocrit) should vary according to the diameter of the vessel.

Information about regional hematocrits is not only of physiological interest, but it is of importance in blood volume measurements using single vascular tracers. It was earlier generally accepted that the only satisfactory method to measure blood volume was to label both erythrocytes and plasma with different tracers and measure their respective volumes separately. Chaplin et al. (1), however, showed that the ratio of total body hematocrit to venous hematocrit (R_{TB}) was fairly constant over a wide peripheral venous hematocrit range. They reported a value of R_{TB} of 0.91 ± 0.026 (SD). Although other workers have found this ratio to be somewhat more variable (14), this value now enables total body blood volume measurements to be made using either red cell or plasma markers.

Several techniques have been used to measure the hematocrit of the whole body (body hematocrit) and that of various organs (regional hematocrit) (1, 3, 7, 18). The central hematocrit ratio (total pulmonary circulation, including heart and large vessels) has been calculated from the mean transit time and flow of plasma and erythrocytes, respectively, and values in humans of 0.98 and 0.92 have been reported (9, 12).

Recently, with the development of new techniques, regional hematocrit within different organs has been measured in vivo. Kobari et al. (7), using a photoelectric method, report the ratio of small to large vessel hematocrit in cat brain capillary of 0.62 and Sakai et al. (17), using single-photon emission tomography, present a value in human brain of 0.74 of the peripheral hematocrit. Furthermore, using positron emission tomography and a method similar to the one described in this paper, Lammertsma et al. (8) report a value in human brain of 0.69 of the arterial hematocrit.

There are no reports of regional lung hematocrit in humans in vivo. Animal studies in vitro have given various results. In male and female rats hematocrit ratios of 0.83 and 0.95 of the peripheral hematocrit have been reported (3), and in dogs the lung hematocrit was 1.03 of the hematocrit of blood samples taken from the right heart (18).

The purpose of this study was twofold: *1*) to develop a method for measuring regional pulmonary hematocrit ratio and to investigate how this varies in normal subjects, and *2*) to determine whether a single value of the lung-to-peripheral hematocrit ratio could be used in the calculation of regional lung blood volume for both normal and pathological conditions when measurements using single vascular tracers are made. This is important because various radioisotopic scanning techniques rely on a regional blood background subtraction as a part of the analytical procedure. In general, blood volume measurements are made by labeling the vascular compartment with either a plasma or a red cell marker; hence, a value of the hematocrit ratio has to be assumed.

The implications of our results on the measurements of regional pulmonary blood volume, pulmonary capillary

lung volume, and extravascular lung density are also discussed.

Glossary of Terms

rH	Regional hematocrit
pH	Venous blood sample hematocrit
R	rH/pH
rV(RC)	Fractional red cell volume (ml/cm^3 of thoracic volume)
rV(P)	Fractional plasma volume (ml/cm^3 of thoracic volume)
rV(WB)	Fractional whole blood volume (ml/cm^3 of thoracic volume)
rC(P)	Regional plasma concentration of plasma marker (μCi/ml)
pC(P)	Plasma concentration of plasma marker in a venous blood sample (μCi/ml) = rC(P)
rC(RC)	Regional red cell concentration of red cell marker (μCi/ml)
pC(RC)	Red cell concentration of red cell marker in a venous blood sample (μCi/ml) = rC(RC)
pCwb(RC)	Whole blood concentration of red cell marker in a venous blood sample (μCi/ml)
pCwb(P)	Whole blood concentration of plasma marker in a venous blood sample (μCi/ml)
rCT(P)	Regional concentration of plasma marker (μCi/cm^3 of thoracic volume)
rCT(RC)	Regional concentration of red cell marker (μCi/cm^3 of thoracic volume)

METHODS

Theory

Measurements of regional hematocrit. The regional hematocrit (rH) can be defined by either of the relationships

$$rH = rV(RC)/rV(WB) \quad (1)$$

or

$$rH = 1/[1 + rV(P)/rV(RC)] \quad (2)$$

where rV(WB), rV(P), and rV(RC) are the regional whole blood, plasma, and red cell volumes, respectively, measured as fractional volumes (i.e., volume per unit organ volume; e.g., ml/cm^3 of thoracic volume).

Positron emission tomography enables quantitative measurements to be made of the regional concentration of positron-emitting isotopes. Thus the rH can be obtained in any region, provided both plasma and red cell volumes can be accurately labeled separately.

The theoretical model of hematocrit measurement is based on the use of two truly intravascular markers, both evenly and exclusively distributed in the plasma and red cell space, respectively. The regional fractional plasma (P) and red cell (RC) volumes are, by definition

$$rV(P) = rCT(P)/rC(P) \quad (3)$$

$$rV(RC) = rCT(RC)/rC(RC) \quad (4)$$

where rCT(RC) and rCT(P) are the regional concentrations of the red cell marker and the plasma marker, respectively (for the thorax, expressed as μCi/thoracic volume), rC(P) is the regional plasma concentration of plasma marker (μCi/ml), and rC(RC) is the regional red cell concentration of red cell marker (μCi/ml). Substituting *Eqs. 3* and *4* into *Eq. 2* gives the regional hematocrit as

$$rH = 1/\{1 + [rCT(P)/rC(P)]/[rCT(RC)/rC(RC)]\} \quad (5)$$

Since rC(P) and rC(RC) are uniform within the body (including sampled blood, it follows that rC(P) = pC(P) and rC(RC) = pC(RC), where the prefix p refers to peripheral venous blood. Hence these parameters can easily be measured in the peripheral blood. A direct measurement of pC(RC), however, requires a red cell and plasma separation procedure, and the problem of trapped plasma would arise. Instead, the whole blood concentration of the red cell marker [pCwb(RC)] is measured, and pC(RC) is calculated using the relation

$$pC(RC) = pCwb(RC)/pH \quad (6)$$

The hematocrit of the peripheral venous sample (pH) is calculated using the relationship

$$pH = 1 - pCwb(P)/pC(P) \quad (7)$$

where pCwb(P) is the whole blood concentration of the plasma marker. Substituting *Eq. 6* into *Eq. 5* gives the regional-to-peripheral blood sample hematocrit ratio (R) as

$$R = rH/pH = 1/\{pH + [rCT(P)/pC(P)]/[rCT(RC)/pCwb(RC)]\} \quad (8)$$

where pH is calculated from *Eq. 7*.

Perfect plasma and red cell markers are, of course, not available. Using the inhalation of ^{11}CO as the red cell marker, however, the activity in the plasma space is negligible (<0.1% of the red cell concentration). The amount of plasma marker found in the red cell and tissue space, using [^{11}C]albumin is more difficult to estimate. [^{11}C]albumin is a stable marker because ^{11}C is part of the albumin molecule, bound to a methyl group by a covalent bond (19). Slow albumin leakage into erythrocytes and tissue is compensated for by extrapolation of rV(P) back to the time of injection (see Fig. 1). Furthermore, the amount of [^{11}C]albumin attached to the erythrocytes can be estimated by comparing the pH, measured by the tracer technique, with the hematocrit measured by standard laboratory procedures [e.g., impedance technique (Coulter S; Ref. 13)]. This attached fraction turns out to be very small and in fact cancels out in R as follows: assume that the red cell concentration of plasma marker ([^{11}C]albumin attached to or absorbed by erythrocytes) is a fraction k of the plasma concentration. Then it is clear that rCT(P) and pCwb(P) in *Eqs. 7* and *8*

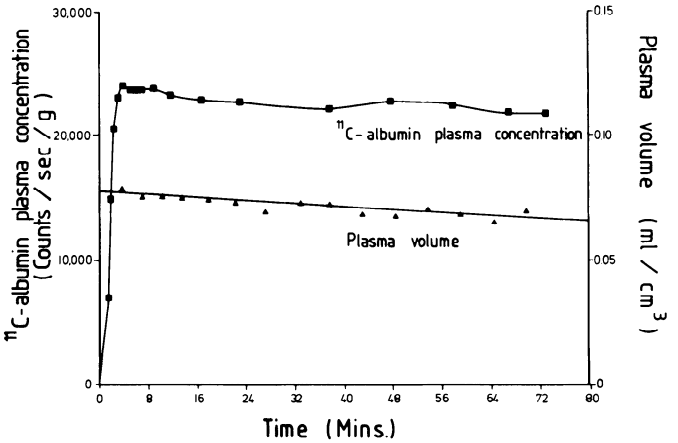

FIG. 1. Plasma concentration of [*methyl*-^{11}C]albumin (*filled squares*) and apparent tissue plasma distribution volume (ml plasma/ml thoracic volume) in 1 of the 4 lung regions (*filled triangles*), both calculated as a function of time for the subject. Intercept (t = 0) of regression line represents true vascular fractional plasma volume. Activity is decay corrected to time of injection (t = 0).

are slightly overestimated. By replacing the measured rCT(P) and pCwb(P) by the true values, [rCT(P) − k·pC(P)·rV(RC)] and [pCwb(P) − k·pC(P)·pH], respectively, in *Eqs. 7* and *8*, it can be shown that R is independent of k (see APPENDIX).

Measurements of pulmonary blood volume and extravascular density. Regional fractional pulmonary blood volume [rV(WB)] was calculated using the equation

$$\text{rV(WB)} = \text{rV(RC)}/\text{rH} \qquad (9)$$

which, using *Eqs. 4* and *6*, can be rewitten as

$$\text{rV(WB)} = [\text{rCT(RC)}/\text{pCwb(RC)}]/\text{R} \qquad (10)$$

Regional extravascular lung density (rDEV) is calculated as the difference between regional lung tissue density (rDL) and regional whole blood density [ρ·rV(WB)], where ρ is the physical density of whole blood (ρ = 1.060 ± 0.004 g/cm^3 from Geigy Scientific Tables).
Thus

$$\text{rDEV} = \text{rDL} - 1.06\cdot\text{rV(WB)} \qquad (11)$$

Positron emission tomography. The technique for measuring rDEV and rV(WB) has previously been described in detail (15) and is only summarized here. The measurement of regional plasma volume using [^{11}C]albumin is analogous to that of blood volume measurement using ^{11}CO. A technique for the preparation of injectable serum [*methyl*-^{11}C]albumin has recently been developed (19).

The measurements were made using an EG&G ORTEC ECAT II positron scanner. The spatial resolution of the instrument is 1.7 cm in each of the three dimensions (measured as the full width at half maximum of the response to a line source of activity). The scanner is used in both emission and transmission modes, based on coincidence detection of the pair of γ-rays originating from a positron-electron annihilation. The information is fed into a computer and a transverse plane is reconstructed in a way similar to that of a CT scan.

In the transmission mode, a ring source of the positron-emitting isotope ^{68}Ge, which completely encircles the subject, is used to provide a quantitative topographical distribution of tissue density in the chosen plane. This information is also used to correct the emission scan for attenuation losses. In the emission mode, a scan is recorded after the introduction of positron-emitting isotopes into the body. With appropriate calibration of the tomographic picture element (pixel) response, a quantitative topographic distribution of the isotope concentration within the tomographic slice is obtained.

Protocol

Measurements were made in a transverse section through the thorax at the midheart level, with the subject in the supine posture. Each study began with a transmission scan, giving regional values of total lung tissue density. Next, a solution containing 10–13 mCi of [*methyl*-^{11}C]albumin was infused intravenously (10 ml during a 30-s period, using a Millipore filter). From 2 min after injection and for the next 60 min, six 3-min scans followed by six to nine 5-min scans were recorded. During this scanning procedure, 16–20 venous blood samples (5 ml each) were taken from the opposite arm using an indwelling cannula (22-gauge/0.8 mm OD) to allow plasma and whole blood isotope concentrations to be measured.

Following these measurements, the subject inhaled ^{11}CO to label the red cell pool. After the inhalation, 3–4 min were allowed for mixing, before a single 10-min emission scan was recorded at the same level. During this scan, three venous blood samples were taken and the whole blood isotope concentration was measured. All the measurements of ^{11}C activity were corrected for the radioactive half-life of 20.3 min.

Data analysis. The basic principles of obtaining the fractional blood and plasma volumes have been discussed. To compensate for possible albumin leakage into the lung interstitial space, the fractional plasma volume was obtained by extrapolating the apparent fractional plasma volume (calculated using *Eq. 3*, with each [^{11}C]-albumin scan corresponding to one measurement) back to the time of injection (Fig. 1). The extrapolation was made by means of linear regression, pixel by pixel.

To relate the plasma isotope concentration to a particular scan and to obtain values of regional plasma volume, the plasma curve was interpolated to obtain the values at midscan time. R was calculated from *Eq. 8*. Regional tissue ^{11}CO concentration was obtained after appropriate subtraction of [^{11}C]albumin residual activity. A previously measured calibration factor was used to convert isotope concentration measured in a well counter (blood and plasma samples) into concentrations corresponding to those measured with the tomograph. To convert isotope concentrations per gram into concentration per milliliter, values of 1.03 for plasma density and 1.06 for whole blood density were used (Geigy Scientific Tables).

An image showing the topographical distribution of R was calculated using *Eqs. 7* and *8*, and from this, the mean R was calculated after dividing the whole lung field into four regions (dorsal and ventral part, left and right

lung). The mean R was also calculated for the heart chambers and for the left and right dorsolateral part of the thoracic wall.

Fractional blood volume (blood volume per unit of thoracic volume) and extravascular lung density (lung tissue and interstitial fluid per unit thoracic volume) were obtained using *Eqs. 10* and *11* and were calculated individually for the four lung regions in normal subjects and patients.

Subjects. Five normal male subjects comprising one smoker (*subj 1*) and four nonsmokers with a mean age of 30 yr (range 23–36) were studied in addition to five patients. One patient had suspected microvascular lung impairment (pancreatitis, *patient 1*), two had low venous hematocrit (renal failure with anemia, *patients 2* and *3*), and the remaining two had high extravascular lung density (pneumonia verified by chest X-ray, *patients 4* and *5*). The mean age of the patients was 53 yr (range 26–76).

The study was approved by the Hammersmith Hospital Research Ethics Committee and the United Kingdom Administration of Radioactive Substances Advisory Committee. Written informed consent was obtained from each subject before the study.

RESULTS

An image of the topographic distribution of R in one normal subject is shown in Fig. 2*D*. For the same person the [^{11}C]albumin time-activity plasma curve and the apparent plasma distribution volume at midscan time, calculated for one of the four lung regions, are shown in Fig. 1. Pooled and individual data of the mean hematocrit ratio, calculated for each of the four lung regions, are shown in Table 1. The regional tissue-to-heart chamber (h) hematocrit ratio (rH/hH) calculated for the whole lung slice is also shown. Pooled data of R, calculated for the thoracic wall, and left ventricular free wall and heart chamber are shown in Table 2. The overall mean value of R for the lung was 0.900 ± 0.014 (SE) in the normal subjects and 0.840 ± 0.008 (SE) in the patients. R of the whole lung slice was slightly below the normal range (0.861–0.943) in all the patients, especially in one of the renal patients (*patient 2*). R was also low in the affected region of the lung in the two pneumonia patients (*patients 4* and *5*). Differences in R between the right (R = 0.897 in the normal subjects) and left lung (0.903) and between the ventral (0.890) and dorsal (0.910) part of the lung are not significant (two-tailed paired *t* test). The range of the mean of R calculated for each of the four lung regions was 0.027 (3.0%) in the normal subjects and 0.030 (3.6%) in the patients. rH/hH, calculated for individual regions, ranged between 0.83 and 0.96 in normal subjects and between 0.80 and 0.94 in patients (20 regions in each group).

The hematocrit ratio calculated for the heart chambers was, as expected, close to 1 [0.999 ± 0.003; (SE) in normal subjects and 0.962 ± 0.012 in the patients]. There was no significant correlation between R and rV(WB), rDEV, pH, or age of the subject (analysis of covariance, Fig. 3). Values of R were also calculated for the thoracic wall [0.941 ± 0.023; (SE)] in normal subjects).

pH was calculated by using both conventional laboratory techniques [centrifugation or impedance technique (Coulter S)] and the tracer technique (*Eq. 7*). The values are shown in Table 1. The value of pH used in the calculations was obtained using the tracer technique. However, the difference between the two measurements was not significant. The amount of any [^{11}C]albumin attached to the surface of the erythrocytes, expressed per milliliter of whole blood as a fraction (k) of the plasma concentration of [^{11}C]albumin, can be estimated as 1 − [H(tracer technique)/H(conventional technique)]. The mean value of k for the normal subjects (0.026) is not significantly different from zero.

Regional blood volume and extravascular density were calculated using R = 0.90 (*Eqs. 10* and *11*). By way of comparison, rDEV was also calculated in accordance with the earlier described technique (Refs. 15 and 21) in the normal subjects, where R was assumed to be 1.0. The difference between rDEV, calculated in the two different ways, was 11%.

DISCUSSION

General Considerations

Previous studies have shown that hematocrit is a function of the diameter of the vessel and the flow velocity. The reason for this is axial streaming of erythrocytes causing a higher mean velocity of these relative to the plasma. The difference is more pronounced in small vessels and capillaries. Hence one would expect R in tissue, containing a mixture of capillaries and small and large vessels, to be <1.0.

R for total body has been measured in several studies, and values of ~0.9 have been found. A value of R = 0.69 in human brain has recently been reported (8). It is reasonable to expect the regional lung hematocrit ratio to be greater than this value, since the fraction of blood in the large vessels is relatively higher in the lung. Compared with the total body hematocrit, it is also reasonable to expect the lung hematocrit ratio to be slightly lower, taking into account the different amount of blood in the capillaries (15–20% in the pulmonary compared with 5% in the systemic circulation). A complicating factor is the difference in blood flow in various organs; the higher the blood velocity through individual capillaries, the lower the R. The fact that blood flow per unit of blood volume in the lung is much greater than that in the systemic circulation would therefore tend to lower the lung hematocrit ratio even more. On the other hand, the total pulmonary resistance is only ~10% of that of the systemic circulation, implying a relatively lower velocity of the blood and hence a higher value of R. It has also been suggested that the pulsatility of flow in the pulmonary vessels may decrease the axial accumulation of erythrocytes (11), so that an R less than unity might only be found in the arterioles and venules and not in the capillaries. However, the mass transport in small capillaries is different from that in larger vessels. Erythrocytes are deformed, and there might also be a "leakback" of plasma (24). In view of these considera-

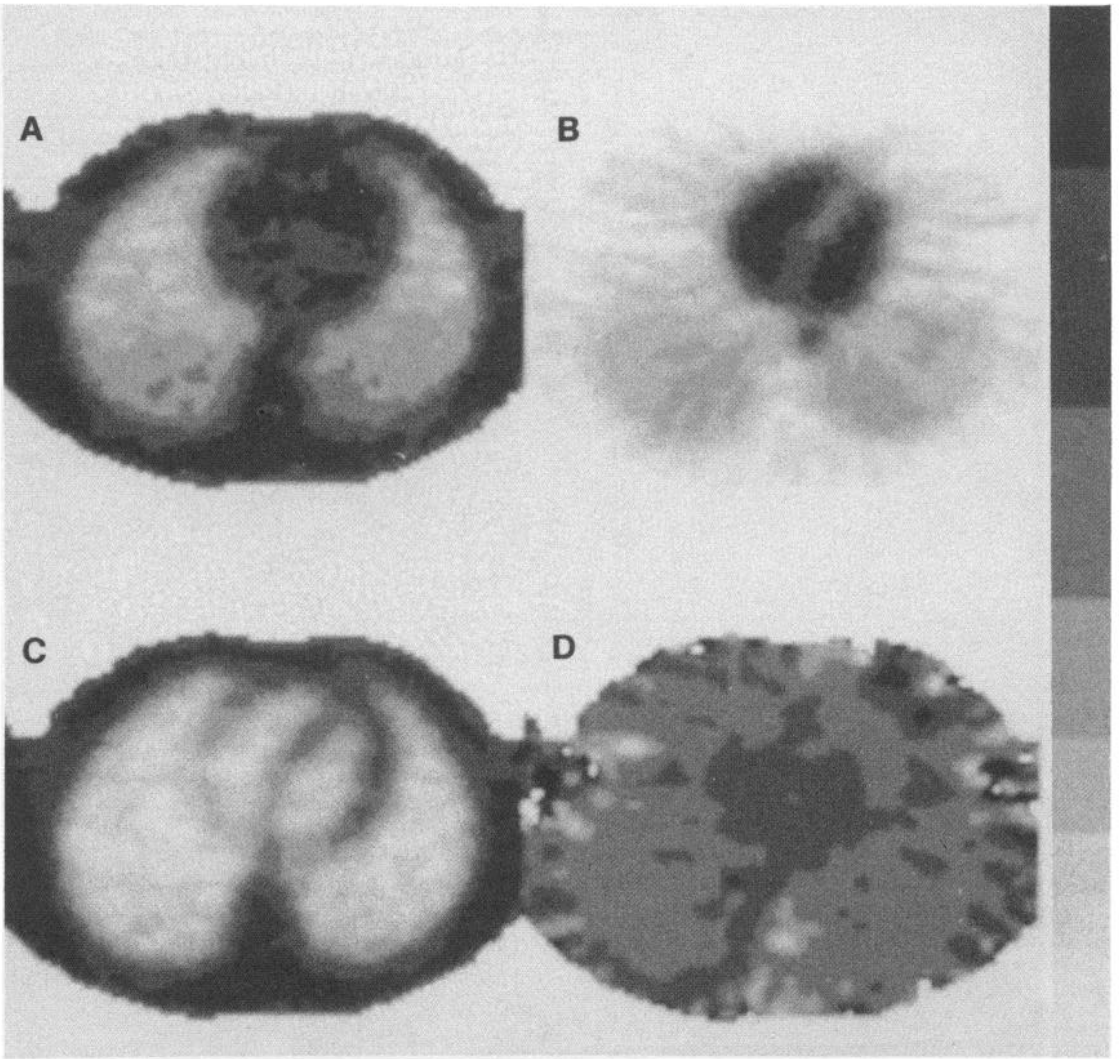

FIG. 2. Calculated images of density (rDL) (*A*); blood volume [rV(WB)] (*B*); extravascular density (rDEV) (*C*); hematocrit ratio (R) (*D*) in a normal subject. rDL and rDEV are scaled to 1.3 g/cm^3 of thorax, rV(WB) to 1.3 ml/cm^3, and R to 1.5.

tions the value of 0.90 for the regional lung hematocrit ratio in normal subjects seems quite reasonable.

Hematocrit ratio in Normal Subjects and Patients

Considering mean values of R, the two renal patients had values significantly below the normal mean (<−2 SD). Furthermore, the remaining three patients fell in the lower normal range (<−1 SD). The lowest mean R value (0.811) was found in renal *patient 2*, in whom the pH was moderately decreased (0.33). However, a similar value of pH (0.35) was found in the subject with the highest R value (*subj. 4*). The mean value of R for the patient group was significantly lower than that for normal subjects ($P < 0.01$, two-tailed paired t test). Concerning rH, low R values (0.815, 0.824, and 0.803) were also found in regions with pneumonic consolidation (*patients 4* and *5*). These patients had the lowest regional pulmonary blood volume, although a normal value was found in one of the three consolidated regions. The reason for low hematocrit regions in some of the patients might be enhanced recruitment of capillaries due to increase in regional blood flow, especially in regions of inflammation. Although significant ($P < 0.01$, two-tailed t test), the difference between R in normal subjects and patients is rather small, and there is no significant correlation between R and regional blood volume, rDEV, or pH.

The value of R calculated for the heart chambers [1.00 ± 0.003 (SE) in normal subjects and 0.96 ± 0.012 in patients] provides an indication of the accuracy of the technique. The reason for the slightly lower value of R calculated for the heart chambers in the patients is not clear. Three different explanations can be put forward. First, the heart chamber to peripheral hematocrit ratio (hH) might have been underestimated due to inadequate positioning of the transaxial slice through the heart or movement of the patient. As a consequence, the measured values of blood volume within the chambers, which should be close to unity, would be low because of the finite spatial resolution of the scanner. However, values of blood volume in the heart chambers bear no relation-

TABLE 1. *Individual and pooled regional lung hematocrit ratios for five normal subjects and five patients*

	Age, yr	pH tracer	pH	Regional Lung Hematocrit Ratio						
				RVL	RDL	LVL	LDL	Total	rH/hH	hH/pH
Normal subj										
1	36	0.390	0.390 (C)	0.901	0.910	0.842	0.905	0.890	0.900	0.989
2	33	0.417	0.411 (I)	0.914	0.902	0.944	0.906	0.917	0.917	0.999
3	27	0.389	0.423 (I)	0.844	0.886	0.831	0.882	0.861	0.859	1.002
4	31	0.353	0.360 (I)	0.936	0.943	0.931	0.962	0.943	0.944	0.999
5	23	0.430	0.451 (I)	0.847	0.883	0.910	0.919	0.890	0.885	1.005
Mean	30.0	0.396	0.407	0.888	0.905	0.892	0.915	0.900	0.901	0.999
±SD ($n-1$)	±5.1	±0.030	±0.034	±0.041	±0.024	±0.052	±0.030	±0.031	±0.032	±0.006
Patients										
1	71	0.331	0.320 (C)	0.844	0.860	0.857	0.829	0.848	0.871	0.973
2	26	0.326	0.320 (C)	0.823	0.788	0.825	0.806	0.811	0.856	0.947
3	34	0.249	0.250 (C)	0.815	0.831	0.833	0.874	0.838	0.901	0.930
4	76	0.378	0.388 (C)	0.903	0.804	0.815*	0.856	0.845	0.886	0.958
5	59	0.428	0.414 (C)	0.921	0.879	0.824*	0.803*	0.857	0.855	1.002
Mean	53	0.342	0.338	0.861	0.832	0.831	0.834	0.840	0.874	0.962
±SD ($n-1$)	±22	±0.067	±0.065	0.048	±0.038	±0.016	±0.031	±0.017	±0.020	±0.027

pH, peripheral venous hematocrit measured with radionuclide tracers (tracer), by centrifuge (C), or impedance technique (I); R, regional lung hematocrit ratio; RVL, right ventral part of lung; RDL, right dorsal; LVL, left ventral; LDL, left dorsal; Total, mean of these four regions; rH/hH, regional-to-heart chamber hematocrit ratio calculated for whole lung slice. See METHODS for definitions of patients. * Regions of pulmonary consolidation.

TABLE 2. *Pooled data of hematocrit ratio calculated for whole lung slice, thoracic wall, and heart chamber*

	Hematocrit Ratio		
	Total	TW	HC
Normal Subj.			
Mean	0.900	0.941	0.999
SD	0.031	0.051	0.006
SE	0.014	0 023	0.003
Patients			
Mean	0.840	0.813	0.962
SD	0.017	0.097	0.027
SE	0.008	0.043	0.012

Total, whole lung slice; TW, thoracic wall; HC, heart chambers.

ship to the measured values of hH, which suggests that hH is measured with similar accuracy on all occasions. The second explanation of the low value of hH in the patients might be an overestimation of pH. Third, there may have been a true difference between pH and hH, but this would be difficult to explain on physiological grounds. If pH in the patients was overestimated, then the regional lung hematocrit might better be related to hH rather than pH in cases where these two values are different. When normalized to hH, the difference in regional lung hematocrit (rH/hH) between normal and patient groups (~3%) is not significant ($P > 0.2$, two-tailed t test). This small difference and the similarity in ranges of rH/hH between normal subjects and patients (0.83 to 0.96 and 0.80 to 0.94, respectively) suggests that there are no real differences in lung hematocrit between the two groups and that a single hematocrit value can be used in measurements of regional pulmonary blood volume. However, the slight uncertainty in the patient values arising from the discrepancy between hH and pH indicates that the mean value of R for the normal subjects (0.90) may be more accurate than the overall mean value (0.87) or the regional-to-heart chamber hematocrit ratio of 0.89 (normal subjects and patients). A working value of R = 0.90 should therefore be a good estimate of the lung hematocrit ratio for subjects with wide ranging values of blood volume and normal to high extravascular density.

Critique of Labeling Techniques

The method for measuring hematocrit described in this paper assumes that [^{11}C]albumin is a true intravascular plasma space marker and that ^{11}CO is a true intravascular red cell marker. The amount of ^{11}CO in plasma was negligible. Possible albumin leakage into the interstitial space has been corrected for by extrapolation back to the time of injection. This gives a true value of the plasma volume, provided there is no immediate equilibration with any compartment other than the intravascular plasma space, nor any albumin attached to the erythrocyte membrane and vessel walls. In fact, R is independent of [^{11}C]albumin attached to the erythrocytes (see *Theory*). A comparison of pH using the tracer technique with that using conventional methods (centrifuging or impedance technique) indicates that the amount of [^{11}C]albumin attached to erythrocytes is <3% of that in plasma.

A limitation of the technique is the spatial resolution of the positron emission tomograph, which restricts the size of the region within which the hematocrit can be measured to a diameter of ~3.4 cm.

In some cases, a slight fall in the apparent plasma volume with time was seen. An explanation for this is a

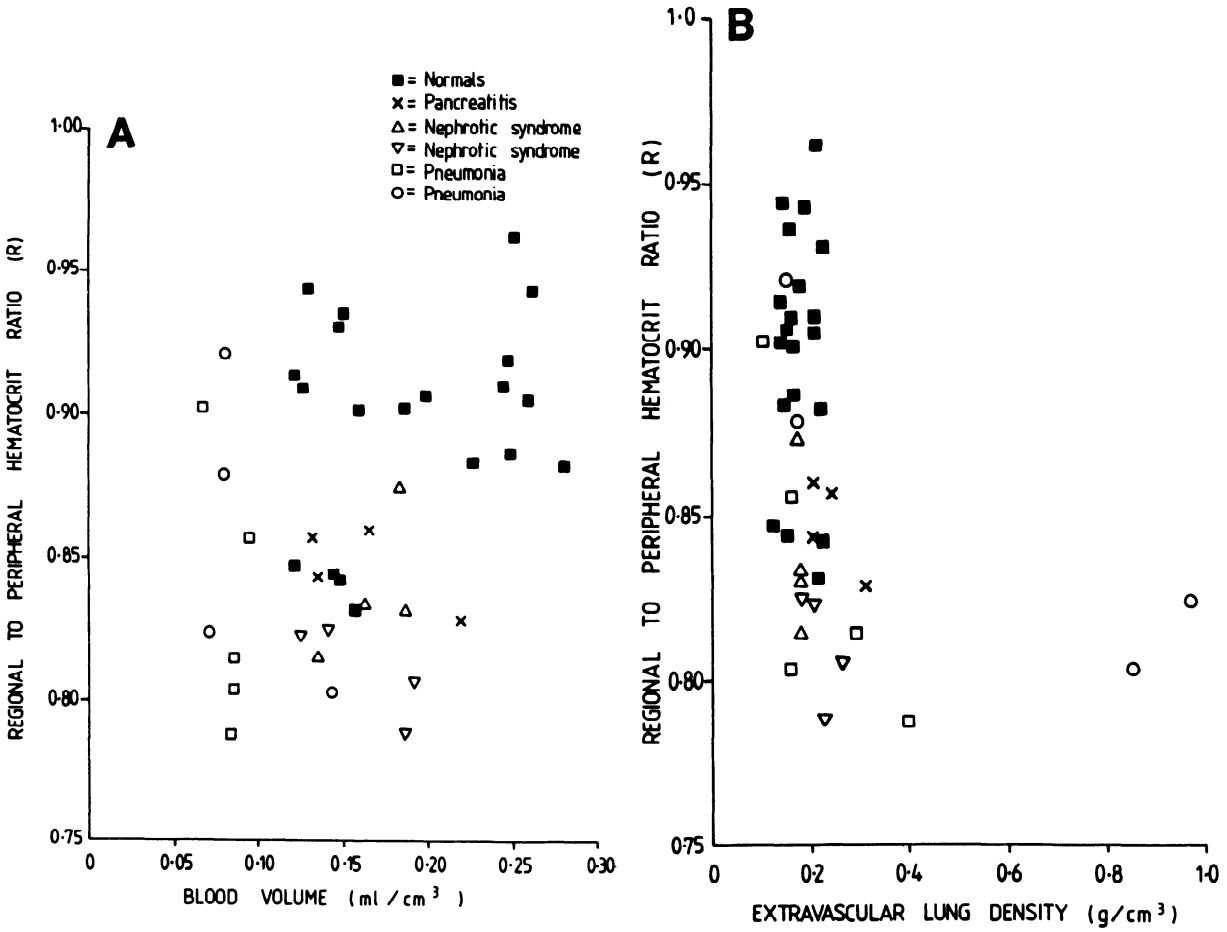

FIG. 3. Relationship among regional lung hematocrit ratio (R), regional blood volume [rV(WB)], and extravascular density (rDEV). There is no significant correlation between R and rV(WB) or rDEV (analysis of covariance). Each point represents 1 of 4 lung regions in each subject and a 5th region in one pneumonia patient (pneumonic consolidation in part of left ventral region).

slow decrease in the blood volume within the slice during the time of the scanning procedure. This might be due to prolonged changes in blood volume when the subject moves from the upright to the supine position, although the injection of [^{11}C]albumin does not usually take place until 45 min after the beginning of the investigation. However, this fall in plasma volume is quite small and does not significantly affect the hematocrit results.

Implications for Measurements of Pulmonary Blood Volume and rDEV

Pulmonary blood volume has been measured using dye-dilution and radiocardiographic techniques, and several studies have been presented (reviewed in Ref. 6). With a lung hematocrit ratio of 0.9, values of pulmonary blood volume obtained using tracers exclusively occupying the plasma space should be reduced by 10%, and those using a red cell tracer should be increased similarly.

Regional rDEV and blood volume measurements have been made in this laboratory on normal subjects (15), patients with interstitial lung disease (22), patients with pulmonary hypertension (21), and patients with congenital heart disease (23). In these studies, R in the lung was assumed to be unity. Therefore, the blood volume of the lung was slightly underestimated and rDEV was slightly overestimated. In this study, rDEV has been calculated using a blood volume corrected for regional hematocrit. As a result of this refinement, an overall lower value of rDEV is obtained (~10%). The difference is greater in the dependent part of the lung giving a smaller ventrodorsal gradient than originally described (15). However, the change in rDEV is small and does not affect the clinical findings of the earlier work to any significant degree.

Implications for Measurements of Pulmonary Capillary Blood Volume

R will influence measurements of blood volume in the pulmonary capillaries (Vc) using the Roughton-Forster technique (16). Although the capillary hematocrit ratio (Rc) is unknown, it is interesting to speculate about its order of magnitude. Consider the total pulmonary blood volume divided into two compartments, with one containing small vessels (including capillaries) and the other containing larger vessels (where R is assumed to be unity). The hematocrit ratio in small vessels (Rsv) is then given by

$$Rsv = 1 - (1 - R)/Fsv \qquad (12)$$

where R is the lung hematocrit ratio in the counting field and Fsv the volume fraction of blood in small vessels.

There are reasons to believe that R is close to one in vessels with a diameter >0.3 mm (10). Vc has been calculated from measurements of the diffusing capacity for CO, taken at different concentrations of inspired O_2, assuming an Rc of one (16). Hence the true blood volume in the capillaries is Vc/Rc. An average value for the pulmonary capillary blood volume by this method is ~80 ml (65–100 ml) (6). The total blood volume in small vessels, including capillaries (Vsv), is (Vc/Rc + Vec), where Vec is the volume in small extracapillary vessels, i.e., 10–20 ml (2). Since Vc/Rc < Vc/Rc + Vec < (Vc + Vec)/Rc, Vsv can be redefined as θ/Rc, where θ ranges between 65 and 120 ml. Dividing θ/Rc by the total lung volume [gas, tissue and blood; lung volume (VL) = 3.5–4.0 liter in supine posture] and by the regional blood volume [V(WB) = 0.17 − 0.20 ml/cm^3 of thorax (mean ± 2 SE), calculated for 5 normal subjects] gives Fsv. Thus

$$\text{Fsv} = \text{f/Rc} \qquad (13)$$

where f = θ/[VL·V(WB)] and ranges between 0.08 and 0.20. But the blood volume in Vec is only ~10% of that in the capillaries and hence the value of Rsv (*Eq. 12*) is approximately equal to Rc. Thus substituting Rc for Rsv in *Eq. 12* and solving Rc in combination with *Eq. 13* gives

$$\text{Rc} = 1/[1 + (1 - \text{R})/\text{f}] \qquad (14)$$

or Rc = 0.57 (range 0.38–0.74) calculated for R values of 0.90 ± 0.028 (±2 SE) and f = 0.135 (0.08–0.20). This value is well in accordance with Rc in cat brain (0.62) found by Sakai et al. (17).

Thus the value of Vc obtained using the Roughton-Forster technique (16) should probably be increased by a factor of 1.4–2.6 Therefore, the average value is ~110–210 ml. This value of Vc is also closer to values of 146 and 150 ml, calculated from anatomical measurements by Weibel (20) and Cumming et al. (2).

APPENDIX

On the assumption that the red cell concentration of plasma marker ([^{11}C]albumin attached to the erythrocytes) is a fraction k of the plasma concentration itself, it is clear that the regional concentration of plasma marker [rCT(P)] and the whole blood concentration of plasma marker [pCwb(P)] are both overestimated. Denoting the measured and true values of venous blood hematocrit by pH and pH*, respectively, and the corresponding values for the regional-to-peripheral blood sample hematocrit ratio by R and R*, and replacing the measured rCT(P) and pCwb(P) by the true values [rCT(P) − kpC(P)·rV(RC) and pCwb(P) − kpC(P)·pH*, respectively] in *Eqs. 7* and *8*, we obtain (for simplicity taking the reciprocal of *Eq. 8*)

$$\text{pH}^* = 1 - [\text{pCwb(P)} - k\cdot\text{pC(P)}\cdot\text{pH}^*]/\text{pC(P)} \qquad (7a)$$

and

$$1/\text{R}^* = \text{pH}^* + \{[\text{rCT(P)} - k\cdot\text{pC(P)}\cdot\text{rV(RC)}]/\text{pC(P)}\}/[\text{rCT(RC)}/\text{pCwb(RC)}] \qquad (8a)$$

Note that the measured R and pH are defined using *Eqs. 7* and *8*. Thus

$$\text{pH} = 1 - \text{pCwb(P)}/\text{pC(P)} \qquad (7)$$

$$1/\text{R} = \text{pH} + [\text{rCT(P)}/\text{pC(P)}]/[\text{rCT(RC)}/\text{pCwb(RC)}] \qquad (8)$$

Substituting *Eqs. 7a, 7,* and *8* into *Eq. 8a* gives

$$1/R^* = 1/R + k[\text{pH}^* - \text{rV(RC)}\cdot\text{pCwb(RC)}/\text{rCT(RC)}] \qquad (8b)$$

From *Eq. 4*, rV(RC) = rCT(RC)/rC(RC), where rC(RC) = pC(RC), and pC(RC) = pCwb(RC)/pH*, [*Eq. 6*, but note that the venous sample hematocrit in this equation is, by definition, the true hematocrit (pH*) and that the only measured value of pH is that defined in *Eq. 7*]. Eliminating rV(RC) from *Eq. 8b* gives

$$1/R^* = 1/R$$

This shows that the measured and true values of R are equal, regardless of the value of k.

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REFERENCES

1. CHAPLIN, H. JR., P. L. MOLLISON, AND H. VETTER. The body/venous hematocrit ratio: its constancy over a wide hematocrit range. *J. Clin. Invest.* 32: 1309–1321, 1953.
2. CUMMING, G., L. K. HARDING, K. HORSFIELD, K. PROWSE, S. S. SINGHAL AND M. WOLDENBERG. Morphological aspects of the pulmonary circulation and of the airways. *NATO Advis. Group for Aerosp. Res. Dev. Conf. Proc.* 65 (23): 1–6, 1970.
3. EVERETT, N. B., B. SIMMONS, AND E. P. LASHER. Distribution of blood (Fe-59) and plasma (I-131) volumes of rats determined by liquid nitrogen freezing. *Circ. Res.* 4: 419–424, 1956.
4. FÅHREUS, R. The suspension stability of blood. *Physiol. Rev.* 9: 241–274, 1929.
5. GUYTON, A. C. *Textbook of Medical Physiology* (6th ed.). Philadelphia, PA: Saunders, 1981, p. 291.
6. HARNIS, P., AND D. HEATH. *The Human Pulmonary Circulation* (2nd ed.). London: Churchill Livingstone, 1977, p. 105, 113–115, 127, 640.
7. KOBARI, M., F. GOTO, M. TOMITA, N. TANAHASHI, AND K. TANAKA. Measurement of the "tissue hematocrit" of feline cerebrocortical tissue (Abstract). *Microvasc. Res.* 24: 218, 1982.
8. LAMMERTSMA, A. A., D. J. BROOKS, R. P. BEANEY, D. R. TURTON, M. J. KENSETT, J. D. HEATHER, J. MARSHALL, AND T. JONES. In vivo measurement of regional cerebral haematocrit using positron emission tomography. *J. Cereb. Blood Flow Metab.* 4: 317–322, 1984.
9. LILIENFIELD, L. S., R. D. KOVACH, P. R. MARKS, L. M. HERSHENSON, G. P. RODNAN, F. G. EBAUGH, AND E. D. FREIS. The hematocrit of the lesser circulation in man. *J. Clin. Invest.* 35: 1385–1392, 1956.
10. MCDONALD, D. A. *Blood Flow in Arteries* (2nd ed.). London: Arnold, 1974, p. 64.
11. MENKES, H. R., K. SERA, R. M. ROGERS, R. W. HYDE, R. E. FORSTER, AND A. DUBOIS. Pulsatile uptake of CO in the human lung. *J. Clin. Invest.* 49: 335–345, 1970.
12. RAPAPORT, E., H. KUIDA, F. W. HAYNES, AND L. DEXTER. The pulmonary blood volume in mitral stenosis. *J. Clin. Invest.* 35: 1393–1403, 1956.
13. RAPHAEL, S. S. Lynch's Medical Laboratory Technology (4th ed.). Toronto, Canada: Saunders, 1983, 677–680.
14. RETZLAFF, J. A., W. N. TAUXE, J. M. KEILY, AND C. F. STROBEL. Erythrocyte volume, plasma volume, and lean body mass in adult men and women. *Blood* 33: 649–667, 1969.
15. RHODES, C. G., P. WOLLMER, F. FAZIO, AND T. JONES. Quantitative measurement of regional extravascular lung density using positron emission and transmission tomography. *J. Comput. Assist. Tomogr.* 5: 783–791, 1981.
16. ROUGHTON, F J. W., AND R. E. FORSTER. Relative importance of diffusion and chemical reaction rates in determining rate of exchange of gases in the human lung, with special reference to true diffusing capacity of pulmonary membrane and volume of blood in the lung capillaries. *J. Appl. Physiol.* 11: 290–302, 1957.
17. SAKAI, F., T. MAKASAWA, Y. TAZAKI, T. KANDA, N. KITAI, H. HINO, H. IGRASHI, AND K. ISHII. Evaluation of human cerebral blood volume and hematocrit with single-photon emission com-

puted tomography. *J. Cereb. Blood Flow Metabol.* 3, *Suppl.* 1: S160–S161, 1983.
18. SNASHALL, P. D., S. J. KEYES, B. MORGAN, B. JONES, AND K. MURPHY. Regional extravascular and interstitial lung water in normal dogs. *J. Appl. Physiol.* 49: 547–551, 1980.
19. TURTON, D. R., F. BRADY, W. W. PIKE, A. P. SELWYN, M. J. SHEA, R. A. WILSON, AND C. M. DE LANDSHEERE. Preparation of human serum (methyl-11C)methylalbumin microspheres and human serum (methyl-11C)methylalbumin for clinical use. *Int. J. Appl. Radiat. Isot.* 35: 337–344, 1984.
20. WEIBEL, E. R. *Morphometry of the Human Lung.* Berlin, FRG: Springer-Verlag, 1963, p. 82.
21. WOLLMER, P., C. G. RHODES, R. M. ALLAN, A. MASERI, AND F. FAZIO. Regional extravascular lung density and fractional pulmonary blood volume in patient with chronic pulmonary venous hypertension. *Clin. Physiol.* 3: 241–256, 1983.
22. WOLLMER, P., C. G. RHODES, AND J. M. B. HUGHES. Regional extravascular density and fractional blood volume of the lung in interstitial disease. *Thorax* 39: 286–293, 1984.
23. WOLLMER, P., A. ROZKOVEC, C. G. RHODES, R. M. ALLAN AND A. MASERI. Regional pulmonary blood volume in patients with abnormal blood pressure and flow in the pulmonary circulation. *Eur. Heart J.* 5: 924–931, 1984.
24. WOLSTENHOLME, G. E. W., AND J. KNIGHT. *CIBA Foundation Symposium on: Circulatory and Respiratory Mass Transport.* London: Churchill, 1969, p. 85–95.