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Edward D. Michaelson, … , Marvin A. Sackner, Robert L. Johnson Jr.

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Research Article

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Vertical Distributions of Pulmonary Diffusing Capacity and Capillary Blood Flow in Man

EDWARD D. MICHAELSON, MARVIN A. SACKNER, and ROBERT L. JOHNSON, JR.

From the Biodynamics Branch, U. S. Air Force School of Aerospace Medicine, Brooks Air Force Base, Texas 78235; the Pulmonary Disease Service, Department of Medicine, Wilford Hall U. S. Air Force Medical Center, Lackland Air Force Base, Texas 78236; the Division of Pulmonary Diseases, Department of Medicine, Mount Sinai Medical Center, Miami Beach, Florida 33140; and the Department of Medicine, University of Texas Southwestern Medical School, Dallas, Texas 75235

ABSTRACT In six normal upright subjects, a 100 ml bolus—composed of equal parts of neon, carbon monoxide, and acetylene (Ne, CO, and C_2H_2)—was inspired from either residual volume (RV) or functional residual capacity (FRC) during a slow inspiration from RV to total lung capacity (TLC). After breath holding and subsequent collection of the exhalate, diffusing capacity and pulmonary capillary blood flow per liter of lung volume (D_L/V_A and $\dot{Q}c/V_A$) were calculated from the rates of CO and C_2H_2 disappearances relative to Ne. The means: D_L/V_A = 5.26 ml/min × mm Hg per liter (bolus at RV), 6.54 ml/min × mm Hg per liter (at FRC); $\dot{Q}c/V_A$ 0.537 liters/minute per liter (bolus at RV), 0.992 liters/minute per liter (at FRC). Similar maneuvers using Xenon-133 confirmed that, during inspiration, more of the bolus goes to the upper zone if introduced at RV and more to the lower, if at FRC. A lung model has been constructed which describes how D_L/V_A and $\dot{Q}c/V_A$ must be distributed to satisfy the experimental data. According to this model, there is a steep gradient of $\dot{Q}c/V_A$, increasing from apex to base, similar to that previously determined by other techniques—and also a gradient in the same direction, although not as steep, for D_L/V_A. This more uniform distribution of D_L/V_A compared with $\dot{Q}c/V_A$ indicates a vertical unevenness of diffusing capacity with respect to blood flow ($D_L/\dot{Q}c$). However, the relative degree of vertical unevenness of D_L/V_A compared with $\dot{Q}c/V_A$ can account only in part for previous observations attributed to the inhomogeneity of D_L/V_A and $\dot{Q}c/V_A$. Thus, a more generalized unevenness of these ratios must exist throughout the lung, independent of gravitation.

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INTRODUCTION

Because of gravity, blood flow per unit lung volume ($\dot{Q}c/V_A$) is greater in the lung base than in the apex of normal upright man. There is an approximately linear increase in $\dot{Q}c/V_A$ with respect to the distance down the lung from apex to base (1, 2), and a similar but less marked vertical gradient for ventilation with respect to lung volume ($\dot{V}A/V_A$) (2). Forster, Fowler, Bates, and Van Lingen (3) and Burrows, Niden, Mittman, Talley, and Barclay (4) have concluded that diffusing capacity per unit of alveolar volume (D_L/V_A) is not uniformly distributed in the lung; but how much of this nonuniformity is due to vertical gradients of D_L/V_A is not known. West, Holland, Dollery, and Matthews (5) reported faster clearance rates of inhaled radioactive carbon monoxide from the lung base than from the apex, but the CO clearance rates were dependent upon both regional blood flow and D_L/V_A making the interpretation of their data uncertain. There has been no good way to relate the unevenness of D_L/V_A to the gravitational distribution of blood flow.

Lobar spirometry (6) and, more recently, radioactive xenon techniques (7) have demonstrated that during an inspiratory vital capacity relatively more gas is distributed to the upper lobes during early inspiration, and relatively more to the lower lobes during late inspiration. Previous work has shown that a mixture of helium and carbon monoxide inspired in the early and late parts of an inspiratory vital capacity maneuver gives different values for diffusing capacity (8); and it has been suggested that the results obtained with the two maneuvers reflect the fact that the test gas is predominantly distributed to regions of the lung having different D_L/V_A ratios.

TABLE I

Anthropomorphic Measurements on Subjects

	Age	Weight	Body height	Lung height*	TLC
	yr	*kg*	*cm*	*cm*	*ml*
A. P.	35	79	173	29.5	6540
R. W.	27	86	188	38.7	10500
E. M.	29	66	170	27.7	6780
J. L.	32	93	183	31.3	7050
C. M.	28	122	170	26.9	5420
M. S.	39	95	188	31.9	7050

* Obtained from the PA X ray (apex to mean costophrenic angle) uncorrected for magnification.

The present study employs a similar technique using smaller volumes of test gas and slower rates of inspiration in order to more efficiently localize the test gas mixture to apical or basal lung regions (9, 10). Boli—each containing equal parts of carbon monoxide, acetylene, and neon (CO, C_2H_2, Ne)—were introduced at the beginning of a slow inspiration from residual volume (RV) to total lung capacity (TLC), or at functional residual capacity (FRC) during a similar maneuver. Disappearance rates of CO and C_2H_2 relative to Ne were measured after these two maneuvers. Both CO and C_2H_2 disappearances were faster when the bolus was introduced at FRC. A lung model has been constructed to show the vertical distribution of diffusing capacity and pulmonary capillary blood flow which would be necessary to explain the observed differences in the disappearance rates.

METHODS

The subjects were six healthy, nonsmoking males trained in respiratory maneuvers. The age, weight, body height, vertical lung height, and TLC of these subjects are shown in Table I. Displaceable lung volumes were determined by spirometry. FRC was measured by body plethysmography. Lung height was measured from X rays (72 in) taken at full inspiration as the distance between the lung apex and the costophrenic angles.

Topographical distribution of a bolus of gas introduced during a slow inhalation. In each subject, the vertical distribution in the lung of a 50 ml, 1 mCi bolus of ^{133}Xe was determined after rapid injection of the bolus either at FRC or RV during a slow (0.4–0.6 liter/s) inspiration from RV to TLC with the subject sitting upright. Four probes with 1¼-in diameter sodium-iodide crystals, photomultiplier tubes, and 6-in long cylindrical lead collimators were spaced at 6- to 6.5-cm intervals against the right posterior chest wall. The outputs from the photomultiplier tubes were fed through appropriate discriminating and amplifying circuits, and the count rates recorded on a multichannel Honeywell visicorder (Honeywell, Inc., Test Instruments Div., Denver, Colo.). The ^{133}Xe bolus was alternately introduced at RV or FRC, and count rates were obtained 20 s after full inspiration was reached. This was followed by rebreathing into a shielded polyvinyl chloride bag until the count rates from each probe were constant, and they were recorded at TLC. The distribution of ^{133}Xe boli is shown for each subject in the upper two panels of Fig. 1.

Bolus technique for measuring regional D_L/V_A and $\dot{Q}c/V_A$. These measurements were made in two laboratories, one in Dallas, the other in Miami. Four of the six subjects were studied in both laboratories. The boli ranged in size from 25 to 116 ml. In Dallas, boli containing equal parts of CO, C_2H_2, and Ne were used, and in Miami, boli containing 25% CO and 75% Helium (He) were used. A bolus was rapidly introduced into the center of the inspired stream alternately at either RV or FRC during a slow (0.4–0.6 liter/s) inspiration from RV to TLC. After each bolus, the breath was held at full inspiration for various intervals from 5 to 20 s followed by a forced exhalation. The first 750–1500 ml of exhalate was discarded and the remainder collected in a polyvinyl chloride bag. Sufficient time was allowed between runs for washout of the test gases from the lungs.

The bolus mixture and exhaled samples were analyzed for CO, C_2H_2, Ne, and O_2 by gas chromatography in Dallas

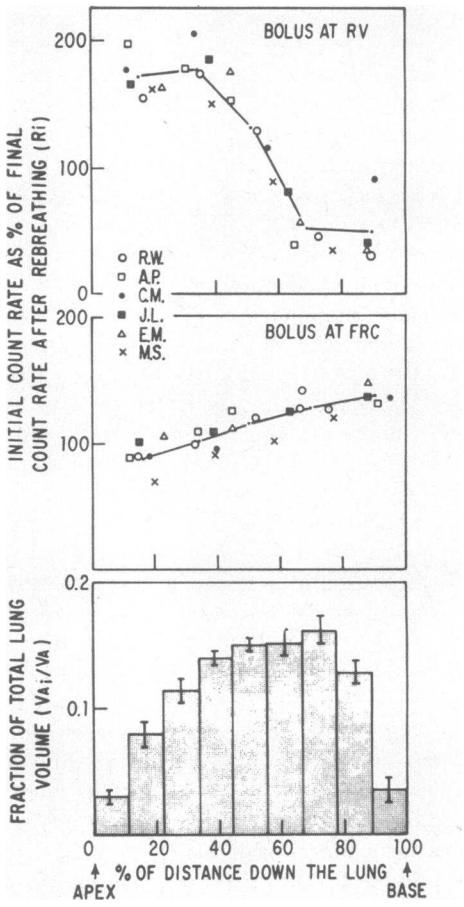

FIGURE 1 The top and middle panels show respectively the vertical gradient in the six subjects at TLC of a ^{133}Xe bolus inspired from RV or FRC where R_i is the ratio of the initial count rate over region i to the count rate over the same region after rebreathing. The solid lines are drawn through the average data at 20% intervals of distance down the lung. The bottom panel shows the average (±1 SD = I) vertical gradient in the six subjects at TLC of fractional lung volume obtained from X rays of the chest.

(11, 12) and for CO and He, respectively, by an infrared analyzer and a He catharometer in Miami. Diffusing capacity per unit of lung volume (D_L/V_A) and pulmonary capillary blood flow per unit of lung and equivalent tissue volume $\dot{Q}c/(V_A + \alpha V\dot{t})$ (13) were computed from the slopes of least squares regression lines of semilog CO and C_2H_2 disappearances (14). α is the Bunsen solubility coefficient for C_2H_2 in tissue at 37°C multiplied by (P_B-47)/760, where P_B is barometric pressure in mm Hg; $V\dot{t}$ is pulmonary tissue volume in milliliters. Since $\alpha V\dot{t}$ is small with respect to V_A, for the sake of simplicity, $\dot{Q}c/(V_A + \alpha V\dot{t})$ will be written as $\dot{Q}c/V_A$ unless otherwise specified.

In two of the subjects, the bolus studies were repeated having the subjects prebreathe 100% O_2 for 5 min before and during each bolus injection.

After the completion of 10–12 measurements on a given subject, blood CO back-pressure was determined by a rebreathing method (15); and the results were used to correct measured values of D_L/V_A.

Topographical distribution of $\dot{Q}c/V_A$ measured with ^{133}Xe. In five subjects, the relative distribution of blood flow at TLC, with respect to lung volume from apex to base, was obtained from regional count rates after the injection of 1 mCi of ^{133}Xe dissolved in saline into the superior vena cava, after the method of Bryan et al. (16).

Lung model. In order to estimate the quantitative significance of our results, we have assumed a range of lung models having different linear distributions of D_L/V_A and $\dot{Q}c/V_A$ from apex to base (Fig. 2). For each model, the differences expected between the measurements of D_L/V_A or $\dot{Q}c/V_A$ after RV and FRC boli of test gas can be calculated if the following are known: (*a*) the distribution of the bolus from apex to base; (*b*) the corresponding distribution of regional lung volume and (*c*) the fraction of the total expirate contributed by each region. The distribution of an inspired bolus was measured by the ^{133}Xe technique as outlined earlier.

In order to estimate regional lung volumes, we have employed PA and lateral 6-ft chest roentgenograms taken at TLC. In these X rays, we have arbitrarily partitioned the thoracic cavity transversely with 10 hypothetical planes of equal vertical distance apart to form 9 lung slices stacked on top of each other from lung base to apex. We have assumed that each lung slice is an elliptical cylindroid (17) and that the volume (V_i) of each slice i can be obtained by further dividing each slice into an even number of smaller slices by an odd number of parallel lines of constant distance (H) apart employing the well known Simpson's rule of integration as follows:

$$V_i = \pi H/12\{W_0L_0 + 4W_1L_1 + 2W_2L_2 + 4W_3L_3 + W_4L_4\}, \quad (1)$$

where $W_0 \cdots W_4$ and $L_0 \cdots L_4$ are the anteroposterior (AP) and lateral diameters of each segment measured from the chest X rays, H is the vertical distance between each segment and the fraction $\pi H/12$ is obtained by multiplying the formula for the area of an ellipse $\{\pi/4W \times L\}$ by $H/3$.

In order to obtain the alveolar volume (V_{A_i}) in each of the nine slices, it is necessary to similarly determine and subtract from V_i the volume of the mediastinum and the volume of the heart or diaphragm which occupy each slice. The average results for the six subjects are shown with standard deviations in the lower panel of Fig. 1. We have assumed that each of these lung regions empties in proportion to its own volume during rapid exhalation (18, 19).

The apparent D_L/V_A which we would expect to measure if any one of the distributions shown in Fig. 2 existed can be calculated, for a lung arbitrarily partitioned from apex to base into nine slices of equal thickness, by the following equation: (See Appendix I for derivation.)

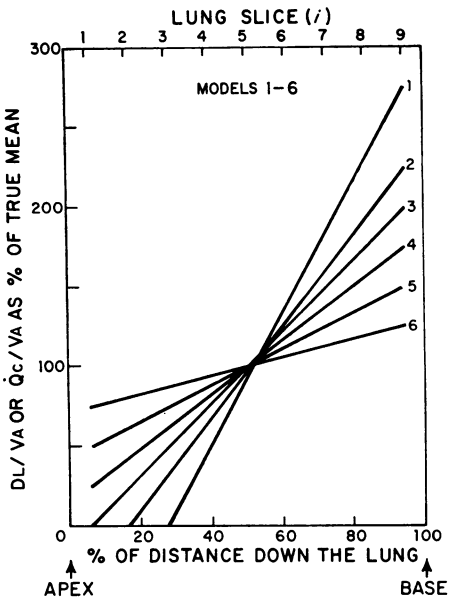

FIGURE 2 Six hypothetical distributions (models 1–6) which were used to calculate the effect of various vertical gradients of D_L/V_A or $\dot{Q}c/V_A$ on the rate of CO or C_2H_2 disappearance with respect to the expected rates of disappearance if D_L/V_A or $\dot{Q}c/V_A$ were uniformly distributed.

$$\text{Apparent } \frac{D_L}{V_A} = \frac{1}{(P_B\text{-}47)t} \times \ln \frac{\Sigma[f_i(F_{ACO_0})_i]}{\Sigma[f_i(F_{ACO_0})_i(F_{ACO}/F_{ACO_0})_i]}, \quad (2)$$

where: f_i = the fraction of expired volume contributed by each slice i to the total exhalate collected after dead space washout between approximately 80% TLC and RV; $(F_{ACO_0})_i$ = the initial concentration of CO in each slice i at the start of breath holding; $(F_{ACO}/F_{ACO_0})_i$ = the alveolar concentration of CO in each slice after breath holding with respect to the initial CO concentration at the start of breath holding in the same slice; t = The time of breath holding in minutes from the end of inspiration to the start of sample collection. The three terms f_i, $(F_{ACO_0})_i$, and $(F_{ACO}/F_{ACO_0})_i$ in equation 2 are estimated as shown below in equations 3 to 6:

$$f_i = V_{A_i}/V_A, \quad (3)$$

where it is assumed that during a fast exhalation, each region contributes to the exhalate in proportion to its initial volume at TLC (18, 19), and where V_{A_i}/V_A is the regional lung volume at TLC in slice i expressed as a fraction of the total lung volume at TLC and is obtained directly from the chest X ray as outlined above.

The term $(F_{ACO_0})_i$ depends not only on the regional dilution of the bolus but also on the amount of CO which disappears during the slow inspiration. The estimate of $(F_{ACO_0})_i$ at the

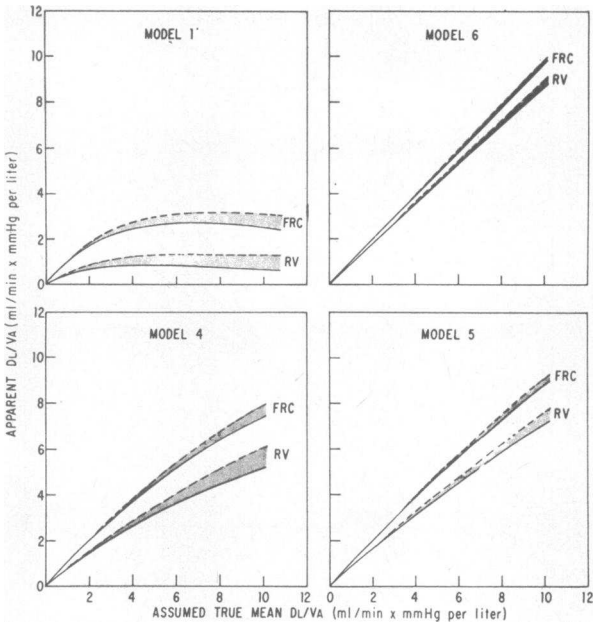

FIG. 3 Solutions for the predicted relationship between apparent (measured) and true DL/VA employing four of the six models for the distribution of DL/VA down the lung, shown in Fig. 2. On the ordinates are the expected values of DL/VA (calculated from Eq. 2) for a bolus given at RV or FRC, compared with various true mean values of DL/VA for the same model. True mean DL/VA is simply the sum of $(DL/VA)_i$, as defined by the model weighted for lung volume (true mean $DL/VA = \Sigma\{(DL/VA)_i \cdot VA_i/VA\}$. Taking into account how DL/VA might change as the lung expands, the broken lines were calculated (Eq. 4) assuming that regional DL increases in proportion to VA as the lung expands (i.e., that DL/VA remains constant); the solid lines were calculated (Eq. 5) assuming that regional DL remains fixed as the lung expands (i.e., that DL/VA decreases). The shaded areas indicate that this range of possibilities remains narrow. For each model, the ratio of apparent DL/VA predicted after a bolus of test gas at RV, to that predicted after a bolus at FRC, varies with the assumed true value for mean DL/VA. The measured value of DL/VA from an FRC bolus can be located on the ordinate of any given model and its horizontal intercept with the FRC curve dropped vertically. The correct model can be determined by trial when the vertical intercept on the RV curve corresponds to the value, on the ordinate, of the measured DL/VA from the RV bolus.

start of breath holding will not be the same, if regional DL/VA varies during inspiration, as it would be if DL/VA remained fixed. Thus, equations 4 and 5 below set upper and lower limits for $(F_{ACO_0})_i$ depending on how DL/VA might change during inspiration.

$$(F_{ACO_0})_i = \left\{\frac{V_{CO_0}/VA}{\Sigma(VA_i/VA \cdot R_i)} \cdot R_i\right\} \cdot \exp\{-t_I(P_B\text{-}47) \cdot (DL/VA)_i\} \quad (4)$$

if it is assumed that DL/VA in each alveolus remains constant during an inspiration from RV to TLC (i.e., that DL increases in proportion to the increase in VA). On the other hand,

$$(F_{ACO_0})_i = \exp\left\{\ln\frac{V_{CO_0}/VA}{\Sigma(VA_i/VA \cdot R_i)} \cdot R_i + \frac{t_I(P_B\text{-}47)(DL/VA)_i}{(V_I/VA)_i} \cdot \ln[1 - (V_I/VA)_i]\right\}, \quad (5)$$

if regional DL remains fixed as the lung expands, so that DL/VA becomes progressively smaller during inspiration.

In equations 4 and 5, R_i = the ratio of the count rate from region i after inspiring a bolus of ^{133}Xe to the count rate from the same region after rebreathing; VI = the volume in milliliters inspired from RV to TLC; $(V_I/VA)_i$ = the volume inspired by each slice i with respect to the total lung volume; V_{CO_0} = the volume in milliliters of CO in the inspired bolus; VA = the alveolar volume in milliliters at TLC; V_{CO_0}/VA = the mean F_{ACO_0} if inspiration had been instantaneous; t_I = the time in minutes from bolus injection to full inspiration; $(P_B\text{-}47)$ = the barometric pressure minus H_2O vapor pressure at 37°C, $(DL/VA)_i$ = the assumed DL/VA in slice i according to the different models (Fig. 2).

Assuming a mean value for DL/VA, the bracketed term on the left in equation 4 represents the dilution of the inspired bolus. The exponent on the right represents the fractional disappearance of CO during inspiration. The derivation of equation 5 is shown in Appendix II.

Finally, in equation 2,

$$(F_{ACO}/F_{ACO_0})_i = \exp\{-(P_B\text{-}47)t \cdot (DL/VA)_i\}. \quad (6)$$

Equations 2 through 6 can be modified for estimating the apparent blood flow per unit of lung and tissue volume $[\dot{Q}c/(VA + \alpha Vt)]$ if $\dot{Q}c/(VA + \alpha Vt)$ were distributed from lung apex to base as in the models shown in Fig. 2, by substituting in those equations α for $(P_B\text{-}47)$, $\dot{Q}c$ for DL, $(VA + \alpha Vt)$ for VA, $F_{AC_2H_2}$ for F_{ACO_0}, and $F_{AC_2H_2}$ for F_{ACO}.

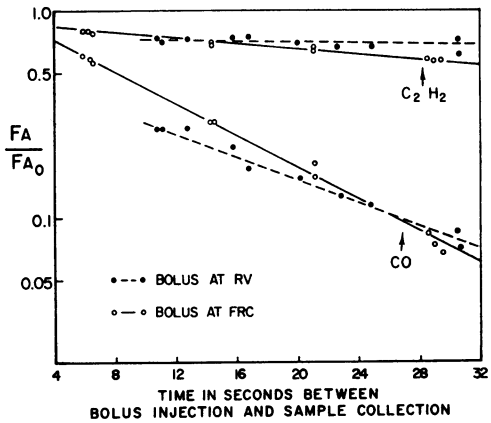

FIGURE 4 Disappearance curves for CO and C_2H_2 in one subject. The straight lines were fitted to the data by the method of least squares. The values for DL/VA and $\dot{Q}c/VA$ are directly proportional respectively to the slopes of CO and C_2H_2 disappearances and are calculated from these slopes as described elsewhere (14).

TABLE II

Breath-Holding Measurements of DL/VA and Q̇c/(VA + αVt) Measured after Inhaling a Bolus of 33% CO, 33% C_2H_2, and 33% Ne (Dallas) or 25% CO and 75% He (Miami)

			Carbon monoxide disappearance				Acetylene disappearance			
			Bolus at RV		Bolus at FRC‡		Bolus at RV		Bolus at FRC‡	
Subject	Date	volume	DL/VA‖	Intercept	DL/VA‖	Intercept	Q̇c/VA¶	Intercept	Q̇c/VA¶	Intercept
Breathing air (average $P_{A_{O_2}}$ = 119 mm Hg)										
A. P.	11/03/69	116	5.23	0.536	6.61	0.965	0.576	0.780	0.923	0.918
	4/29/70	116	5.10	0.581	6.74	0.880	0.220	0.754	0.838	0.850
	*4/07/71	100	4.23	0.850	6.38	1.008				
R. W.	11/05/69	116	4.41	0.515	7.08	1.008	0.429	0.837	1.136	0.932
	4/28/70	116	5.01	0.591	6.30	0.959	0.355	0.839	0.672	0.898
E. M.	2/12/70	116	4.75	0.501	6.27	0.864	0.585	0.818	1.123	0.938
	3/12/70	116	4.49	0.633	6.05	0.892	0.355	0.853	0.789	0.952
	*5/23/70	100	4.30	0.690	6.10	0.810				
	*4/24/71	25	4.05	0.752	4.92	1.004				
C. M.	3/10/70	116	9.15	0.690	9.23§	0.998§	1.435	0.796	1.677§	0.914§
	*6/06/70	100	7.69	0.600	8.17	0.810				
	*4/28/71	25	6.58	0.895	7.14	1.010				
M. S.	*7/22/70	100	5.40	0.950	6.73	1.005				
	1/08/71	116	4.31	0.842	5.35	1.096	0.339	0.844	0.774	0.920
	*4/22/71	30	3.86	0.584	4.96	0.671				
Mean			5.26	0.681	6.54	0.932	0.537	0.815	0.992	0.915
SD			1.50	0.145	1.13	0.109	0.383	0.035	0.114	0.030
Breathing 100% oxygen (average $P_{A_{O_2}}$ = 646 mm Hg)										
A. P.	7/22/70	116	2.44	0.895	3.02	1.074	0.508	0.876	1.087	0.974
R. W.	5/06/70	116	2.02	0.944	2.59	1.232	0.000	0.786	0.516	0.869

* Measurements performed in Miami.

‡ The statistical significance of the difference between individual values of DL/VA or Qc/VA obtained at FRC and corresponding values obtained at RV was determined by Student's *t* test for the difference between the slopes of two regression lines. The significance of the difference between intercepts was also determined by Student's *t* test.

§ These values obtained with an FRC bolus were not significantly different at the $P < 0.5$ level from corresponding results obtained with an RV bolus.

‖ Milliliters/minute × mm Hg per liter.

¶ liters/minute per liter.

Where: α = the Bunsen solubility coefficient for C_2H_2 at 37°C multiplied by (PB-47)/760; Vt = pulmonary tissue volume (13); 760 = 1 atmosphere in mm Hg; $(F_{Ac_2H_{2_0}})_i$ = the initial concentration of C_2H_2 in slice i at the start of breath holding; $(F_{Ac_2H_2}/F_{Ac_2H_{2_0}})_i$ = the concentration in each slice after breath holding with respect to the initial concentration at the start of breath holding in the same slice.

The solution for equation 2 varies with the average DL/VA assumed for the entire lung. Based on the mean distribution of a bolus of test gas injected at RV or FRC after a slow inspiration to TLC (upper two panels of Fig. 1) and the mean distribution of lung volume from apex to base estimated from X rays (lower panel of Fig. 1), the calculated relationships between apparent DL/VA and various values for true mean DL/VA, for four of the six lung models in Fig. 2, have been plotted (Fig. 3). The vertical distribution (Fig. 2) of DL/VA which can best account for the measured values of DL/VA, obtained from RV and FRC boli, can then be determined by fitting these measured values to the graphical solutions of the models shown in Fig. 3. By modifying equation 2 for blood flow, as described earlier, a similar determination of the vertical distribution of Q̇c/VA best explaining the measured values, can be made.

RESULTS

The slopes of the disappearances of CO and C_2H_2 were significantly greater when the bolus was given at FRC than at RV (Fig. 4). Since more of the inspired bolus introduced at RV went to upper lung zones and more of the bolus introduced at FRC went to the lower zones, the faster disappearances of CO and C_2H_2 after the FRC bolus suggest that DL/VA and Q̇c/VA are greater in the lower zones. Individual and mean values of DL/VA and Q̇c/VA obtained on the six subjects breathing air and on the two subjects breathing oxygen are shown in Table II. The values of DL/VA and Q̇c/VA in Table II were calculated from the slopes of least-square regression lines for CO and C_2H_2 disappearances during breath holding, similar to those shown in Fig. 4.

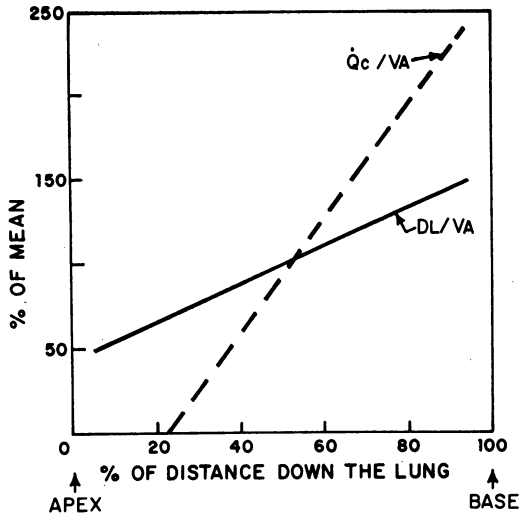

FIGURE 5 Vertical distributions of DL/VA and Q̇c/VA which best satisfy the experimental data in Table II.

Results obtained in four subjects, both in Dallas and in Miami, were similar—indicating that the results are reproducible in different laboratories and were independent of whether He or Ne was used as the inert insoluble reference gas.

The vertical distribution of DL/VA which best explains the differences between the mean values for RV and FRC data in Table II was determined, as outlined above, by fitting these values to the graphical solutions of the model. (See Fig. 3.) A similar fitting of the data to the model was carried out for blood flow.

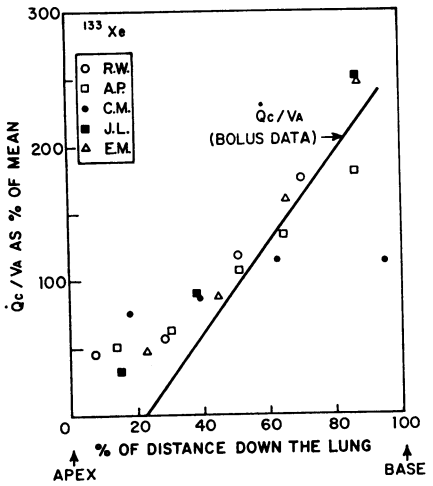

FIGURE 6 Individual data in five subjects for distribution of Q̇c/VA by the ^{133}Xe technique. The solid line is the model distribution best fitting the mean C_2H_2 bolus data. Subject C. M., represented by the closed circles, shows the most uniform distribution of Q̇c/Vφ by the ^{133}Xe technique; he also has the smallest difference between RV and FRC C_2H_2 bolus measurements. (See Table II.)

The distributions of DL/VA and Q̇c/VA which must exist (based on the linear models shown in Fig. 2) to best explain the mean experimental data are shown in Fig. 5. There is a steep gradient for Q̇c/VA increasing from apex to base and a gradient in the same direction though not as steep for DL/VA. In two subjects, A.P. and R.W., the bolus measurements were repeated while the subjects breathed 100% O_2. The model distributions in Fig. 2 best fitting the 100% O_2 data were the same as those fitting the air data in these two subjects. The similar vertical gradient of DL/VA for air and 100% O_2 suggests that both pulmonary capillary blood volume (Vc) and membrane diffusing capacity (DM) are similarly distributed from apex to base.

The C_2H_2 bolus studies appear to show a slightly steeper distribution of Q̇c/VA compared with regional ^{133}Xe measurements of Q̇c/VA (Fig. 6); nevertheless, the increase of Q̇c/VA down the lung estimated by either the bolus or ^{133}Xe method is steeper than that estimated for DL/VA by the bolus method.

DISCUSSION

Considerations of assumptions and possible errors

Changes in regional DL as the lung expands. As discussed in the methods section, interpretation of our results will vary somewhat, depending upon whether we assume that regional DL remains constant or increases as the lung expands. Single breath measurements of DLCO at different lung volumes suggest that the overall DLCO increases as the lung expands (20–23), but such observations of total DL may not be representative of what happens to regional DL during lung expansion. Regional DL may remain constant, whereas effective DL of the whole lung could progressively increase during lung expansion owing to the sequential way in which the lung fills—apical regions with a low DL expanding first, followed later by expansion of basal regions where DL is higher. Thus, there is no solid experimental basis for choosing which assumption is correct; fortunately, the range of error introduced into our calculations by choosing the wrong assumption is small (Fig. 3). However, there are differences in the exponential CO disappearance which should be apparent in our results, depending upon whether regional DLCO remains constant or whether it increases as the lung expands. The intercept obtained by linearly extrapolating the fall of F_{ACO}/F_{ACO_0} back to zero time should be near 1.0 if DL increases in proportion to VA as the lung expands; the intercept should be significantly depressed if DL remains constant as the lung expands. Furthermore, the intercept should be more depressed for measurements made with the bolus inspired from RV compared with FRC. As shown in Fig. 4 for one subject and in Table II for all subjects,

the latter situation predominates—being more consistent with the assumption that regional DL remains relatively constant as the lung expands.

Effect of regional differences in alveolar oxygen tension ($P_{A_{O_2}}$). As a result of the vertical gradient for ventilation and blood flow in the lung of upright man, West (1) calculated that at midcapacity, a 43 mm Hg $P_{A_{O_2}}$ difference must exist between the apex and base. Due to the competition between CO and O_2 for hemoglobin, a higher $P_{A_{O_2}}$ results in a slower uptake of CO (24). Assuming no gradient for DL/VA and assuming generaly accepted normal values for DL, DM, and Vc (24), a 50 mm Hg apex to base $P_{A_{O_2}}$ difference would cause about a 10% fall in DL/VA from apex to lung base. Thus, no more than 10% of the total gradient which we have estimated for DL/VA could be explained by vertical gradients of alveolar oxygen tension.

Initial regional alveolar CO concentrations. If the regional CO concentration were high enough and the blood flow slow enough, CO uptake could be partly flow-limited in that region (25)—causing DL/VA, as measured by the bolus technique, to be spuriously low in the lung apex after an RV bolus. Based on the measured bolus distribution, the highest concentration of CO that could have occurred in the lung apex after a 100 ml bolus of 33% CO at RV would be approximately 0.9%. In order to evaluate the possibility that high enough CO back pressures might be occurring in relatively stagnant apical capillaries to significantly lower apparent regional DL, we have employed smaller boli (25–30 ml) in three of our subjects for comparison with the results using 100 ml boli. The smaller boli would reduce the maximum regional CO concentration to only about 0.2%. The small differences between the results obtained with large and small boli were not statistically significant. From this observation and those reported by Hyde, Marin, Rynes, Karreman, and Forster (25), it seems unlikely that enough CO back pressure occurs in regions of low blood flow to account for a significant portion of the vertical gradient of DL/VA we estimated.

Nonlinear models. The vertical distributions of DL/VA and $\dot{Q}$c/VA derived from the bolus data are based on models which assume a linear distribution from apex to base. At low lung volumes, blood flow is reduced in the lowest portions of the lung (26) and, therefore, the possibility of a nonlinear vertical distribution of DL/VA might exist. From our data, we cannot define the exact shape of the distribution; we can define only the direction and the relative steepness of the gradient for DL/VA and $\dot{Q}$c/VA. Models of an infinite variety of shapes could be derived to explain our results; but the gradients for DL/VA and $\dot{Q}$c/VA in nonlinear models would still have to be in the same general direction as our assumed linear model, with a similar average steepness, if a realistic value for true mean DL/VA is to be maintained.

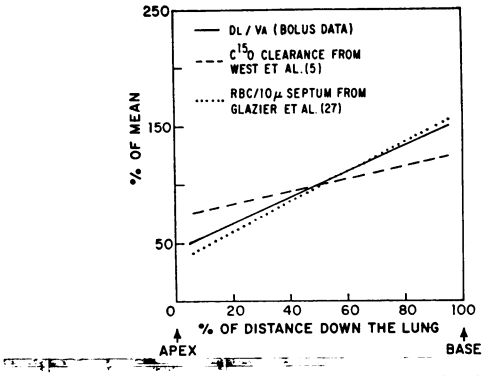

FIGURE 7 Comparison of the vertical distribution of DL/VA best fitting the mean bolus data with the distribution of radioactive CO clearance done at midcapacity (5); and with the anatomically determined distribution of red blood cells (27). The comparison with the anatomical data of Glazier was made assuming that zone I extends 16% of the distance from apex to base and that zone II extends a distance equivalent to the mean pulmonary artery pressure down the lung in centimeters of H_2O.

Comparison with data previously reported by others

Our data suggest that the decrease of DL/VA with distance above the lung base is slightly greater than that derived from the radioactive CO-clearance studies of West et al. (5), but is quite similar to the vertical distribution of red blood cells per unit of alveolar septum determined anatomically by Glazier, Hughes, Maloney, and West (27) in dog lungs (Fig. 7). Our bolus data also show a sharper decrease in $\dot{Q}$c/VA with distance up the lung than has been previously reported by regional perfusion studies with radioactive CO_2 (5) or xenon (2, 16, 26) as well as with ^{133}Xe in our own subjects (Fig. 6). Perhaps the most likely source for the discrepancies in Fig. 6 lies in the interrelationship between the ^{133}Xe measurements and the interpretation of the C_2H_2 bolus measurements. Owing to imperfect collimation and radiation scatter, the ^{133}Xe method tends to underestimate differences in ^{133}Xe concentrations between lung regions; therefore, the unevenness of bolus distribution between lung apex and base and the steepness of the $\dot{Q}$c/VA gradient down the lung tend to be underestimated by the radioactive gas techniques. On the other hand, if the ^{133}Xe method underestimates the bolus separation between lung apex and lung base, we will, as a consequence, tend to overestimate the steepness of the $\dot{Q}$c/VA and DL/VA gradient down the lung from the CO, C_2H_2 bolus data. Based on this argument, the true gradient for $\dot{Q}$c/VA in Fig. 6 probably lies somewhere between that derived from the ^{133}Xe infusion data and from the C_2H_2 bolus

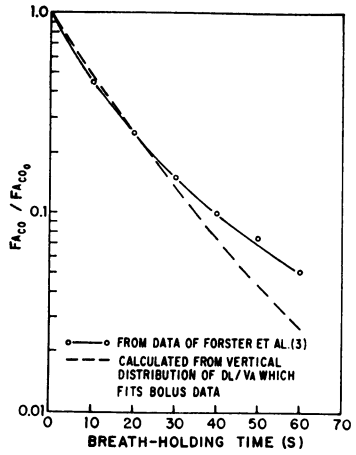

FIG. 8 Comparison of CO disappearance curve obtained from the data of Forster et al. (3) with the CO disappearance curve calculated from the vertical distribution of DL/VA fitting the bolus data.

data since the errors inherent to the two methods are in opposite directions. There are two other possible sources which should be considered for the discrepancies between the ^{133}Xe and the bolus measurements of the $\dot{Q}c/VA$ gradient down the lung.

(*a*) Our bolus experiments require prolonged breath holding which may affect the gradients of DL/VA and $\dot{Q}c/VA$ because of the prolonged absence of respiratory motion, or because of the tendency to perform a Valsalva particularly late in breath holding. The distribution of $\dot{Q}c/VA$ derived from the intra-alveolar partition of xenon, after an intravenous bolus, is not subject to the effects of prolonged breath holding; the intravenous ^{133}Xe bolus enters the lung in a reproducible way only if a Valsalva is not performed.

(*b*) In addition to the well-recognized gravitational distribution of ventilation and blood flow, there is now evidence (28, 29) for a significant gradient of ventilation and blood flow decreasing from center to periphery of the secondary lobule along the isogravity axis. This stratification theory of Read (28) is of interest since it is not taken into consideration in our vertical models. Since there is evidence for a low $\dot{Q}c/VA$ toward the periphery of the secondary lobule (28, 29), it can be speculated that, if a bolus introduced at low lung volumes were primarily distributed to the periphery of a lobule (and to the proximal portion for a bolus inspired from FRC), the apparent $\dot{Q}c/VA$ measured by the bolus technique at RV would be low with respect to that measured with a bolus at FRC—independent of the gravitational distribution of blood flow. Under these circumstances, the intralobular stratification of $\dot{Q}c/VA$ would have an additive effect to that of the vertical distribution of $\dot{Q}c/VA$ on the results of our bolus experiments but would not be measured by the ^{133}Xe method.

In spite of small differences in the steepness of the vertical gradient for $\dot{Q}c/VA$ between the ^{133}Xe and C_2H_2 bolus techniques, the relative differences between subjects are similar by both methods. There is a positive correlation between the vertical gradients for both $\dot{Q}c/VA$ and DL/VA as determined by the bolus technique with lung height ($r = 0.65$); and individual distributions of $\dot{Q}c/VA$ in each subject by the ^{133}Xe method showed a positive correlation with each subject's $\dot{Q}c/VA$ by the bolus method ($r = 0.71$), although the scatter of the data is such that ($0.05 < P < 0.1$) for both correlations. Subject C. M. who was quite obese (Table I) had the most uniform vertical distribution of $\dot{Q}c/VA$ by both the bolus (Table II) and ^{133}Xe (Fig. 6) techniques. This suggests that the bolus method is able to detect variations in the vertical distribution of $\dot{Q}c/VA$ between individuals.

Relation to other measures of uneven distribution

Uneven DL/VA. In 1954, Forster and co-workers showed that during prolonged breath holding, the disappearance of CO from the alveoli was not consistent with a single exponential time constant. They concluded that the upward curvature of the $\ln F_{ACO}$ disappearance curve was most likely the result of uneven DL/VA ratios throughout the lung (3, 30). A similar conclusion was arrived at by Burrows and co-workers using a CO washin-washout technique (4). In order to determine to what extent the vertical unevenness of DL/VA estimated from our data migh explain the findings of Forster et al., we compared CO disappearance curves calculated assuming that DL/VA was distributed as predicted from the average bolus data, with the original CO disappearance curves of Forster et al. (3). There is not sufficient vertical unevenness of DL/VA described by the model to fully explain the upward curvature of the CO disappearance curve measured by Forster (Fig. 8). The discrepancy of our findings with those of Forster could be due to differences between subjects, the effect of an inadvertent Valsalva maneuver by Forster's subjects, or by the existence of more generalized unevenness of DL/VA ratios scattered throughout the lung independent of gravitational force.

Burrows et al. (4) suggested that because of uneven distribution of diffusing capacity, the breath holding technique would slightly underestimate the true DL; Hyde, Rynes, Power, and Nairn (31) calculated that the underestimate would be about 7% which is similar to that obtained from our bolus data.

Discrepancies between steady state and single breath DL. It is unlikely that the degree of vertical uneven-

ness of D_L/V_A required to explain the bolus data can account for the well-known observations that steady-state estimates are less than single breath at rest, since the vertical distribution of ventilation ($\dot{V}_A$) (1, 5) with respect to lung volume ($\dot{V}_A/V_A$) is quite similar to the vertical distribution of D_L/V_A. Therefore, the bolus data are consistent with previous calculations (32) which suggest that a more generalized unevenness of $\dot{V}_A/D_L$ would be necessary to account for discrepancies between single breath and steady-state methods.

Uneven $D_L/\dot{Q}c$ or uneven red cell transit times. Estimates in two of our subjects of CO disappearance by the bolus technique while breathing 100% oxygen as well as air indicate that both membrane diffusing capacity with respect to lung volume (D_M/V_A) and V_c/V_A decrease proportionately from lung apex to base. If regional diffusing capacity is proportional to regional Vc, then our results confirm that a vertical unevenness of red cell transit times must exist with red cells at the apex almost stagnant. This is supported by several lines of evidence. First, the frozen lung studies (27) which show red cells to be present in capillaries under zone I conditions where alveolar exceeds arterial pressure and no flow occurs. Secondly, studies by Glaister (33) using [^{125}I]-polyvinylpyrrolidone and ^{133}Xe show that pulmonary blood volume is more evenly distributed than blood flow from apex to base. Thirdly, recent studies of the pressure-volume characteristics of the pulmonary capillary bed in isolated dog lungs (34) indicate that an alveolar pressure which exceeds capillary blood pressure cannot expel all the blood from lung capillaries; thus, even under zone I conditions, Vc and D_L do not fall to zero.

According to our measurements, as well as those of West et al. (5), the vertical increase in blood flow from lung apex to base is steeper than the vertical increase of D_{LCO}. This situation, as alluded to earlier, will create an uneven distribution of $D_L/\dot{Q}c$ or red cell transit times from apex to base. Calculations elsewhere (31, 32) have indicated that the degree of unevenness in $D_L/\dot{Q}c$ caused by these different vertical gradients is grossly insufficient to explain the observed discrepancies between $D_{L_{O_2}}$ and breath-holding D_{LCO} at rest. A more generalized unevenness of red cell transit times throughout the lung must exist independent of gravitation.

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APPENDIX I

Derivation of Equation for Apparent D_L/V_A (Equation 2)

In each slice i of a nine slice model lung, the dilution of neon (Ne) inspired in the bolus is represented by the ratio $(F_{A_{Ne}}/F_{I_{Ne}})_i$, where $(F_{A_{Ne}}/F_{I_{Ne}})_1$ is the top slice, $(F_{A_{Ne}}/F_{I_{Ne}})_2$ the second slice, and so forth down to $(F_{A_{Ne}}/F_{I_{Ne}})_9$ representing the slice at the base of the lung. $(F_{A_{Ne}})_i$ is the initial Ne fraction in slice i and is a different value for each slice in accordance with the different dilutions. $F_{I_{Ne}}$ represents the inspired Ne fraction which is the same for each slice. During exhalation at the end of breath holding, each slice i will contribute a fraction f_i to the total exhalate collected after dead space washout. Thus, if the volume of the total exhalate from 80% TLC to RV is VE, the volume of Ne contributed to the exhaled sample from slice i will be $f_i V_E (F_{A_{Ne}})_i$, and the total volume of neon (V_{Ne}) in the exhalate will be as follows:

$$\begin{aligned} V_{Ne} &= f_1 V_E (F_{A_{Ne}})_1 + f_2 V_E (F_{A_{Ne}})_2 + \cdots + f_9 V_E (F_{A_{Ne}})_9 \\ &= V_E \{ f_1 (F_{A_{Ne}})_1 + f_2 (F_{A_{Ne}})_2 + \cdots + f_9 (F_{A_{Ne}})_9 \}, \end{aligned} \tag{1a}$$

or in more compact form:

$$V_{Ne} = V_E \sum_{i=1}^{i=9} f_i (F_{A_{Ne}})_i. \tag{2a}$$

The fractional concentration of Ne is the composite exhalate ($F_{A_{Ne}}$) will be as follows:

$$F_{A_{Ne}} = V_{Ne}/V_E = \sum_{i=1}^{i=9} f_i (F_{A_{Ne}})_i. \tag{3a}$$

Therefore, the apparent dilution of neon in the lung calculated from the exhalate would be as follows:

$$F_{A_{Ne}}/F_{I_{Ne}} = \frac{\sum_{i=1}^{i=9} f_i (F_{A_{Ne}})_i}{F_{I_{Ne}}} = \sum_{i=1}^{i=9} f_i (F_{A_{Ne}}/F_{I_{Ne}})_i, \tag{4a}$$

where $(F_{A_{Ne}}/F_{I_{Ne}})_i$ represents the dilution of inspired neon in slice i.

The fractional concentration of CO in the lung at the start of breath holding ($F_{A_{CO_0}}$) assuming inspiration was instantaneous, will be estimated from the ratio $F_{A_{Ne}}/F_{I_{Ne}}$ measured in the composite exhalate as follows:

$$\text{Estimated } F_{A_{CO_0}} = (F_{A_{Ne}}/F_{I_{Ne}}) \times F_{I_{CO}}, \tag{5a}$$

thus,

$$\text{Estimated } F_{A_{CO_0}} = F_{I_{CO}} \sum_{i=1}^{i=9} f_i (F_{A_{Ne}}/F_{I_{Ne}})_i. \tag{6a}$$

$F_{I_{CO}}$ represents the inspired CO fraction which is the same for each slice. By a similar course of reasoning, the CO fraction ($F_{A_{CO}}$) in the composite exhalate will be as follows:

$$\text{Estimated } F_{A_{CO}} = \sum_{i=1}^{i=9} f_i (F_{A_{CO}})_i, \tag{7a}$$

which is the same as saying that:

$$\text{Estimated } F_{ACO} = f_1(F_{ACO})_1 + f_2(F_{ACO})_2 + \cdots + f_9(F_{ACO})_9. \quad (8a)$$

Consequent to all of this, the final estimate of the ratio F_{ACO_0}/F_{ACO} which will be obtained by analyzing the exhaled sample will be found by combining equations 6*a* and 7*a*, as follows:

$$F_{ACO_0}/F_{ACO} = F_{ICO}\frac{\sum_{i=1}^{i=9} f_i(F_{ANe}/F_{INe})_i}{\sum_{i=1}^{i=9} f_i(F_{ACO})_i}. \quad (9a)$$

Dividing the numerator and denominator of the righthand side of equation 9*a* by F_{ICO} gives

$$F_{ACO_0}/F_{ACO} = \frac{\sum_{i=1}^{i=9} f_i(F_{ANe}/F_{INe})_i}{1/F_{ICO}\sum_{i=1}^{i=9} f_i(F_{ACO})_i}. \quad (10a)$$

Since F_{ICO} is the same for each slice

$$F_{ACO_0}/F_{ACO} = \frac{\Sigma f_i(F_{ANe}/F_{INe})_i}{\Sigma f_i(F_{ACO}/F_{ICO})_i}. \quad (11a)$$

Furthermore,

$$(F_{ANe}/F_{INe})_i = (F_{ACO_0}/F_{ICO})_i,$$

so that

$$F_{ACO_0}/F_{ACO} = \frac{\Sigma f_i(F_{ACO_0}/F_{ICO})_i}{\Sigma f_i(F_{ACO}/F_{ICO})_i}. \quad (12a)$$

Since $(F_{ACO}/F_{ICO})_i$ can be found as the product $(F_{ACO}/F_{ACO_0})_i\ (F_{ACO_0}/F_{ICO})_i$

$$F_{ACO_0}/F_{ACO} = \frac{\Sigma f_i(F_{ACO}/F_{ICO})_i}{\Sigma f_i(F_{ACO}/F_{ACO_0})_i(F_{ACO_0}/F_{ICO})_i} \quad (13a)$$

and,

$$F_{ACO_0}/F_{ACO} = \frac{\Sigma f_i(F_{ACO_0})_i}{\Sigma f_i(F_{ACO})_i(F_{ACO}/F_{ACO_0})_i} \quad (14a)$$

and the apparent D_L/V_A (Equation 2) is

$$\text{Apparent } D_L/V_A = \frac{1}{(P_B\text{-}47)t} \times \ln\frac{\Sigma[f_i(F_{ACO_0})_i]}{\Sigma[f_i(F_{ACO_0})_i(F_{ACO}/F_{ACO_0})_i]}.$$

By a similar course of reasoning, equation 2 can be modified to estimate the apparent $\dot{Q}c/(V_A + \alpha Vt)$ down the lung if appropriate substitutions are made as shown in the paragraph following equation 6 in the text.

APPENDIX II

Derivation of Equation for $(F_{ACO_0})_i$ Assuming that D_L Remains Constant as the Lung Expands (Equation 5)

Assume that a bolus volume of carbon monoxide, V_{CO_0}, is inspired into an initial lung volume, V_{A_0}, followed by a slow constant rate of inspiration such that the lung volume, V_A, at any time t after the start of inspiration is $V_{A_0} + bt$; b = a constant indicating the rate of volume increase in milliliters per minute. All volumes are in milliliters and time in minutes. As inspiration proceeds, the volume of CO remaining in the lung progressively decreases owing to CO uptake by blood. If V_{CO} is allowed to represent the volume of CO remaining at any time t then the rate of decrease in V_{CO} is given by the following equation:

$$dV_{CO}/dt = -F_{ACO}(P_B\text{-}47)D_L, \quad (15a)$$

where F_{ACO} = alveolar CO fraction at time t; P_B = barometric pressure in mm Hg; 47 = water vapor tension; D_L = diffusing capacity of the lung in (milliliters/minute) per mm Hg. However, $F_{ACO} = V_{CO}/V_A$ so that

$$dV_{CO}/dt = V_{CO}/V_A(P_B\text{-}47)D_L. \quad (16a)$$

But since during a slow inspiration, $V_A = V_{A_0} + bt$

$$dV_{CO}/dt = V_{CO_t}/(V_A + bt)(P_B\text{-}47)D_L, \quad (17a)$$

Rearranging and integrating

$$\left|\ln V_{CO}\right|_{V_{CO_0}}^{V_{CO}} = \left| -\frac{(P_B\text{-}47)}{b} D_L \ln(V_{A_0} + bt)\right|_0^{t_I}, \quad (18a)$$

where t_I is the time of inspiration. Thus,

$$\ln(V_{CO}/V_{CO_0}) = -(P_B\text{-}47)D_L/b \ln(V_{A_0} + bt_I)/V_{A_0}. \quad (19a)$$

Since $bt = V_I$ = volume inspired during the time of inspiration, t_I, and $V_A = V_{A_0} + V_I$ = lung volume at the end of inspiration, then

$$\ln(V_{CO}/V_{CO_0}) = -\frac{t_I(P_B\text{-}47)}{V_I} D_L \ln\frac{V_A}{V_A - V_I} \quad (20a)$$

or

$$\ln(V_{CO}/V_{CO_0}) = \frac{t_I(P_B\text{-}47)}{V_I/V_A}\cdot\frac{D_L}{V_A}\ln\left(1 - \frac{V_I}{V_A}\right). \quad (21a)$$

Rearranging,

$$\ln V_{CO} = \ln V_{CO_0} + \frac{t_I(P_B\text{-}47)}{V_I/V_A}\cdot\frac{D_L}{V_A}\ln\left(1 - \frac{V_I}{V_A}\right), \quad (22a)$$

and taking the exponential of both sides

$$V_{CO} = \exp\left[\ln V_{CO_0} + \frac{t_I(P_B\text{-}47)}{V_I/V_A}\cdot\frac{D_L}{V_A}\ln\left(1 - \frac{V_I}{V_A}\right)\right]. \quad (23a)$$

Dividing both sides by the alveolar volume at the end of inspiration (V_A),

$$\frac{V_{CO}}{V_A} = \frac{1}{V_A}\exp\left[\ln V_{CO_0} + \frac{t_I(P_B\text{-}47)}{V_I/V_A}\cdot\frac{D_L}{V_A}\ln\left(1 - \frac{V_I}{V_A}\right)\right] \quad (24a)$$

but $V_{CO}/V_A = F_{ACO_0}$ at the start of breath holding. Thus,

$$F_{ACO_0} = \exp\left[\ln\frac{V_{CO_0}}{V_A} + \frac{t_I(P_B\text{-}47)}{V_I/V_A}\cdot\frac{D_L}{V_A}\left(1 - \frac{V_I}{V_A}\right)\right] \tag{25a}$$

or in a regional lung slice i the CO fraction at the start of breath holding $(F_{ACO_0})_i$ is given by equation 5.

$$(F_{ACO_0})_i = \exp\left\{\ln\frac{V_{CO_0}/V_A}{\Sigma(V_{A_i}/V_A\cdot R_i)}\cdot R_i + \frac{t_I(P_B\text{-}47)(D_L/V_A)_i}{(V_I/V_A)_i}\cdot\ln[1 - (V_I/V_A)_i]\right\}. \tag{5}$$

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