Pulsatile Uptake of CO in the Human Lung

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ABSTRACT The instantaneous uptake of CO in the lungs was measured with a water-filled body plethysmograph in normal man. First, control measurements of plethysmograph pressure were made while the subject held his breath for 7 sec after breathing gas mixtures prepared to bring his alveolar P_{O_2} and P_{CO_2} close to mixed venous levels. Then, CO uptake measurements were made while he held his breath after inhaling the same gas mixtures with added CO (2.0%). The change in lung volume on CO minus the change in lung volume during the control measurement was a measure of the CO uptake in the lungs. Cardiopneumatic changes in lung gas volume were subtracted electrically. All of five subjects showed pulsatile CO uptake. The mean CO uptake was 103 ml/min. A peak uptake of 2.0 (range 1.6–2.3) times the mean uptake occurred 0.3–0.4 sec after the R wave of the EKG and a minimum uptake of 0.4 (range 0.2–0.5) times the mean uptake occurred during the tenth of a second before the R wave of the EKG. These results suggest that pulmonary capillary blood volume is pulsatile during the cardiac cycle.

INTRODUCTION

In 1955, Lee and DuBois (1) showed that blood flow into the pulmonary capillaries¹ was pulsatile during the cardiac cycle. However, it is not known if the pul-

monary capillary blood volume is also pulsatile. The absorption of CO in the lungs is dependent on the diffusing surface of the lung and the pulmonary capillary blood volume. During changes of blood flow, it has been shown that these usually vary in the same direction (2). Therefore, by measuring the rate of CO uptake, one should be able to deduce changes in pulmonary capillary blood volume. Ordinarily, when carboxyhemoglobin is formed in the lung, CO displaces oxygen from the hemoglobin. Since a plethysmograph allows one to measure changes in the lung gas volume, one would not detect the uptake of CO if the CO were replaced by an equal volume of O_2 . However, Roughton (3) has shown that at oxyhemoglobin saturations below 75%, when CO combines with hemoglobin, it does not displace an equal volume of oxygen; in fact, if the oxygen tension is low enough, more O_2 combines with hemoglobin at a given P_{O_2} if carboxyhemoglobin is present (Fig. 1). Therefore, it is possible to measure the uptake of CO in a plethysmograph if the alveolar O_2 tension is reduced to 45 mm Hg or lower, because the O_2 displaced is less than the CO absorbed.

During the measurement of instantaneous uptake of CO using a plethysmographic technique, alveolar concentrations of CO must be high enough to allow sufficient CO uptake so that accurate measurements can be made. However, concentrations which are too high will be dangerous to the subject. In addition, very high concentrations will cause the CO uptake to be flow limited rather than limited by diffusion. That is, if the alveolar P_{O_2} is high enough and/or the transit time of blood through pulmonary capillaries long enough, a back pressure of CO in the blood builds up reducing the amount of CO diffusing from alveoli to blood. If the alveolar concentration is adjusted to produce an uptake of 2 ml CO/cardiac cycle in a subject with a stroke volume of 100 ml (CO capacity equal to 20 volumes/100 ml), the blood leaving the capillaries would have a mean concentration of 10% carboxyhemoglobin. Such

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¹ The term capillaries refers to gas exchange vessels.

FIGURE 1 Oxygen dissociation curves of human blood at pH 7.40 and 38°C, containing various percentages of carboxyhemoglobin. Fig. 1 was reproduced with the permission of Dr. F. J. W. Roughton and The American Physiological Society from Handbook of Physiology, Section 3, Vol. I. 767-825. 1964. Fig. 10 (see reference 3).

a COHb concentration² is safe in normal subjects and the rate of CO uptake turns out to be independent of blood flow. A water-filled body plethysmograph has the necessary sensitivity to measure such a low uptake of gas.

When a subject sits in a plethysmograph, pressure changes within it can be used to calculate changes of the subject's lung gas volume. However, the changes of lung gas volume are caused both by compression or decompression of lung gas and by gas absorption. During the cardiac cycle, mechanical events occur which result in the compression and decompression of lung gas (4). The effects of these mechanical events are called the "cardiopneumatic" changes. We found these changes could be nullified by subtracting a signal proportional to the change in alveolar pressure, which equals mouth pressure with a closed breathing tube, from the signal produced by changes of pressure in the plethysmograph.

Five normal subjects were used in this study. Their physical characteristics are given in Table I.

METHODS

A detailed description of the water-filled body plethysmograph is in preparation.³ After the subject applied EKG

² The mixture used in these experiments was approached gradually and cautiously. 2% CO in low O₂ results in a low arterial oxygen saturation, and therefore the mixture was held in the lungs for only a few seconds of breathholding. During this time, there was a rapid decrease of alveolar Pco toward safer levels. 2% CO in low oxygen would be unsafe for steady-state breathing.

TABLE I
Description of Subjects

Subject	Age	Height	Weight	FRC*
	yr	cm	kg	liters
H. M.	31	176	74	3.3
A. D.	44	190	91	3.3
R. H.	39	180	73	3.6
J. D.	24	174	64	3.6
R. G.	34	179	75	3.3

* FRC, functional residual capacity (BTPS) measured with an air filled body plethysmograph (7).

underwater leads, a nose clip, and face mask, he climbed into the plethysmograph which contained water maintained at 35°C (Fig. 2). He placed lead weights on his knees, sat on a stool, and breathed through a three way valve connected to a Hans-Rudolph valve which opened into a breathing compartment. One orifice of the Hans Rudolph valve was connected via a J valve to a Douglas bag. Another orifice opened to a Haldane tube with a volume of 200 ml which extended to a bag-in-bottle system. The air around the bag was connected to a 13 liter spirometer. Alveolar air samples could be drawn from an opening in the Haldane tube close to the Hans Rudolph valve.

After the plethysmograph was filled with water and the lid lowered onto it, the hydrostatic pressure within it was lowered until ambient atmospheric pressure was at the subject's shoulders. The breathing compartment, previously pressurized for breathing comfort, was then opened to room air and the experiment started.

First, the subtractor circuit was adjusted as follows (5): The subject inhaled room air then held his breath at functional residual capacity. He sealed the plethysmograph by closing the mouthpiece valve and the standpipe opening. Records of EKG, plethysmograph pressure, mouth pressure, and an electrical sum of the plethysmograph pressure signal plus the mouth pressure signal were monitored and recorded. The subject did brief Valsalva maneuvers while an operator adjusted the amplification of the mouth pressure signal until the summed signal was flat during the Valsalva. Fig. 3 shows the mouth pressure signal, plethysmograph pressure signal, and the electrical sum of the two signals during this procedure. Even with optimal adjustment so that the Valsalva produced no deflection, the summed signal continued to decrease because of gas absorption (R effect). In general, gas absorption produces a fall in pressure both in the plethysmograph and at the mouth. This gas exchange was eliminated by inspiration of a gas mixture which brought the alveolar O₂ and CO₂ to a mixed venous level. The mouth pressure amplification which was set during this Valsalva procedure was not changed during subsequent measurements.

A few minutes later, control measurements were obtained as follows: The subject expired to residual volume then inspired a gas mixture from the Douglas bag which contained 12% oxygen in nitrogen. He then expired to residual volume and inspired a mixture of about 10% CO₂ in N₂ from the bag-in-bottle. After expiring to functional residual capacity, he sealed the plethysmograph and held his breath with open glottis (Fig. 4). After about 7 sec, he did a

³ Kawakami, Y., H. A. Menkes, and A. B. DuBois. Manuscript in preparation.

brief Valsalva maneuver, unsealed the plethysmograph, and delivered an expired sample into the bag-in-bottle. Alveolar samples were drawn from the Haldane tube at the beginning of breathholding and after the subject had expired to residual volume into the bag-in-bottle. The CO_2 content of the gas mixture inspired from the bag-in-bottle was varied until the net uptake of gas in the subject's lungs during the breathholding period was minimal. When consistently satisfactory control records had been obtained, an experimental run was made, following the same procedure except that the gas mixture inspired from the bag-in-bottle system contained 2.0% CO and 1% Ne in addition to the CO_2 and N_2 (Fig. 5). The subject was not aware whether the mixture he inspired contained CO or not. In any one day, a subject inspired the single breath CO mixture only twice because of the possible dangers of carboxyhemoglobin accumulation.

On a subsequent day, pulmonary capillary blood flow was determined from measurements of N_2O uptake in the lungs. The subject repeated the same breathholding maneuver as in the CO uptake measurements, inhaling gas mixtures which were the same as before, except that the CO, neon, and about half of the N_2 in the bag-in-bottle had been replaced by N_2O .

Alveolar samples were analyzed for oxygen by a paramagnetic oxygen analyzer. CO and Ne concentrations were determined with a gas chromatograph (6). Alveolar N_2O concentrations were measured with a Liston-Becker infrared N_2O meter (model 16).

The plethysmograph was calibrated by injecting a known volume of water into it when it was filled with water, sealed, and without a subject. Mouth pressure calibration was done with a water manometer.

FIGURE 2 Diagram of water-filled body plethysmograph. Abbreviations: S, rubber stopper; H_1 , pipe from heater, filter, and circulating pump unit; H_2 , pipe to heater, filter, and circulating pump unit; MP, mouth pressure transducer; and PP, plethysmograph pressure transducer.

FIGURE 3 Record obtained during the adjustment of the subtracter circuit which was performed after the subject inspired air. MP, mouth pressure; PP, plethysmograph pressure; PP + K. MP, plethysmograph pressure signal plus an electrically added signal proportional to the mouth pressure. The downward slope of this summed signal is caused by gas absorption (R effect) during the procedure.

Calculations. The uptake of gas in the subject's lungs during breathholding was calculated with the following equation:

$$\Delta V_{LGA} = C \left[\Delta P_s - \frac{\Delta P_s^V}{\Delta P_L^V} \cdot \Delta P_L \right] \quad (1)$$

ΔV_{LGA} , change in volume of lung gas due to absorption or evolution of gas

C, calibration factor used to convert summed signal change to volume change

ΔP_s , change in summed signal during breathholding

ΔP_s^V , change in summed signal during a brief Valsalva maneuver

ΔP_L^V , change in mouth pressure (alveolar pressure) during a brief Valsalva maneuver

ΔP_L , change in mouth pressure during breathholding. C is dimensionless. ΔP_s is calibrated in milliliters. Then ΔV_{LGA} is in milliliters.

The derivation of this equation will be explained.³

Lung volume was calculated using changes in mouth pressure and plethysmograph pressure during a brief Valsalva and applying Boyle's law (7).

When control records were subtracted from the CO and N₂O records, the gas uptake resulting from CO and N₂O absorption, respectively, was obtained. However, when CO or N₂O is absorbed during breathholding in the water-filled body plethysmograph, a small correction must be made for the following effect³. The concentrations of the other gases in the alveoli increase because lung volume shrinks as CO or N₂O is absorbed. Therefore, there will be absorption of the other gases as well. Assuming a lung volume of 3.3 liters, a P_{ACO₂} of 40 mm Hg, and a CO₂ dissociation slope of 2.2 ml/mm Hg for lung

tissue and pulmonary capillary blood (8), when CO or N₂O is absorbed, the amount of gases that go into solution can be calculated.³ When the total uptake of gas is measured, 92% of it is due to CO or N₂O uptake, 6% due to H₂O uptake, and 2% due to CO₂ uptake.

Diffusing capacity was calculated from the following formula (9).

$$DL_{CO} = \frac{V_A}{(P_B - 47)(t_2 - t_1)} \cdot \ln (F_{ACO_{t_1}}/F_{ACO_{t_2}}) \quad (2)$$

DL_{CO} , diffusing capacity in ml/min per mm Hg

V_A , alveolar volume in ml equals lung volume—dead space

$P_B - 47$, barometric pressure minus the pressure of water vapor at 37°C in mm Hg

$t_2 - t_1$, time of breathholding in minutes

$F_{ACO_{t_1}}$ and $F_{ACO_{t_2}}$, fractional concentration of alveolar CO at the beginning and end of breathholding, respectively.

Neon dilution was used to calculate alveolar P_{CO} during inspiration. It was also used to check that alveolar samples were not contaminated before analysis.

Pulmonary capillary blood flow was calculated from the following formula.

$$\dot{Q}_c = \frac{\dot{V}_{AN_2O} \cdot 1.08 \cdot (P_B - 47)}{P_{AN_2O} \cdot \lambda_{N_2O}} \quad (3)$$

$\dot{Q}_c$, pulmonary capillary blood flow in liters per minute

FIGURE 4 Control record in subject R. H. after he inspired gas mixtures prepared to bring his alveolar P_{O₂} and P_{CO₂} close to mixed venous levels. Amplified: PP + K. MP, the summed signal which has been amplified. Notice that the amplified signal is not flat. One reason is the noise which is transmitted from the floor. A second is that the subtracter circuit has been set for a lung volume different from the volume during this particular breathholding period. This is shown by the deflection produced during the Valsalva. A correction for this imperfect subtraction was made using equation 1 when the records were analyzed.

FIGURE 5 CO uptake record in subject R. H. Abbreviations in Fig. 4 are applied to this figure. Notice that there is a very small deflection of the amplified signal during the Valsalva indicating that pressure changes in the lungs had very little effect on the amplified signal during the procedure. The uptake of gas is pulsatile and can be seen to decrease during the period of breathholding.

- $\dot{V}_{AN_2O}$, apparent rate of uptake of N_2O (N_2O record-control) in milliliters per minute
- 1.08, a combination of correction factors including:
- (a) absorption of CO_2 (-2%), because it is concentrated when N_2O is absorbed
 - (b) the evolution of N_2O by lung tissue as P_{AN_2O} decreases ($+8\%$) (10)
 - (c) the evolution of N_2 by the venous blood as it enters the capillaries ($+2\%$) (10)
- PB - 47, barometric pressure minus the pressure of water vapor at $37^\circ C$, in mm Hg
- P_{AN_2O} , mean alveolar pressure of N_2O during the measurement in mm Hg
- λ_{N_2O} , Ostwald solubility coefficient of N_2O in blood (470 ml BTPD/liter blood) (11).

RESULTS

Tables II A and II B contain the results obtained in the five subjects. The gas uptake resulting from CO absorption during four to six cardiac cycles was calculated using two independent methods. First, the amount of gas uptake during the four to six cardiac cycles was calculated from the value of DL_{CO} using formula 2. Results obtained by this method are shown under the 6th column of figures in Table II A. Second, net gas uptake during the four to six cardiac cycles was calculated directly from the slope of the plethysmograph pressure

signal. Control measurements were subtracted from the CO measurements. Results obtained in this way are shown under the 7th column of figures. The measured gas uptake was reasonably close to the calculated gas uptake, even though we would expect some oxygen displacement from hemoglobin at the alveolar oxygen tensions measured.

Gas uptake during each tenth of a second during four cardiac cycles was measured as $\Delta V/\Delta t$ in each subject and normalized, and is shown in Fig. 6. All subjects showed a peak uptake between 0.3 and 0.4 sec after the R wave of the EKG. The maximum uptake was 2.0 (range 1.6-2.3) times the mean uptake. Minimum uptake occurred on the average during the tenth of a second before the R wave of the EKG and was equal to 0.4 (range 0.2-0.5) times the mean uptake. Lower values were obtained occasionally at other times of the cardiac cycle in individual subjects. Fig. 7 shows the results obtained in subject J. D. Fig. 8 shows results obtained in subject R. H. In Fig. 9, N_2O uptake is plotted. The alveolar O_2 and CO_2 were at mixed venous levels. It can be seen that a peak uptake of 1.9 (range 1.8-2.1) times the mean uptake occurred 0.2-0.3 sec after the R wave of the EKG and a minimum uptake of 0.4 (range 0.3-0.5) times the mean uptake occurred during the tenth of a second after the R wave of the EKG.

DISCUSSION

The principal new finding is that the uptake of carbon monoxide in the lungs is pulsatile during the heart cycle, when alveolar O_2 and CO_2 tensions are at mixed venous

levels. We have rejected a number of possible explanations for this. First, if the concentration of alveolar CO had been high enough, the hemoglobin might have become saturated during its passage through the capillaries. In that case, the uptake of CO would have been dependent on the rate of blood flow through the capillaries. Since $P_{A_{CO}}$ in our subjects was never more than 5 mm Hg during the measurements and DL_{CO} was less than 55 ml/min per mm Hg, if the mean blood flow was 100 ml/sec, the hemoglobin would become 23% saturated. At this carboxyhemoglobin concentration and

a P_{O_2} of 40 mm Hg, the back pressure of CO would be less than 0.1 mm Hg. Therefore, it seems unlikely that the rate of blood flow through the capillaries significantly affected the rate of CO uptake. However, there was still the possibility that the transit time of some blood in the capillaries might have been long enough to allow a slowly moving part of the hemoglobin to become saturated. But the DL_{CO} calculated for the first 2 or 3 sec of breathholding was no greater than that for the whole period. This rules out a large stagnant volume.

TABLE II A
Uptake of CO in the Five Subjects

Subject	LV	HR	DL_{CO}	No. of cardiac cycles	Gas uptake		Maximum DL_{CO}		Minimum DL_{CO}		$P_{A_{O_2}}$	$P_{A_{CO}}$	
					Calc.	Meas.	Amount	Time	Amount	Time		1st Sample	2nd Sample
	liters	beats/min	ml/min $\times$ mm Hg		ml	ml/min $\times$ mm Hg	ml/min $\times$ mm Hg	sec after QRS	ml/min $\times$ mm Hg	sec after QRS	mm Hg	mm Hg	mm Hg
A. D.	3.4	76	30	6	7.3	8.1	58	0.3-0.4	-25	0.6-0.7	35	6.5	2.0
	3.0	77	30	6	9.2	7.9	55	0.4-0.5	-3	-0.1-0.0	34	6.4	1.7
	Mean	3.2	77				52*	0.3-0.5	5*	0.0-0.1			
H. M.	3.0	69	47	5	8.0	8.5	125	0.3-0.4	-8	0.7-0.8	35	5.3	0.9
	3.0	73	48	4	7.4	7.5	106	0.4-0.5	-28	0.6-0.7	35	5.5	1.1
	Mean	3.0	71				104*	0.3-0.4	-8*	0.7-0.8			
R. H.	3.9	62	50	4	6.1	8.1	116	0.3-0.4	30	0.0-0.1	38	4.3	0.6
	4.4	60	(50)†	4			(96)†	0.4-0.5	(18)†	-0.2-0.0			
	Mean	4.2	61				98*	0.3-0.4	27*	0.0-0.1			
J. D.	3.1	79	39	4	4.7	5.2	89	0.3-0.4	12	-0.1-0.0	41	5.1	0.5
R. G.	3.5	86	39	4	5.3	7.3	61	0.3-0.4	20	-0.1-0.0	44	4.0	1.3

Abbreviations used: LV, lung volume; HR, heart rate; DL_{CO} , diffusing capacity; Calc., calculated (see text); Meas., measured (see text); $P_{A_{O_2}}$, alveolar oxygen tension during the breathhold maneuvers (mean of initial and final samples); $P_{A_{CO}}$, alveolar CO tension as measured from the 1st sample taken just before the start of breathholding, and the 2nd sample taken just after the completion of breathholding.

* These mean curve figures do not necessarily represent the average of the numbers above them because the time interval in the cardiac cycle for the maximal or minimal DL_{CO} varied from run to run.

† Brackets surround numbers whose alveolar gas samples were lost. Yet the relative maximum and minimum for pulsatility could be measured.

TABLE II B
Uptake of N_2O in the Five Subjects

Subject	LV	HR	$\dot{Q}_c$	Maximum $\dot{Q}_c$		Minimum $\dot{Q}_c$		P_{AN_2O}	Rate of gas uptake
				Amount	Time	Amount	Time		
	liters BTPS	beats/min	liters/min	liters/min	sec after QRS	liters/min	sec after QRS	mm Hg	ml/min
A. D.	3.3	74	8.9	16	0.2-0.3	2.9	0.7-0.8	97	450
H. M.	3.0	84	8.2	15	0.2-0.3	2.4	0.6-0.7	60	290
R. H.	3.8	70	6.6	12	0.2-0.3	2.8	0.0-0.1	85	360
J. D.	2.8	73	6.1	13	0.3-0.4	1.2	-0.1-0.1	54	203
R. G.	3.9	81	7.1	13	0.2-0.3	2.4	0.0-0.1	118	534

Abbreviations used: LV, lung volume; HR, heart rate; $\dot{Q}_c$, pulmonary capillary blood flow; P_{AN_2O} , mean alveolar N_2O tension calculated from measurements of N_2O in gas samples collected just before and after the breathholding period. The N_2O tension was assumed to fall exponentially during the breathholding period. Rate of Gas Uptake was calculated from the difference between the slope of the N_2O record and the slope of the control record.

FIGURE 6 Normalized uptake of CO in the five subjects. Mean values for each tenth of a second are represented by solid circles. This curve does not represent the entire cardiac cycle length for all subjects because the cycle varied from subject to subject.

Since CO uptake depends on the number of red blood cells present in the capillaries, another possible cause for pulsatile CO uptake during the cardiac cycle is that the hematocrit of capillary blood changed during the heart cycle. Blood is not a Newtonian fluid so that its viscosity depends on the size and shape of its conducting vessels. Furthermore, the passage of fluid across capillary walls is dependent on transmural pressure gradients. It is conceivable that when arterial pressure is highest and the diameter of conducting vessels opening into the capillaries is at a maximum, the hematocrit of capillary blood changes. However, we are not aware of experimental evidence to support this view.

A more plausible explanation for the changing rate of CO uptake during the cardiac cycle is that the volume of blood in the capillaries and/or the surface area available for diffusion varies during the cardiac cycle. The determination of DL_{CO} has been used extensively to estimate pulmonary capillary blood volume. Rosenberg and Forster (12) using isolated cat lungs, found that DL_{CO} increased 33% when the intravascular pressure was

FIGURE 7. CO uptake in J. D. Each bar represents the standard error for measurements obtained for four cardiac cycles.

FIGURE 8 CO uptake in R. H. Each bar represents the standard error for measurements obtained for four cardiac cycles.

raised 10 mm Hg above the mean. Karp, Graf, and Nadel (13) who perfused supine dogs with a nonpulsatile pump, found that when arterial pressure was greater than alveolar pressure, which in turn was greater than venous pressure, DL_{CO} increased 5%/mm Hg increase in arterial pressure from a base line level of 14 ml/min per mm Hg. When left atrial pressure was greater than alveolar pressure, increasing pulmonary arterial pressure had less effect on DL_{CO} . Glazier, Hughes, Maloney, and West (14) correlated pulmonary vascular pressures with capillary dimensions, in quickly frozen dog lungs. They were able to correlate the number of red blood cells in the alveolar septum with intravascular pressure. Furthermore evidence to associate rapid changes in DL_{CO} with changes in the pulmonary capillary blood volume was provided by Johnson, Spicer, Bishop, and Forster (2), who found that the transient changes in DL_{CO} seen in normal subjects during a period of exercise were accompanied by parallel changes in capillary blood volume.

There is a good deal of evidence suggesting that capillary volume would not be constant during the cardiac cycle. In 1959, Engelberg, and DuBois (15) esti-

FIGURE 9 Normalized uptake of N_2O in the five subjects. Mean values for each tenth of a second are represented by solid circles. A complete cycle is not shown here because the length of the cardiac cycle varied from subject to subject.

mated that the pulmonary capillaries of rabbit lungs contributed about 15% of the total compliance of the vascular bed. Linderholm, Kimbel, Lewis, and DuBois (16) measured pulmonary artery and wedge pressures and N_2O uptake simultaneously in patients during cardiac catheterization. They were able to estimate the drop from pulmonary artery pressure to pulmonary capillary wedge pressure in relation to the flow of blood into the capillaries and found them remarkably in phase. The longitudinal pressure drop along the pulmonary blood vessels was measured by Brody, Stemmler, and DuBois (17). Using the pulmonary arterial and wedge pressure curve as measured by Lagerlöf and Werkö and shown in Fig. 3 of reference 18, and using the curve shown in Fig. 8 of reference 17, we calculated the intravascular pressure at the midpoint of the pulmonary capillaries. It varied from 7 mm Hg, found 0.6–0.7 sec after the QRS, to 12 mm Hg, found 0.2–0.3 sec after the QRS. Such calculations are only approximate because of difficulties in timing pressures measured in different parts of the vascular bed as well as

the error inherent in calculating resistance during pulsatile flow using measurements obtained during steady flow. However, even these rough calculations suggest that there should be significant changes in capillary volume during the cardiac cycle. In addition, it is logical to suppose that more blood flows into the capillaries during systole than during diastole and more blood flows out of the capillaries during diastole than during systole.

Whether a change in volume of capillaries reflects distention of already open blood vessels, the opening of new blood vessels, or simply a change from flattened to cylindrical shape is open to conjecture. Permutt (19) recently reported work supporting the hypothesis that changes in pulmonary capillary blood volume reflect the opening of new vessels rather than distention of old ones. The anatomic studies of Glazier et al., (14) would tend to support the hypothesis that vessels in zone III, where venous pressure exceeds alveolar pressure, distend when intravascular pressure rises, whereas capillaries in zone I, where alveolar pressure is greater than atrial pressure, open when arterial pressure is raised.

FIGURE 10 Hypothetical pulmonary capillary blood volume during the cardiac cycle. These curves were calculated assuming that the pulmonary capillary blood volume was directly proportional to the rate of CO uptake shown in Fig. 6. Curve 1 is based on the assumption that 1 ml of blood produced 1% of the measured CO uptake, so that the mean pulmonary capillary blood volume would be 100 ml. Curves 2, 3, and 4 are based on mean capillary blood volumes of 50, 33, and 17 ml of blood respectively.

FIGURE 11 Cumulative inflow into the capillaries and outflow from the capillaries during the cardiac cycle. On the ordinate, volume equals integrated inflow or outflow starting arbitrarily 0.1 sec before the R Wave. The top curve represents the integrated capillary inflow curve from data shown in Fig. 9 and data given in Table II B. The shaded area under curve 4 in Fig. 10 represents a hypothetical capillary volume during the cardiac cycle. By subtracting the change in capillary volume computed from this curve from the inflow curve, the cumulative outflow curve 4 in Fig. 11 was calculated. Curves numbered 1-3 in Fig. 11 were calculated in a similar way from curves numbered 1-3 in Fig. 10. The volume out curves, when below 0, are explained by a retrograde reflux from veins to capillaries. We believe curve 3 is closest to the actual outflow curve (see text).

Let us compare the mean CO uptake in this study with that which is to be expected. Our subjects had relatively high single breath-diffusing capacities (mean 41 ml/min per mm Hg). The low alveolar oxygen tension would cause a high diffusing capacity because the concentration of reduced hemoglobin is increased, facilitating uptake of CO by the red cells (3). A second cause for a high diffusing capacity was that our subjects were completely immersed in water, but with a reference level 10 cm below the mouthpiece. Guyatt, Newman, Cinkotai, Palmer, and Thomson (20) found that diffusing capacity increased 16% when subjects

were immersed in water to the neck. Ross, Ley, Coburn, Eller, and Forster (21) found that inflation of a pressure suit over the lower part of the body produced a 25% increase in the diffusing capacity when PA_{O_2} was 125 mm Hg. A third cause of high diffusing capacity in our subjects would be their exposure to 10% CO_2 in the gas mixtures inspired before breathholding. Rankin, McNeill, and Forster (22) found a significant 5% increase in DL_{CO} when 10% CO_2 was added to the inspired CO mixture during a breathholding DL_{CO} measurement. According to Hyde, Lawson, and Forster (23), this action of CO_2 appeared to depend upon its effect on the vessels down-

stream from the pulmonary capillaries, or upon the capillary bed itself including the blood within it because an increase in the P_{CO_2} of the pulmonary arterial blood is relatively ineffective if alveolar P_{CO_2} is not increased as well. We believe these factors, all tending to increase DL_{CO} , adequately account for the high value of DL_{CO} seen in our subjects.

With regard to the pulsatile component of CO and N_2O uptake, since all of our CO uptake measurements were made after a brief exposure to low oxygen, we measured N_2O uptake at low oxygen tensions so that we could compare CO and N_2O uptake under the same conditions. The effect of a short exposure to low oxygen on pulmonary hemodynamics is not known, although it is apparent that the flow pulse in capillaries in Fig. 9 was not blunted after the short exposure to low oxygen.

Differences in pulsatility between the apex and base could conceivably contribute to an exaggerated pulsatility of CO uptake. However, it seemed unlikely that DL_{CO}/V_A inequality contributed significantly to the apparent pulsatility of our measurements because in our subjects the measurements of CO uptake were not done until at least 7–10 sec after the inspiration of CO, and were completed within 15 sec after inspiration. If, during this period, the inequalities of DL_{CO} affected the CO uptake, then the decay of CO should deviate from an exponential line. However, Forster and others (24) have shown that alveolar CO disappearance curves are nearly exponential during the first 20 sec of breathholding, and it isn't until after the first 20–30 sec that a marked upward shift from the exponential decay occurs.

Fig. 10 shows hypothetical pulmonary capillary blood volumes during the cardiac cycle assuming that capillary volume is directly proportional to the rate of CO uptake. Curve 1 assumes that 1 ml of blood contributes 1% of the CO uptake or DL_{CO} . Then the mean capillary blood volume would be 100 ml. Curves 2, 3, and 4 assume that 1 ml of blood contributes 2, 3, and 6% of the CO uptake corresponding to mean capillary blood volumes of 50, 33½, and 16½ ml, respectively.

Fig. 11 shows calculated capillary inflow and outflow which have been integrated during the cardiac cycle. The inflow curve was calculated from the N_2O uptake measurements. The outflow curves, which are numbered, were obtained by subtracting the volume changes shown in the previous figure from the integrated inflow curve. We believe that curve 3 would be closest to the actual pulmonary capillary outflow curve. Although it is not completely satisfactory, it is a compromise between curve 1, which is based on capillary volumes close to those we would expect but which would demand a large tidal backflow of blood from the veins and curve 4 which is based on very small capillary blood volumes but which

would be acceptable with respect to the amount of backflow of blood from the veins.

None of these venous outflow curves are completely satisfactory. They depend on the assumption that capillary volume is directly proportional to the rate of CO uptake. Such an assumption disregards the effects of changing capillary hematocrit, of changing membrane conductance, of stagnant blood in the capillaries, and of unequal ratios of diffusing capacity to lung volume throughout the lung. Furthermore, we measured pulmonary capillary blood volume in two of the subjects, RWH and HAM, while they were in the water-filled plethysmograph. Using the method of Roughton and Forster (25), calculations of capillary volume were 160 and 170 ml respectively. These values would be more compatible with curve 1 than curve 3 in Figs. 10 and 11 but use of curve 1 to calculate venous outflow would result in large retrograde flows greater than left auricular stroke volume. Such a retrograde flow could only occur during tidal surges resembling those found in the Bay of Fundy.

In conclusion, we found definite and large CO uptake changes during the cardiac cycle. These probably reflect large pulmonary capillary blood volume changes, but we cannot be sure of the amount of these volume changes at the present time.

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