Indicator Dilution Measurements of Extravascular Water in the Lungs

CARL A. GORESKY, ROBERT F. P. CRONIN, and BRITA E. WANGEL

From The McGill University Medical Clinic, Montreal General Hospital, Montreal 100, Quebec, Canada

ABSTRACT Multiple indicator dilution studies of the pulmonary circulation were carried out in conscious, resting and exercising, and anesthetized dogs under conditions where there was no pulmonary edema. Labeled red cells, water, and albumin were injected together into the pulmonary artery, and effluent dilution patterns were obtained from the descending thoracic aorta. The product of the mean transit time differences between labeled water and red cells, and the pulmonary water flow was used to estimate extravascular parenchymatous water; and this was expressed as a proportion of the water content of the blood-drained lung at postmortem examination. These estimates of the proportional water content were found to increase with flow, and to approach an asymptotic value. Reconsideration of the flow patterns in capillaries, however, led to the postulate that extravascular water should be calculated, utilizing as the appropriate vascular reference a substance that uniformly labels the water in red cells and plasma, and which is confined to the circulation, rather than a tracer that only labels red cells. The mean transit time of this substance is approximated by the sum of the mean transit times of labeled red cells and albumin, each weighted according to the proportion of the water content of blood present in that phase. The values for lung water content so computed also increased with flow, and appeared to approach an asymptote that corresponded to approximately two-thirds of the wet lung weight. The estimated values for the water space after pentobarbital anesthesia corresponded to the lower values obtained in the resting conscious animals. When the anesthetized animals were also bled, the estimated water space was disproportionately large, in relation to the previous values. These experimental results support the hypothesis that dilutional estimates of the lung water space reflect pulmonary capillary filling; that this filling increases with exercise; and that a relative increase in filling also occurs as part of the response to hemorrhage.

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INTRODUCTION

The morphological structure of the lung is unique. The major part of it is "spongy" tissue that allows free exchange of gases between the blood and the atmosphere by arranging for an intimate contact between capillary blood and alveolar air. The basic element is the alveolus, with a mean diameter of approximately 280 μ, its wall enclosing a dense network of capillaries distributed in the form of continuous hexagons. The mean maximum intercapillary distance in the network is of the order of 9 μ (1). With dimensions of this order of magnitude, all of the water in the tissue phase would be expected to be available for diffusion equilibration with the water in perfused capillaries.

When labeled red cells and labeled albumin (vascular labels) are injected into the pulmonary circulation together with labeled water, the mean transit time of the labeled water is much larger than that of the vascular label. This phenomenon was first demonstrated by Chinard and Enns (2), and later confirmed by Lillienfield, Freis, Partenope, and Morowitz (3). The latter used a lumped model analysis of the transit patterns of labeled water and albumin to estimate pulmonary extravascular water. This lumped analysis rested on the assumption that the tissue concentration of labeled water could be computed from the simultaneous downstream relation between the two outflow curves. Later, reasoning from the more general logic relating transit times and volumes (4), Chinard, Enns, and Nolan (5), Chinard (6), and Ramsey, Puckett, Jose, and Lacy (7) quantitated the excess volume of distribution available to the water label by multiplying the difference between the mean transit times of labeled water and albumin by

the blood flow. This volume was expressed in terms of equivalent milliliters of blood/kg body weight; the average values reported for anesthetized dogs (6, 7) were 3.5 and 4.2 ml/kg. These values represent less than half the weight of water in lungs drained of blood, and thus there is a major discrepancy between the accessible lung water measured in this way and the total lung water (6).

Capillaries have length. The patterns observed at their outflow are reflections of events that occur upstream, and that are removed in time and space from the point of observation. A lumped model analysis of these events therefore becomes inadequate. The only feasible physical way to describe such a system is to use a distributed model system, a system with length explicitly defined. In such a model the red cell in the capillary, the intravascular label, is considered as a concentration wave moving with a certain velocity. If a diffusible label is then introduced into the capillary as an impulse function, it will be distributed into the extravascular space around the capillary by diffusion as well as transported by flow, and the outflow concentration wave will be modified by the interaction of these two phenomena. In the simplest case, treated by Goresky (8), it was assumed that the walls of the capillary present no barrier to diffusion, and that the organ is so well perfused that diffusion equilibration occurs continuously along the length between contiguous vascular and extravascular spaces. The diffusible label then behaves simply as a concentration wave propagating with a velocity less than that of red cells (it travels through a larger space), and hence it is retarded at the outflow in relation to red cells. This concept cannot be applied to a set of dilution curves to test its validity, in a particular organ, without an adequate model of the distribution of capillary transit times. In the case of the liver, Goresky assumed that the variance of transit times in the large vessels is so small that the variation of transit times through the whole organ was essentially confined to the capillaries. The distribution of capillary transit times for diffusible labels could then be shown to be a function of that for red cells (the vascular label), to be the result of a correspondingly slower passage of the diffusible label concentration wave along each capillary (8). When, in addition, the whole of the organ is perfused, the extravascular water content computed from dilution curves will correspond to the water content of the blood-drained organ. The computed value is the product of the difference in transit times of labeled water and the vascular label, and the flow of water (i.e., it represents the product of the excess volume of distribution defined above and the proportion of blood which is water [g/ml]). If there are nonperfused regions in the organ, the computed water content will be expected to correspond only to the region perfused.

In the lungs, the gravitational gradient induces a gradient in perfusion, which increases from above downwards (9, 10). The upper parts are less well perfused. During exercise, the gradient in perfusion tends to disappear, the upper portions of the lungs becoming better perfused (11). The diffusing capacity for carbon monoxide increases with exercise, and the increase has been thought to be dependent on an increase in the filling of the pulmonary capillary bed, an increase in the number of capillaries that are perfused (12).

In this paper, dilution studies of the pulmonary circulation have been carried out with two reference labels (red cells and albumin) and labeled water. The extravascular water is quantitated from the dilution curves and this estimate of the water content is compared to the actual water content of the blood-drained lung. In order to be able to make this comparison, we used dogs as the subjects for these experiments. Since the dilution method quantitates only the extravascular water in contact with perfused capillaries, the dilution estimates of water content should vary with capillary filling. The studies cited above imply that pulmonary capillary filling varies with the pulmonary blood flow, and so the experimental protocols were designed to provide a wide variation in flow under circumstances where there was no pulmonary edema. Conscious dogs were studied, both at rest and at several levels of exercise; and anesthetized animals, with and without bleeding or sympathetic blockade.

In addition, consideration is given to two theoretical problems: (*a*) Are the forms of the dilution curves for water compatible with flow-limited distribution of the label; and (*b*) Which substance or group of substances provides an appropriate vascular reference transit time for the dilutional estimates of extravascular water? We attempt to provide a practical answer to the latter question.

METHODS

Conscious animals. The dogs studied in the conscious state were trained to exercise by walking or running on a motor-driven treadmill at speeds up to 11 km/hr. After training, chronic indwelling catheters were passed into the aorta and main stem pulmonary artery from the neck vessels under pentobarbital anesthesia. The aortic catheter tip was positioned at the level of the diaphragm. The catheters were led out under the skin to the back of the neck where they were covered by a protective collar when not in use. One of us (RFPC) had previously shown that when these catheters are flushed daily with physiological saline, they remain free of thrombus for as long as required, usually a period of two weeks (13). Each animal was fasted overnight and was then studied while conscious and unrestrained. The animal was studied both at rest and at several levels of exercise. In general, two runs were performed on any particular day, and the exercise studies were carried out during the final minute of an 8 min exercise period. The

animal was allowed to recover for at least 3 days before being restudied.

The indicator substances used in these experiments included ^{51}Cr-labeled red cells, tritium-enriched water, and a plasma albumin label (either T-1824, as a label for the dog's albumin, or ^{125}I- or ^{131}I-labeled human serum albumin). The injection mixture was reconstituted to a hematocrit equal to that of systemic venous blood.

The mixture was placed in a calibrated flow-through injection cuvette and, at a prearranged signal, was delivered rapidly with a saline flush into the pulmonary artery catheter (2 mm inside diameter). In the early experiments the output of the injection mixture from the cuvette was recorded with a photocell placed at the exit from the cuvette. From the mean duration of the recorded curve a value for the transit time through the input catheter and the injection duration was calculated. In later experiments the duration of injection of the indicator mixture and flush was recorded and, from a knowledge of the volumes of the catheter, cuvette and connections, and flush, both the mean transit time of the injection mixture through the input catheter and the shortest duration of the bolus of indicator mixture were calculated. In general, 20 ml of flush was used to deliver 1.5 ml of injection mixture, the whole being injected over 2.0 sec. Beginning at the prearranged signal, blood was withdrawn from the aortic catheter via a Sigmamotor finger pump and delivered into a serial collection rack. 36 samples were collected over a suitable time interval (from 18 to 60 sec). The rate of sampling had been previously calibrated and from this rate and the volume of the aortic catheter and collecting system, the mean transit time through the output collection system was calculated. Residual activity in the cuvette and pulmonary artery catheter was ascertained and this was subtracted from the original activity, to yield a corrected figure for the injected activity.

Anesthetized animals. This set of studies was directed towards obtaining information at lower cardiac outputs. Distemper-free animals were selected and anesthetized with pentobarbital (25–30 mg/kg). Catheters were placed and the animal was then studied under one of the following sets of conditions:

(*a*) Continuing anesthesia. Four dogs were studied.

(*b*) Anesthesia plus saline infusion. Three of the four animals studied during continuing anesthesia were given 300 ml of saline intravenously and a second study was performed on them.

(*c*) Anesthesia plus sympathetic blockade. Four animals were given an infusion of saline containing Arfonad (trimethaphan camphorsulfonate) in a concentration of 0.1 mg/ml, in amounts necessary to reduce the arterial pressure to 30–70 mm Hg, before study. These animals generally received 100–150 ml saline.

(*d*) Anesthesia plus bleeding. The cardiac output of the animals was reduced by bleeding the animal from the aortic catheter. The systemic pressure was monitored and the mean pressure was kept above 70 mm Hg. It was noted that bleeding under these circumstances elicited a gross increase in rate and depth of respiration, but that no significant change in heart rate occurred. Four dogs were studied.

Postmortem studies. At the conclusion of a set of experiments the dog was killed and the lungs were dissected out. The trachea was transected four rings above the carina, and the lungs were drained of blood and then weighed. In one instance pneumonia was present and that set of experiments was discarded. In most experiments the lungs were then inflated, air-dried, and finally dried further in a vacuum oven at 105°C for 2 days. The dry weight was recorded and, from this, the total water content was ascertained. In four instances the lungs were dried in the vacuum oven at 45°C for 2 days, before drying at 105°C, in order to ascertain whether the higher temperature produced a large increment in weight loss. Water contents of the plasma and blood were also determined from the difference between wet and dry weights.

Analytical methods. Standards were prepared from the injection mixture by addition, in serial dilution, of blood obtained from the aorta before the collection of samples. An aliquot of sample or standard was diluted with saline, and centrifuged. This was assayed in an automatic dual-channel well-type scintillation–crystal gamma ray spectrometer for gamma rays of appropriate energy. When two gamma emitters were present (^{51}Cr and ^{131}I, or ^{15}Cr and ^{125}I), the sample was counted in two channels and the counts were corrected, using appropriate standards, so that the activity due to each substance was evident. The supernatant was assayed for T-1824 color in a 1 cm microcuvette at 620 mμ in a Unicam SP-500 spectrophotometer. Tritium activity was determined in water isolated from the supernatant by use of a microsublimation method (14), or on the supernatant obtained by alcohol deproteinization of the plasma. Hematocrit values were obtained on arterial blood, using a microcapillary method; these were corrected for trapped plasma.

RESULTS

The primary data to be dealt with were the groups of dilution curves in the aortic stream. In order to provide a basis for comparison among the group the total amount injected of each material was defined as 1 unit, and the outflow patterns were expressed in terms of a fraction of the amount injected/ml of blood (i.e., a reciprocal volume). Fig. 1 illustrates a typical experiment. The outflow fraction/ml for red cells is highest in the first samples; it reaches the highest and earliest peak, and decays most quickly. The values for the albumin label are lower on the upslope; the peak is slightly lower and later, and the downslope decays slightly less

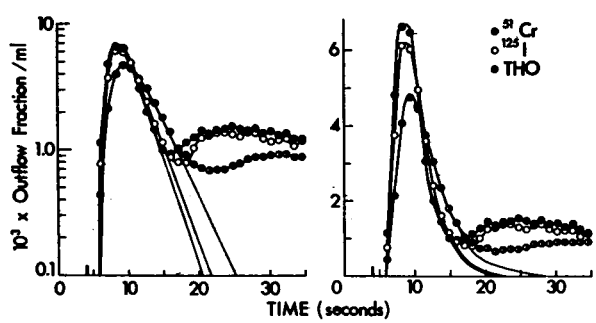

FIGURE 1 A typical set of dilution curves. This set was obtained in an animal which was anesthetized and given Arfonad. *Ordinates*: Outflow fraction per milliliter. A logarithmic scale is used in the left hand panel, and a linear scale, in the right hand panel. *Abscissae*: Time in seconds (the time length of each sampling interval in this experiment is 1.09 sec). The black block indicates the injection time and duration. It has been displaced by a time corresponding to the input and output delays.

quickly. The values for the labeled water are most displaced from those for the red cells; the upstroke of the curve rises least quickly, the peak is delayed and approximately located on the downslope of the red cell label curve, and the curve then falls least quickly.

The numerical values for parameters derived from individual experiments are assembled in Tables I and II. The values for flow, listed in the tables and elsewhere, refer to blood flow. Mean transit times are obtained from raw curves, and are then corrected for instrumental input and output delays by subtracting the appropriate times.

Flows and recoveries. The dilution curves were corrected for recirculation by linear extrapolation of the downslope of a semilogarithmic plot, after the classical manner of Hamilton (15). The values for flow in each experiment were calculated in the usual manner (4). Since the equations used depend upon the assumption that all of the label that is put into the system finally leaves it, the value obtained for flow from each label will cor-

TABLE I

Conscious Animals at Rest and during Exercise

Exp. No.	Body wt	Treadmill rate	Blood flow	$\bar{t}_{RBC}$	$\bar{t}_{Alb}$	$\bar{t}_{THO}$	$\bar{t}_{Alb\ calc}$	Wet lung wt
	kg	*km/hr*	*ml/sec*	*sec*	*sec*	*sec*	*sec**	*g*
1a	13	Rest	56.7	1.72		3.23	2.10	194
1b		2	79.1	2.15		3.90	2.50	
1c		4	76.8	2.07		3.53	2.42	
2a	15	Rest	56.7	4.15		6.10	4.54	209
2b		6	104.8	2.54		4.02	2.92	
2c		2	83.9	3.52		4.99	3.87	
2d		4	87.0	2.35		3.62	2.67	
2e		8	143.7	1.72		2.78	2.03	
2f		10	138.3	1.89		2.97	2.29	
3a	11	3	80.2	2.36		3.75	2.69	159
3b		9	90.3	0.96		2.03	1.27	
3c		Rest	61.1	3.41		5.15	3.76	
3d		9	95.3	2.48		3.69	2.80	
4a	16	6	103.1	1.14		2.18	1.45	163
4b		9	107.1	3.24		4.36	3.55	
4c		Rest	86.1	3.49		4.79	3.82	
4d		3	101.9	2.84		4.01	3.16	
5a	16	3	62.7	5.02	5.48	6.94		215
6a	14	3	62.5	2.88	3.12	4.30		199
6b		12	132.0	2.07	2.39	3.18		
6c		Rest	51.5	3.70	3.97	5.57		
7a	15	2	52.9	4.58	4.97	6.61		209
7b		11	86.8	3.42	3.78	4.76		
7c		6	69.8	4.23	4.65	5.92		
7d		Rest	38.4	4.41	4.87	6.90		
8a	27	Rest	57.8	4.37	4.70	6.19		206
8b		10	152.5	3.10	3.44	3.97		
8c		6	122.6	3.57	3.83	4.53		
9a	18	Rest	49.7	4.59	4.93			167
9b		3	65.1	3.55	3.91			
9c		6	86.4	3.70	4.21			
9d		3	83.2	4.42	4.75			
9e		6	108.9	3.50	3.71			
9f		9	118.3	3.14	3.54			
10a	17	Rest	54.9	5.02	5.49			154
10b		3	68.4	3.31	3.66	4.76		
10c		6	87.8	3.16	3.64			
10d		3	70.3	3.33	3.60			
10e		6	101.1	2.96	3.16			
10f		9	88.9	3.08	3.28			

* $\bar{t}_{Alb}$ was calculated by substituting the appropriate experimental parameters into equations 6 and 7.

TABLE II
Anesthetized Animals

Exp. No.	Treatment during anesthesia	Body wt	Blood flow	$\bar{t}_{RBC}$	$\bar{t}_{Alb}$	$\bar{t}_{THO}$	Lung wt
		kg	*ml/sec*	*sec*	*sec*	*sec*	*g*
1a	None	17	33.8	12.03	14.34	12.48	258
2a		16	35.8	12.78	13.14	14.68	158
3a		18	56.7	10.17	10.73	12.19	174
4a		17	20.3	6.79	7.15	9.15	83
1b	Saline infusion		22.9	13.75	14.40	20.32	
2b			31.4	13.00	13.51	16.44	
3b			51.4	10.39	11.63	12.64	
5	Sympathetic blockade	17	39.7	5.24	5.78	7.66	155
6		23	23.0	7.09	7.48	9.96	169
7		15	25.9	6.51	7.16	9.42	127
8		15	22.4	6.84	7.56	10.40	164
9		18	29.2	4.99	5.49	6.88	131
9a	Graded hemorrhage	16	29.5	7.43	7.76	11.11	211
9b			5.7	28.98	31.50	45.39	
10a		18	30.7	5.81	6.22	10.28	224
10b			20.6	7.82	8.10	12.94	
10c			20.0	8.05	8.37	12.55	
11a		22	59.5	5.31	5.83	7.35	201
11b			14.3	13.37	14.15	19.35	
11c			8.2	18.02	18.61	24.56	
12a		20	32.8	5.31	5.67	8.36	160
12b			14.3	10.23	11.07	16.97	
12c			12.1	12.62		21.00	

respond to that from the others so long as the areas under the curves are equal. For 52 experiments (Tables I and II) the ratio of the area under the labeled water curve to the area under the labeled red cell curve was 0.995 ±0.049 (SD); for 41 experiments the ratio for labeled albumin was 1.017 ±0.033 (SD). Thus all three of the labels yield equivalent values for flow.

Initial measurement of extravascular water, from the dilution curves. In order to relate measurements from one experiment to another, the weight of the lungs, when these had been excised and drained of blood, was taken as a common frame of reference. In these initial calculations, labeled red cells were taken as the vascular label appropriate for use as the reference for calculation of the extravascular water space. The extravascular lung water was expressed in terms of a proportion, P, of the total lung weight. The equation used for these calculations was

$$P = \dot{Q}(\bar{t}_{THO} - \bar{t}_{RBC})\, p, \qquad (1)$$

where $\dot{Q}$ is the blood flow (ml $sec^{-1}g^{-1}$ drained lung), $\bar{t}_{THO}$ is the mean transit time for labeled water (sec), $\bar{t}_{RBC}$ is the mean transit time for labeled red cells (sec), and p is the proportion of an arterial blood sample that is water (g/ml). The bottom panel of Fig. 2 illustrates the relationship between the extravascular water, expressed as a proportion of drained lung weight, and flow, for the experiments done on conscious dogs, and on the anesthetized animals. The points obtained from the conscious unrestrained resting and exercising animals (the filled circles) are distributed in a curvilinear manner. P, the extravascular water expressed as a proportion of total lung weight, increases with flow, but the rate of increase diminishes at high values of flow. Since the proportion of the pulmonary capillaries filled increases with exercise, one would expect that P would approach an asymptote corresponding to the total accessible extravascular water, as total filling of the capillary bed is approached. Similarly, since the estimated water content corresponds only to the perfused part of the lungs, and since the perfused proportion of the capillary bed has been shown to diminish progressively with diminution in flow, the value for P would also be expected to diminish as flow is decreased.

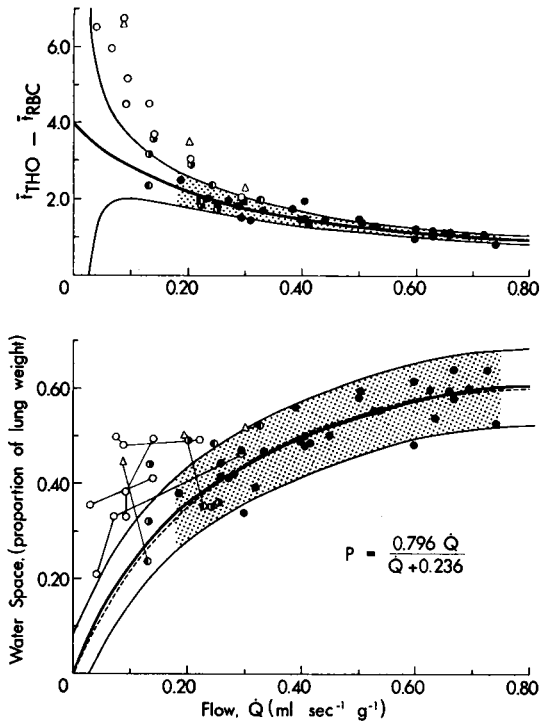

FIGURE 2 *a*. The difference between the mean transit times of labeled water and red cells, as a function of $\dot{Q}$. The heavy line is the locus corresponding to the least squares hyperbola in the bottom panel; and the outer lines correspond to the limits displayed in the lower panel. The shaded area corresponds to the range of the data obtained on conscious animals. The key to the data is the same as that for *b*. (*b*). The relationship between the extravascular water, *P*, expressed as a proportion of drained wet lung weight, and flow per gram of lung weight, $\dot{Q}$. Labeled red cells have been used as the vascular label. The closed circles were obtained from experiments on conscious animals; the left half-closed circles, from those on animals anesthetized only; the open triangles, from those on animals anesthetized and given 300 ml of saline; the right half-closed circles, from those on animals anesthetized, and then given Arfonad; and the open circles, from those on animals anesthetized and bled. The heavy line through the data represents a least squares hyperbola, fitted to the data from the conscious animals; and the outer lines represent a range of ±2 SEE. The dashed line represents a least squares rising exponential. The shading represents the range of the data obtained on conscious animals.

Any number of arbitrary curves could be used to provide a quantitative description for the data. Table III lists those curves with which we have tried to provide a fit to the data from conscious animals (these data were derived from those 29 experimental runs listed in Table I, for which mean transit times of labeled water are available). In each instance the least squares method was used to provide a criterion for goodness of fit, and the necessary calculations were carried out by use of an IBM 360 model 50 digital computer. The number of degrees of freedom was based on the number of observations. Table III lists only the kinds of curve used, and the corresponding values for variance and for the standard error of the estimate (the latter is defined as the standard deviation of the vertical deviations of the data from the least squares line (16)). The usual straightforward analytical expressions were used for the computation of the straight line and of the polynomials through the origin and not through the origin (17). Initial values were derived for the parameters of the rising exponential by use of the graphical procedure described by Perl (18), and these estimates were improved by using an iteration procedure designed on the basis of Newton's method. Similarly, the two parameters of the rectangular hyperbola were first estimated using the Eadie modification of the Lineweaver-Burk method (19), and then improved by use of an iteration procedure with Newton's method. The curvilinear models provide a closely similar fit within the range of the data.

The straight line does not approach an asymptote. The best fit polynominal not through the origin provided the best fit but deviated in a direction opposite to that expected, above and below the range of the data from the conscious animals; and the best fit polynominal through the origin deviated similarly above the range of the data. The two fitted expressions that seemed most consistent with the expectations outlined above were:
(*a*) The rising exponential

$$P = 0.625\ (1 - \exp^{-4.15\dot{Q}}) \qquad (2)$$

where the first numerical parameter is an asymptotic P_{max}, and the second, a constant with dimensions reciprocal to those of $\dot{Q}$; and
(*b*) The rectangular hyperbola

$$P = \frac{0.796\dot{Q}}{\dot{Q} + 0.236} \qquad (3)$$

where the parameter in the numerator is an asymptotic P_{max}, and that in the denominator, K, is that value for

TABLE III

Models Used To Fit the Variation of P Values with $\dot{Q}$, in the Conscious Animals (n = 29)

Model	Variance	SE*
Straight line	0.001665	0.0408
Rising exponential	0.001578	0.0397
Rectangular hyperbola	0.001539	0.0392
Polynomial through (0,0) (optimum of degree 4)	0.001492	0.0386
Polynomial not through (0,0) (optimum of dgree 4)	0.001420	0.0377

* Standard error.

$\dot{Q}$ which corresponds to a P value which is half the asymptote.

The last curve fitted the data for the conscious animals slightly better, and is superimposed upon Fig. 2, as a solid line, with two standard deviations outlined above and below. The area corresponding to the data from conscious animals is shaded. The rising exponential is also illustrated, as a dashed line. There is a gross disparity between the P_{max} values of the two curves. This presumably reflects a lack of uniqueness of fit of either curve. The disparity may have been smaller if higher values for flow could have been attained during exercise.

The values for the animals anesthetized but not treated otherwise lie within the extrapolated lower range; whereas saline infusion in these animals raised the values above this range. Those for the group also subjected to sympathetic blockade tend to lie at the upper border of the range (they received saline, but in smaller amounts); and those for the group which were bled generally lie above the extrapolated lower range, the departure from the range tending to increase with bleeding. The difference between the conscious animals and those anesthetized and bled is portrayed in a striking (albeit exaggerating manner) in Fig. 3, by use of the Eadie modification of the Lineweaver-Burk relation for a hyperbola:

$$\frac{\dot{Q}}{P} = \frac{\dot{Q}}{P_{max}} + \frac{K}{P_{max}} \qquad (4)$$

The values that would correspond to the points for the animals anesthetized and bled are $P_{max} = 0.525$, and $K = 0.027$ ml $sec^{-1}g^{-1}$.

In the upper panel of Fig. 2 the difference between the transit times of labeled water and labeled red cells has been plotted against $\dot{Q}$. The solid line is the locus corresponding to the hyperbola in the lower panel. It is obtained by equating equation 1 to equation 3, by inserting the p value (0.84) corresponding to the average hematocrit (0.40), and then by solving for the difference of the transit times at a given $\dot{Q}$. The difference in transit times for labeled water and red cells, found in the animals anesthetized and bled, lies above the extrapolated lower range corresponding to the hyperbolic relation, as expected.

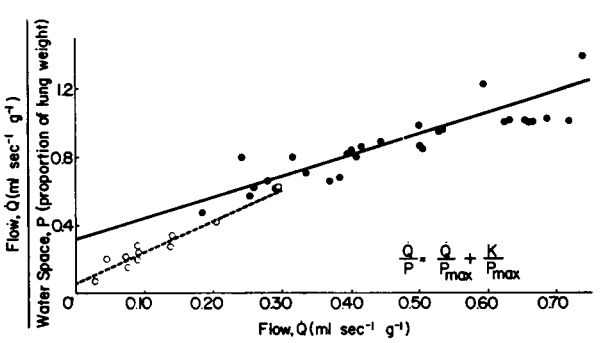

FIGURE 3 The linearized form of the hyperbolic relationship between the dilutional estimates of extravascular water, P, and flow per gram of lung weight, $\dot{Q}$. Once again the closed circles were obtained from experiments on conscious animals; the open circles, from those on anesthetized animals. The correlation coefficient for the closed circles is 0.93; for the open circles, 0.89.

Postmortem studies. The lungs from 23 dogs were excised, and the average lung weight:body weight ratio for these animals was found to be 10.7 ±2.9 (SD) g/kg. The proportional water content of 16 of these lungs was found, by vacuum drying at 100°C, to be 0.782 ±0.023 (SD) g/g. Four of these were previously dried at 48°C for 2 days, and the average incremental loss at the higher temperature was 0.024 g/g.

Changes in the central blood volume with changes in cardiac output. The blood volume from the pulmonary artery to the descending thoracic aorta is provided from the present data by use of the following relation:

$$CBV = \dot{Q} \cdot \bar{t}_{RBC} \qquad (5)$$

where CBV is the central blood volume. Since $\dot{Q}$ is expressed in terms of ml $sec^{-1}g^{-1}$ drained-lung, the values for CBV are thereby normalized for the lung size.

The lower panel of Fig. 4 illustrates the group of values obtained for the experiments on the conscious and the anesthetized and bled animals. There is a general tendency for the cardiopulmonary blood volume to rise with increase in flow. The data obtained from animals during rest and exercise have been divided into two groups—those in which the input duration and pulmonary artery catheter lag were computed from the duration of the saline flush (closed circles) and those in which they were computed from photometric recording of the output from the cuvette (half-filled circles). There is a distinct difference between the two groups. For the whole group the mean regression line is

$$CBV = 1.79\ \dot{Q} + 0.61;\ r = 0.64. \qquad (5\ A)$$

For the flush-timed group the relation is

$$CBV = 2.31\ \dot{Q} + 0.59;\ r = 0.90. \qquad (5\ B)$$

The data from the dogs anesthetized and bled, obtained with use of the flush-timed method, are also illustrated. The regression line for this group is

$$CBV = 2.79\ \dot{Q} + 0.62;\ r = 0.86. \qquad (5\ C)$$

The slope of this line is larger than that for the corresponding flush-timed group of conscious animals. This would indicate that the central blood volume in the animals anesthetized and bled is somewhat higher than it would have been in the conscious animals, for corresponding flow rates.

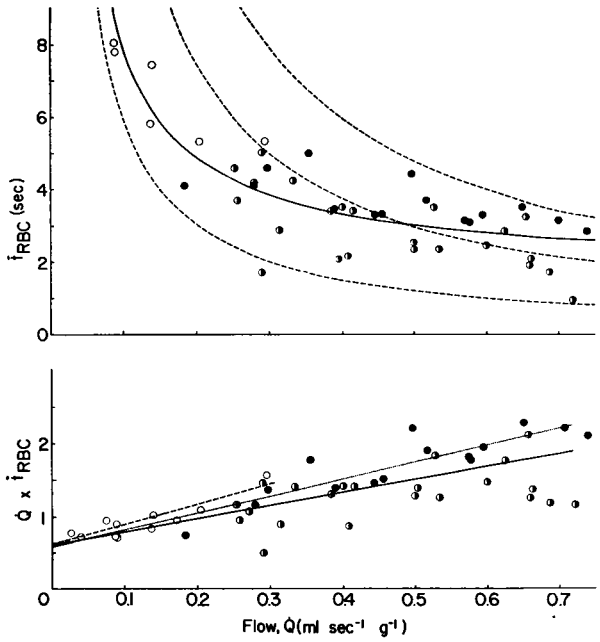

FIGURE 4 *a*. The mean transit times for labeled red cells, corrected for input and output delay, are plotted against $\dot{Q}$. The dotted lines represent the patterns the transit times would have, from above downwards, for cardiopulmonary volumes of 2.4, 1.5, and 0.6 ml/g of drained wet lung. The solid line defines the locus of the transit times corresponding to the solid line in the lower panel, the mean variation in cardiopulmonary blood volume in the resting and exercising conscious animals with $\dot{Q}$. *b*. The cardiopulmonary blood volume per gram of lung is plotted against $\dot{Q}$. The closed circles represent data obtained from experiments on conscious animals in which the input flush was timed, and the half-closed circles, data from experiments on conscious animals, in which the input was photometrically recorded. The open circles represent data from the bled and anesthetized animals. The solid line is the mean squares regression line for the values from all experiments in the conscious animals; the middle line is that for the flush-timed group of conscious animals; and the upper line is that for the flush-timed bled and anesthetized group.

The upper panel of Fig. 4 illustrates how the red cell mean transit time varies with flow; it changes little at the higher flow rates and then begins to rise sharply at lower flow rates. Meaningful interpretation of this kind of a plot cannot be made unless the reader knows the shape of those loci relating transit time to flow in constant volume systems. Three isovolume lines have therefore been superimposed on the upper panel of Fig. 4. The mean relation for the data obtained from the resting and exercising animals crosses the isovolume lines in a manner that demonstrates the increase in cardiopulmonary blood volume with flow.

Change in the extra plasma space in the lungs with flow. Almost all of the red cell plasma albumin label separation that occurs in the central circulation occurs in the small vessels in the lungs (20). The separation, the difference in transit times of labeled albumin and labeled red cells, may be used to quantitate an extra plasma space, a space accessible to labeled albumin but not to labeled red cells:

$$PL = \dot{Q}\,(\bar{t}_{Alb} - \bar{t}_{RBC})(1 - Hct) \qquad (6)$$

where PL is the extra plasma space, expressed in terms of equivalent milliliters of plasma/g drained lung weight, $\bar{t}_{Alb}$ is the mean transit time for albumin, and Hct is the hematocrit of the arterial blood, corrected for trapped plasma. The lower panel of Fig. 4 illustrates values for the extra plasma space, plotted as a function of $\dot{Q}$. The extra plasma space appears to rise linearly as a function of flow. The data from the conscious animals were fitted to a least squares regression line:

$$PL = 0.154\,\dot{Q} + 0.021\,;\; r = 0.68 \qquad (7)$$

This line, together with limits of ± 1 SE of the estimate, is plotted on the lower panel of Fig. 5. The data from all

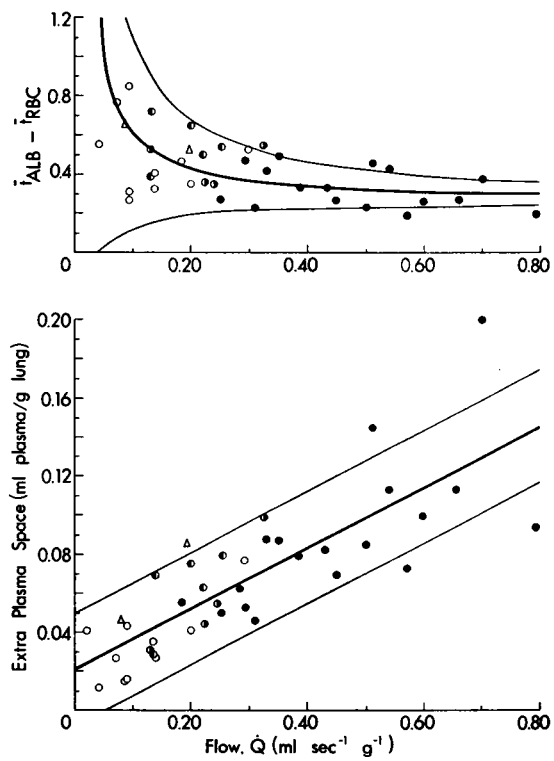

FIGURE 5 The extra plasma space, and the difference in mean transit times of labeled albumin and red cells. *a*. The difference between the mean transit times of labeled albumin and red cells is plotted against $\dot{Q}$. The heavy line corresponds to the least squares regression line in the lower panel; and the outer lines, to the limits displayed on the lower panel; and the outer lower panel. *b*. The extra plasma space (milliliters of plasma per gram of wet lung weight) is plotted against $\dot{Q}$. The heavy line represents the mean squares regression line for the conscious animals, and the outer lines, a range of $\pm$ 1 SEE.

the anesthetized animals, most of which lie below the range of the data obtained from the conscious animals, scatter around the same regression line. The differences between the mean transit times of labeled albumin and labeled red cells are plotted on the upper part of Fig. 5. The relationship corresponding to the regression line of the lower panel was obtained in the following manner: equation 6 was set equal to equation 7; the value corresponding to the average hematocrit (0.40) was inserted, and the relation was solved for the difference in transit times of labeled albumin and red cells at a given $\dot{Q}$. The difference in transit times changes little with changes in $\dot{Q}$, at the higher values of $\dot{Q}$; whereas at low values of $\dot{Q}$, the difference increases sharply as $\dot{Q}$ diminishes.

Are the forms of the dilution curves for labeled water compatible with flow-limited distribution of label? In the introduction it was pointed out that the form of dilution curves could be used to test the hypothesis of flow-limited distribution only if some assumptions were made about the form of the distribution of capillary transit times (the term flow-limited distribution is used once again to describe that situation in which the capillary walls present no barrier to diffusion, and in which the tissue is so well perfused that diffusion equilibration occurs virtually instantaneously between contiguous vascular and extravascular spaces at each point along the length of a capillary). If we adopt the assumption used by Goresky to examine dilution curves from the liver, that there is essentially no variance in the transit times of large vessels (8), then we can proceed to test the hypothesis of flow-limited distribution.

All of the calculations to this point have carried with them the implicit assumption that labeled red cells are the appropriate reference for the vascular space. If we continue with this assumption, then the following considerations may be applied to the data. When a diffusible label is undergoing flow-limited distribution into a space outside the volume accessible to red cells the velocity of propagation of its concentration wave is diminished in relation to that of red cells by the ratio (accessible vascular space: total space of distribution). This results in a proportionate dilution of the diffusible label in the outflow, in comparison with the red cell values. This kind of behavior can be detected by carrying out the following graphical maneuvers (8):

(*a*) The ratio of the peak red cell: peak diffusible label fractional recoveries is found. This test ratio can be equally well obtained from the values at other corresponding times on the curve (e.g., the mean transit times).

(*b*) The diffusible label fractional recoveries are increased by this ratio.

(*c*) The time spent in the vascular space is subdivided into that spent in the large vessels (up to t_0) and that spent in the capillaries (after t_0) by use of this ratio. The quotient (time of the diffusible label peak minus t_0)/(time of the red cell peak minus t_0) is set equal to the ratio in (*a*). This equality defines the numerical value of t_0.

(*d*) The capillary transit times of the diffusible label samples (measured times minus t_0) were decreased by the inverse of the ratio in (*a*); the new times for the diffusible label samples were thus this corrected time plus t_0.

(*e*) The transformed diffusible label curve was then plotted.

If flow-limited distribution of the diffusible label is occurring in relation to the red cell (or vascular) label, the transformed diffusible label curve will superimpose upon that curve (8). This superimposition means that, if the frequency distribution of capillary transit times for red cells is $h(t - t_0)$, the distribution of transit times of the diffusible label is $\frac{1}{a}h\left(\frac{t - t_0}{a}\right)$. The left hand panel of Fig. 6 illustrates the superimposition of the transformed labeled water and labeled albumin curves upon the labeled red cell curve, for the data illustrated in Fig. 1. Goresky has previously shown that, when this technique of superimposition of labeled albumin and labeled water curves is used for a set of outflow dilution curves from the liver, the derived subdivision of the labeled red cell transit times into parts spent in capillaries and large vessels was the same for each diffusible label. In the present experiments, this subdivision differs for the two labels. The labeled red cell capillary transit time derived by use of the labeled water curve is larger than that derived from the labeled albumin curve. This finding implies that some phenomenon besides flow-limited dis-

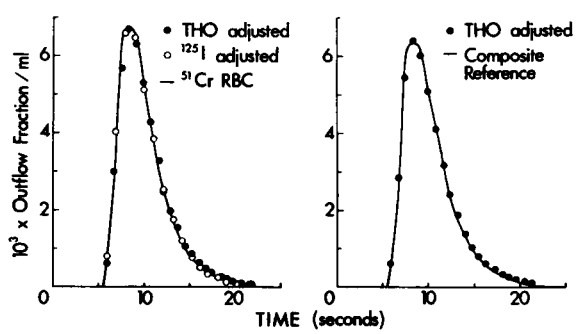

FIGURE 6 The superimposition relations for the data of Fig. 1. *a*. This illustrates the superimposition of the appropriately adjusted labeled water and labeled albumin curves upon the labeled red cell curve. The t_0 for labeled albumin is 5.25 sec; and that for labeled water is 5.90 sec. *b*. This illustrates the superimposition of the appropriately adjusted labeled water curve upon the synthesized composite vascular reference curve. The t_0 for labeled water is now 5.97 sec.

tribution of the plasma label into an immobile space is contributing to its displacement from the red cell curve; that some or all of the red cell–albmin label separation may be hydrodynamic and intravascular in origin.

Goresky and Silverman (21) have shown that the effect of large vessels and of the collecting system is to alter the relationship bewteen the vascular reference and diffusible label curves, in such a manner that the t_0 is decreased. Capillary transit times estimated from raw curves, in the manner illustrated above, are therefore too large. The large vessels and catheters are linear systems and do not destroy the relation between the diffusible and reference label curves that underlies the superimposition maneuver. They will not produce the kind of change in the relation between albumin and water curves which would lead to the observed difference between the t_0 values estimated by utilizing each of these curves. In addition, the large vessel and catheter distortion will not change estimates of the sizes of extravascular spaces of distribution of diffusible substances, based upon transit time differences between diffusible labels and red cells. Raw curves were therefore used both to illustrate the superimposition relationship illustrated above, and to provide estimates of the extravascular water space and the extra plasma space.

Do labeled red cells provide an appropriate reference for the estimation of extravascular water from dilution curves? In the previous section, attempts to fit the dilution curves to a distributed model led to the inference that the red cell-plasma albumin label separation in the lungs was probably not simply the result of flow-limited distribution of the albumin label into an immobile space outside that accessible to red cells. Chinard has found that a large group of substances yield pulmonary outflow patterns which virtually superimpose upon those for labeled albumin (6). The most logical explanation for these two observations is that labeled albumin and the substances which yield identical outflow patterns do not leave the vascular space during one passage through the lungs (i.e., no significant fraction of the label enters the extravascular space of the lungs in this time). If we assume that the separation of red cell and plasma albumin labels during a single passage through the lungs occurs intravascularly, then the appropriate vascular reference label for the estimation of extravascular water would not be labeled red cells; it would, rather, be one which uniformly labels the red cell and plasma water, which is confined to the capillary circulation during one passage through the lungs, and which freely exchanges between red cells and plasma during a single passage. The adoption of this vascular reference will necessarily change the estimates of P; it will necessarily reduce them. It will also resolve the difficulty with the distributed model, illustrated above.

How can the appropriate vascular reference curve for the estimation of extravascular water be defined? There is no known substance which will remain within the capillary circulation, yet freely exchange between the water of the red cells and the plasma. On the other hand, the labeled red cell and plasma albumin curves are available. These two curves are so close to one another that a unimodal curve may be synthesized from them according to the water content of each phase. This curve will not have quite the precise shape of the theoretically ideal reference, but it will be a good approximation, and the value for the mean transit time of this curve will be the same as that of the theoretically ideal reference (22). This curve corresponds to that which would be found for a less ideal substance, for one which travels with the red cells and with the plasma in proportion to the water content, and does not exchange between the two phases. The curve is synthesized in the following manner. If α = the water content of red cells (0.70 g H_2O/ml cells), β = the water content of plasma (0.93 g H_2O/ml plasma), and p = the water content of blood (g H_2O/ml blood), then by definition

$$p = \alpha Hct + \beta(1 - Hct) \tag{8}$$

and

$$C(t)_{Comp} = \frac{\alpha Hct}{p} C(t)_{RBC} + \frac{\beta(1 - Hct)}{p} C(t)_{Alb} \tag{9}$$

where $C(t)_{Comp}$, $C(t)_{RBC}$, and $C(t)_{Alb}$ are the outflow fractions/ml for the composite reference curve, labeled red cells, and labeled albumin, each at the same time, t. Similarly, the mean transit time for the composite reference is

$$\bar{t}_{Comp} = \frac{\alpha Hct}{p} \bar{t}_{RBC} + \frac{\beta(1 - Hct)}{p} \bar{t}_{Alb}. \tag{9 A}$$

Combination of equations 8 and 9 A yields a rather simple expression for the difference between the transit times of the composite reference and labeled red cells,

$$\bar{t}_{Comp} - \bar{t}_{RBC} = \frac{\beta(1 - Hct)}{p} (\bar{t}_{Alb} - \bar{t}_{RBC}).$$

The transit pattern of the composite reference, synthesized according to equation 9, lies between those of labeled red cells and albumin, as expected (see Fig. 7).

The correct expression for the calculation of the proportion of drained lung weight that represents extravascular water, from a set of dilution curves, then becomes

$$P_e = \dot{Q}p (\bar{t}_{THO} - \bar{t}_{Comp}) \tag{10}$$

Fig. 8 illustrates the recalculated values, P_e, for those experiments illustrated in Fig. 2. In those experiments where an albumin label was not included in the injec-

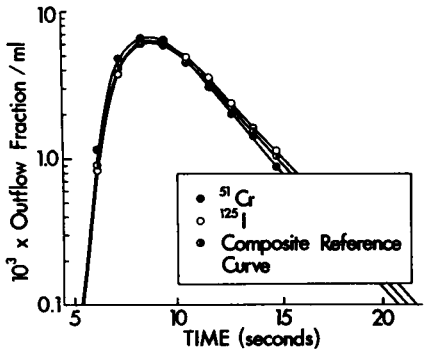

FIGURE 7 The relation between the composite reference and the labeled red cell and albumin transit patterns, for the data illustrated in Fig. 2. The composite reference pattern is synthesized by adding αHct/p, (red cell outflow fraction per milliliter) and $\beta(1 - \text{Hct})/\text{p}$, (albumin outflow fraction per milliliter), for each sample.

tion mixture, the albumin transit times were calculated by use of equations 6 and 7, and these calculated values were used to estimate mean transit times of the composite reference (see Table I).

The values for P_c are displayed as a function of $\dot{Q}$ in Fig. 8. The arbitrary curve models used to fit the data of Fig. 2 were used once again to fit this data. Because the data from the conscious animals and from those anesthetized but not bled appear to belong to the same group, the curves were fitted to the data from both groups (29 conscious and 4 anesthetized animals). The variances and standard errors of the estimate are displayed in Table IV. The two fitted expressions approach-

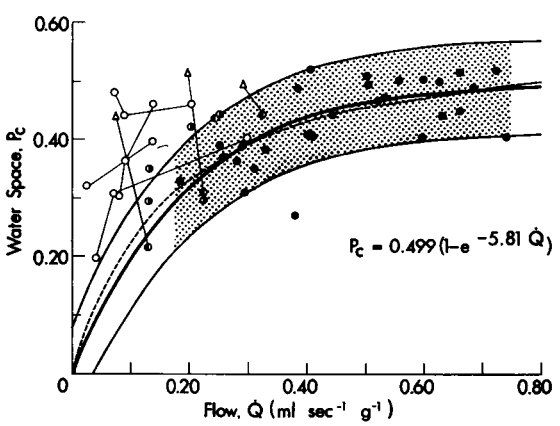

FIGURE 8 The relationship between the corrected estimates of extravascular water, P_c, expressed as a proportion of drained wet lung weight, and flow per gram of lung weight, $\dot{Q}$, when the "composite reference" curve has been treated as the appropriate vascular reference curve. The code for the data points is the same as that used in Fig. 2. The heavy line corresponds to the least squares rising exponential; the outer lines to a range of ± 2 SD about this; and the dashed line to the least squares hyperbola.

TABLE IV

Curves Used To Fit the Variation of P_c Values with $\dot{Q}$, in the Conscious Animals, and in Those Anesthetized only ($n = 33$)

Model	Variance	SE*
Straight line	0.002506	0.0501
Rising exponential	0.001761	0.0420
Rectangular hyperbola	0.001868	0.0432
Polynomial through (0,0) (optimum degree 4)	0.001683	0.0410
Polynomial not through (0,0) (optimum degree 4)	0.001680	0.0410

* Standard error.

ing asymptotic values are:

$$P_c = 0.499\ (1 - e^{-5.81\dot{Q}}) \tag{11}$$

and

$$P_c = \frac{0.611\dot{Q}}{\dot{Q} + 0.166} \tag{12}$$

The asymptotic values have diminished, as expected, but are still considerably different. The form of the best fit curve has also changed somewhat. In the curve fitted by use of the hyperbolic relation this is exemplified by a decrease in the value of K, that $\dot{Q}$ value which corresponds to a half-maximal P_c, from 0.236 to 0.166.

The values for the animals anesthetized and bled continue to be above the extrapolated lower range of the asymptotic relations.

The appropriate transformation of the labeled water curve produces superimposition of the transformed curve upon the composite reference curve. This is illustrated in the right-hand panel of Fig. 6. It should be noted that the composite reference curve in the right hand panel is shifted in relation to the red cell curve of the left-hand panel, so that the values on the upslope are lower, the peak is slightly lower and delayed, and the values on the downslope are higher. The superimposition upon the composite reference is as good as it was upon the labeled red cell curve. We cannot choose either upon the basis of goodness of fit but we can say that the form of the dilution curve for labeled water appears compatible with the hypothesis offered, that of flow-limited distribution of the water label from capillaries which are relatively impermeable to labeled albumin.

DISCUSSION

Variation of the detected extravascular water with flow. In the present study the extravascular water detected by the multiple indicator dilution technique increases with flow, but in a nonlinear manner. The in-

crease is proportionately less, at the upper ranges of flow induced by exercise in the conscious state. When a rising exponential is used to model this change, the values at the heaviest levels of exercise approach their fitted asymptote (see Fig. 8).

The dog running on a treadmill is in a position such that the vertical distance of lung above and below the pulmonary hilus is minimized. In man erect man the depth of lung and the effect of the gravitational gradient are maximized, and there is a gradient in perfusion, increasing from apex to base (9–11). Thus in the exercising dog the gradient in perfusion will be minimized both by position, and by exercise. The pulmonary capillary perfusion would be expected to approach a maximum with exercise; and hence the estimated extravascular water of the present study, which is essentially "seen" from perfused capillaries and which is made up chiefly of the water contained in the endothelial cells, interstitial space, and alveolar septal cells, would also be expected to approach a maximum, the parenchymal extravascular water content of the lung.

The measured pulmonary–diffusing capacity for carbon monoxide is dependent on the proportion of the capillary bed that is perfused (12). In man, the values obtained by steady-state methods increase approximately hyperbolically with oxygen uptake during exercise (23–25); and in dogs the variation of breath-holding values with oxygen uptake could also have been fitted by a relationship of the same form (26). Since there is a relatively linear relationship between oxygen uptake and cardiac output (13), the diffusing capacity varies approximately hyperbolically with flow. Since both the diffusing capacity and the dilution estimates of pulmonary extravascular water reflect capillary perfusion, the similar approximately hyperbolic variation of both of these measurements with flow is not surprising.

In an erect resting conscious man, where the gravitational gradient in perfusion is maximized, the flow through the lungs would not be expected to be grossly above those values that give half maximal estimates of the water space. The variation in dilutional water space with exercise should be more marked.

The effect of bleeding and anesthesia on the estimated extravascular water. The values found for the water space after anesthesia alone corresponded to the range of values found in the conscious animals. However, in those animals studied after bleeding and prolonged anesthesia, the estimated extravascular water approached the asymptotic maximum at much lower flow rates. Values below the maximum were obtained only when the cardiac output had been grossly reduced by bleeding. These findings imply that the pulmonary capillary bed was relatively completely filled.

The disproportionately large values for estimated extravascular water after bleeding are unexpected, since anesthesia alone, of short duration, did not produce similar results. During exercise a sympathetic noradrenergic mechanism reduces the capacity of the postcapillary vessels of the systemic vascular bed, and contributes to the translocation of blood to the lungs (27). Bleeding produces a similar reduction in the capacitance vessels, mediated by the sympathetic nervous system (28). In the present experiments the response to bleeding may have produced a relative shift of blood from the periphery to the lungs. In addition, although pentobarbital anesthesia initially produces tachycardia and hypertension in dogs (29), with longer time, the cardiac output falls (30). Larger doses produce cardiac failure (31, 32), and so the possibility exists that a rise in pulmonary venous pressure had produced increased filling of the pulmonary capillary bed (33). However, the lungs were not wet at postmortem examination immediately afterwards, and the lung weight: body weight ratio of the anesthetized animals which were bled was not different from that of the conscious group, and so it may be deduced that the pulmonary venous pressure was not raised to that level necessary to cause the accumulation of edema fluid (34–36).

One other possible explanation exists: that the findings of an increased water space are artefactual. Oriol, Sekelj, and McGregor have pointed out that coronary recirculation occurs during a relatively early part of the dilution curve when hemorrhagic hypotension has been induced and that it is not possible to exclude this recirculation by linear extrapolation of the downslope on a semilogarithmic plot (37). This phenomenon would lead to a decrease in the value for flow, and to a disproportionate increase in the values for the transit times of labeled water and the vascular reference labels. The transit times encountered in these experiments were large (see Table II) and so it is quite possible that a part of the increase in the water space is artefactual. We cannot satisfactorily assess the quantitative importance of any included recirculation, in the present experiments.

Cardiopulmonary blood volume. The pulmonary circulation is unique in that increased flow is accompanied by the opening up of new channels in the absence of any striking change in pulmonary arterial pressure (38). It would be expected that the increased flow that occurs with exercise would therefore be accompanied by a measurable increase in the cardiopulmonary blood volume. In the present study, where the cardiopulmonary blood volume (pulmonary artery to descending thoracic aorta) has been estimated by the indicator dilution method, the increase is well documented. The volume doubles with a threefold increase in cardiac output, in the conscious animals. This measured increase occurs despite the decrease in the left ventricular component of the volume which Rushmer, Smith, and Franklin have demonstrated in the dog during treadmill exercise (39).

When pulmonary blood volume (pulmonary artery to left atrium) has been determined in man, unequivocal increases have not usually been demonstrated with exercise (40). These studies have usually been carried out in the supine position, and the exercise has been performed with the legs elevated. Both of these factors would be expected to produce more uniform filling of the alveolar capillaries and to minimize the gradient of perfusion. Increase in the pulmonary blood volume with exercise would, however, be expected in man in the erect position, and a preliminary report of its demonstration has appeared (41).

Similarly, it would be expected that where estimates of the pulmonary capillary blood volume have been made by means of measurements of the pulmonary diffusing capacity for carbon monoxide, an effect of position and of exercise would have been encountered. Passive tilting of normal subjects to 60° with heads up produces a decrease in the single breath diffusing capacity and the estimated pulmonary capillary blood volume of about 20% (42). Normal subjects studied at rest and then in the supine position were found to decrease their single breath diffusing capacity by about 10%. The difference found with position at rest was abolished by exercise (43). The increase in the steady-state diffusing capacity with exercise has been shown to be virtually completely due to changes in the pulmonary capillary volume rather than in the membrane component (44); and Johnson and associates have shown by use of the single breath diffusing capacity that the increase in pulmonary capillary blood volume with maximal exercise is of the order of twofold (45).

Red cell-plasma label separation in the pulmonary circulation. The experimental fact of the red cell-plasma label separation in the pulmonary circulation is once again demonstrated in the present study. The transit times for red cells and plasma in the conscious animals reported here are much shorter than those previously reported from anesthetized animals (46, 47), although the transit time differences are comparable.

There is one major discrepancy in the present data that must be resolved. The extra plasma space for the animals bled and anesthetized is disproportionately small in relation to the data for the conscious animals, if the high extravascular water volume is taken to be an index of capillary filling. The major experimental variable that differs under these two circumstances is the total transit time. The velocity along the pulmonary capillaries is much smaller in the bled and anesthetized dogs. If the bulk of the extra plasma space occurs in the capillaries, and if it is intravascular, the above findings lead us to suggest that the red cells undergo a deformation during their passage along the capillary, which makes their transit more rapid than that of plasma, and that the degree of deformation is flow dependent, that it increases as the velocity of flow increases. Such behavior has been demonstrated in a model system, the flow of large liquid bubbles through rigid tubes. The thickness of the film of suspending liquid surrounding the bubbles increases with increasing flow, the bubbles become thinner and more elongated, and, as a result, more of the suspending liquid is bypassed (48). Branemark and Lindstrom have shown that red cells are deformed into thimble-shaped paraboloids (49). Guest, Bond, Cooper, and Derrick (50) have shown that this deformation occurs during free flow in capillaries, that it increases with the velocity of flow, and that when the flow is stopped, the red cells immediately revert to biconcave discs which occupy a wider part of the stream. These observations make the above suggestion a reasonable one.

The extravascular water space. The final assumption used to provide figures for the magnitude of the extravascular water space from the dilution studies was that red cell–plasma albumin label separation occurred within the vessels, that it was not the result of transcapillary exchange. Reasonable arguments were presented for these assumptions but they must be regarded as unproved, for there is no unequivocal way of proving them at present. The tissue perfused by the pulmonary circulation is the parenchymatous fraction of the lung, and so the maximum proportion of the lung tissue which could be "seen" from the pulmonary circulation is the parenchymatous fraction of lung. The two arbitrary asymptotic curves used to fit the dilution data were not unique, and so there is no way of knowing which of the values for the asymptotes, 0.50 and 0.61 g H_2O/g lung corresponds more closely to the parenchymatous fraction of lung tissue. Since the postmortem studies have shown that 78% of the lung tissue is water, these values correspond to parenchymal gravimetric fractions of lung tissue of 0.64 and 0.78.

In the blood-drained lung there was, in addition to parenchymatous extravascular tissue, both nonparenchymatous tissue and some trapped blood. The large vessels of these lungs were empty and the lungs were an exceedingly light pink color when they were expanded, and so the amount of trapped blood (which would have been expected to be present chiefly in the capillaries) could not have been large.

The quantitative anatomical studies of Weibel (1) show that the nonparenchymatous tissue forms 10% of the pulmonary volume. The solid content of this is more than twice as high as that of the parenchymal tissue. However, these anatomical estimates are not good enough to provide an independent anatomical estimate of the proportion by weight of the lung which is parenchyma.

The relation of these studies to studies where pulmonary edema has been induced. Chinard has pointed

out that a threshold difference between vascular pressure and plasma colloid osmotic pressure must be reached before edema formation begins around a given vessel (51); and Levine, Mellins, Senior, and Fishman have demonstrated this threshold phenomenon in the lungs (52). Our studies were carried out at levels below this threshold, at levels in which even capillary filling was incomplete, and there was no evidence for edema formation. Levine and associates found that at low rates of accumulation of edema, the dilution technique appeared to be insensitive. Some of this insensitivity would disappear if their data were calculated in a form utilizing the water content of the blood. These authors have also suggested that the water content of the lungs at postmortem examination should be expressed in terms of g H_2O/g dry lung. This mode of expression appears to be more practical for the study of edema formation than is the use of g H_2O/g wet weight. However, for the purposes of the investigation presented in this paper, wet weight appears more useful.

Implications of this study. The implications of the present study are that indicator dilution measurements of the extravascular water in the lungs reflect to a major extent the degree of capillary filling in the lungs. So long as conditions are not appropriate for pulmonary edema formation, the measurement appears to reflect the water content of the pulmonary parenchymal cells and extracellular spaces in contact with perfused capillaries. Tissues in contact with capillaries that are not perfused are not "seen" by this method. Studies of the permeability of lung capillaries in which the extravascular distribution of the substance being studied is assessed by tissue sampling should therefore contain some information which relates to the degree of capillary filling in the lung at the time of the study.

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