

Continuous Distributions of Ventilation-Perfusion Ratios in Normal Subjects Breathing Air and 100% O₂

PETER D. WAGNER, RAYMOND B. LARAVUSO, RICHARD R. UHL, and
JOHN B. WEST

*From the Departments of Medicine and Anesthesia, School of Medicine,
University of California San Diego, La Jolla, California 92037*

ABSTRACT A new method has been developed for measuring virtually continuous distributions of ventilation-perfusion ratios (\dot{V}_A/\dot{Q}) based on the steady-state elimination of six gases of different solubilities. The method is applied here to 12 normal subjects, aged 21–60. In nine, the distributions were compared breathing air and 100% oxygen, while in the remaining three, effects of changes in posture were examined. In four young semirecumbent subjects (ages 21–24) the distributions of blood flow and ventilation with respect to \dot{V}_A/\dot{Q} were virtually log-normal with little dispersion (mean log standard deviations 0.43 and 0.35, respectively). The 95.5% range of both blood flow and ventilation was from \dot{V}_A/\dot{Q} ratios of 0.3–2.1, and there was no intrapulmonary shunt (\dot{V}_A/\dot{Q} of 0). On breathing oxygen, a shunt developed in three of these subjects, the mean value being 0.5% of the cardiac output. The five older subjects (ages 39–60) had broader distributions (mean log standard deviations, 0.76 and 0.44) containing areas with \dot{V}_A/\dot{Q} ratios in the range 0.01–0.1 in three subjects. As for the young subjects, there was no shunt breathing air, but all five developed a shunt breathing oxygen (mean value 3.2%), and in one the value was 10.7%. Postural changes were generally those expected from the known effects of gravity, with more ventilation to high \dot{V}_A/\dot{Q} areas when the subjects were erect than supine. Measurements of the shunt while breathing oxygen, the Bohr CO₂ dead space, and the alveolar-arterial oxygen difference were all consistent with the observed distributions. Since the method involves only a short infusion of dissolved inert gases, sampling of arterial blood and expired gas, and measurement of cardiac output and minute venti-

lation, we conclude that it is well suited to the investigation of pulmonary gas exchange in man.

INTRODUCTION

It has been known for many years that the distribution of ventilation-perfusion ratios (\dot{V}_A/\dot{Q}) is uneven in the lungs of normal subjects. The work of Martin, Cline, and Marshall (1) in 1953 and of Mattson and Carlens (2) in 1955 demonstrated interlobar differences in O₂ and CO₂ concentrations best explained by regional differences in ventilation and blood flow. Measurements using radioactive gases (3) demonstrated unevenness of both ventilation and blood flow topographically from apex to base, and indicated a range of \dot{V}_A/\dot{Q} of from approximately 3 at the apex to 0.6 at the base in 16 seated normal volunteers. Since external counting methods cannot cover all regions of the lungs, and in addition represent averages in those areas within the counting fields, this range of \dot{V}_A/\dot{Q} is likely to be an underestimate of the actual degree of ventilation-perfusion inequality. Thus radioactive gas measurements do not permit accurate definition of the shape, position, or dispersion of the distribution of \dot{V}_A/\dot{Q} in normal subjects, and certainly in lung disease where the inequality is more marked, external counting gives little information on the distribution.

Several workers, notably Riley, Cournand, and Donald (4,5) and Briscoe (6) have developed methods for quantifying the degree of \dot{V}_A/\dot{Q} inequality in terms of two or three parallel \dot{V}_A/\dot{Q} compartments. Riley and Cournand, for example, divided the lungs into three units on the basis of the arterial and expired pressures of O₂ and CO₂. One unit was unventilated, one unperfused, and the third was the ideal compartment. The amount of blood flow in the unventilated unit was termed venous admixture and the ventilation in the unperfused unit was called physiological dead space,

This work was presented in part at the national meeting of the Federation of American Societies for Experimental Biology, April 1973.

Received for publication 30 November 1973 and in revised form 18 February 1974.

measurements widely used in clinical practice. Although such analyses can always account for the abnormalities in gas exchange in individual patients, they give little insight into the characteristics of the \dot{V}_A/\dot{Q} distributions that actually exist. Not only do factors other than the shape, position, and dispersion of the distribution affect these parameters, but more than one \dot{V}_A/\dot{Q} distribution may be found consistent with the measured venous admixture and physiological dead space.

A third approach, based on the pulmonary exchange of poorly soluble inert gases (7), also suggested the presence of ventilation-perfusion inequality in normal man, but again, although distributions compatible with the measurements could be found, there was insufficient information to define the characteristics of the actual distributions.

Lenfant and Okubo (8, 9) reported the first continuous distributions of \dot{V}_A/\dot{Q} using a method based on the continuously measured arterial P_{O_2} and expired nitrogen concentration during a nitrogen washout. Their results depended on a lack of change of the distribution as the inspired O_2 concentration was raised, an assumption that Lenfant himself (10) pointed out may be unjustified. A further assumption was that none of the alveolar-arterial P_{O_2} difference at any inspired O_2 concentration was due to alveolar-capillary diffusion impairment. While this is reasonable in normal subjects, it may not be so in some patients with lung disease. Finally, the mathematical basis of the method has been criticized (11) as being insensitive.

We recently described a method (12) for measuring the distribution of \dot{V}_A/\dot{Q} based on the simultaneous steady-state pulmonary elimination of six inert gases of widely different solubilities. In this procedure, we made use of the principles governing inert gas exchange in the lung described by Farhi (13) and applied by Klocke and Farhi (14) and Yokoyama and Farhi (15). The method is suitable for experimental animal studies and also for studies both of normal subjects and of patients with acute or chronic lung disease. The position, shape, and dispersion of the distributions of both ventilation and blood flow are derived, and in addition the true intrapulmonary shunt and amount of ventilation to unperfused areas are determined. It is therefore possible to discriminate directly between shunting and ventilation-perfusion inequality as causes for hypoxemia in any individual case, without the need for breathing 100% O_2 , which, as pointed out, may alter the distribution and thereby give rise to error.

This paper reports the application of this method in 12 normal human volunteers ranging in age from 21 to 60. In nine of the subjects, measurements were made in the semirecumbent position both during air and

100% O_2 breathing, while in the remaining three, measurements were made in the supine and erect positions.

METHODS

General outline. Indwelling catheters were placed in the radial artery and a peripheral arm vein, and a narrow catheter was introduced via an antecubital vein to the region of the shoulder. The six gases, sulfur hexafluoride (SF_6), ethane, cyclopropane, halothane, diethyl ether, and acetone, are dissolved in a suitable solvent, such as 5% dextrose or normal saline, and the resulting mixture is infused into the peripheral venous catheter at 2-5 ml/min for some 20 min to reach a steady state of gas exchange within the lungs. Samples of mixed arterial blood and mixed expired gas are collected at this time, and minute ventilation and cardiac output (dye dilution) are measured. The concentrations of the six gases in each sample are determined by gas chromatography (16) and the solubility of each gas in blood is also measured. By using the Fick principle, the mixed venous concentration of each gas is then calculated, and two graphs are drawn. The first is the plot of the ratio of arterial to mixed venous concentrations against solubility (retention-solubility curve) and the second is the plot of the ratio of mixed expired to mixed venous concentrations against solubility (excretion-solubility curve). Then, by techniques of numerical analysis described elsewhere (12), the retention-solubility curve is transformed into a virtually continuous plot of blood flow against \dot{V}_A/\dot{Q} , and the excretion-solubility curve is similarly transformed into the plot of ventilation against \dot{V}_A/\dot{Q} .

Selection of subjects. Seven male volunteer college students, aged 21-24, and five male volunteers, aged 39-60, were chosen for these studies. The procedures and their risks were carefully explained to each subject and informed consent was obtained before the study.

The following criteria for selection were used: (a) A history of never having smoked tobacco. (b) A negative history of cardiopulmonary disease, except for the usual viral infections. (c) No known disease in any other organ system. (d) A history of no general anesthesia with halothane in the last year. The reason for this criterion was to minimize the very slight risk of halothane liver damage. (e) Normal physical examination. (f) Normal chest X-ray. One subject, E.L., showed a minimal old apical scar, never associated with symptoms of tuberculosis or functional impairment, and this was not deemed sufficient ground for exclusion from the study. (g) Normal standard pulmonary function tests, including vital capacity, total lung capacity, functional residual capacity (helium dilution), residual volume, closing volume, and a forced expiratory maneuver. (h) Normal electrocardiogram, hemoglobin, and hematocrit. Anthropometric data appear in Table I.

It is of interest that of 10 applicants in the 39-60 yr age group, five were found on physical examination or laboratory test to have significant abnormalities unknown to them. Each was rejected for this study but referred for further evaluation.

Preparation of subjects. The subjects were studied in the morning in the fasting state. With local anesthesia (1% Xylocaine [Astra Pharmaceutical Products, Inc., Worcester, Mass.] without adrenalin) and sterile technique, 20-gauge Medicut cannulas (A. S. Aloe Co., St. Louis, Mo.) were inserted into the radial artery of the nondominant hand and into the contralateral arm peripheral vein. In each subject, adequate ulnar arterial supply was first established to guard against the risk of digital ischemia from the radial artery cannula. A catheter (Bardic radio-opaque inside needle catheter, C. R. Bard, Inc., Murray Hill, N. J.) was introduced

TABLE I
Anthropometric Data

Subject	Group I				Group II					Group III		
	1 R. D.	2 M. H.	3 M. S.	4 P. B.	5 W. C.	6 A. H.	7 E. L.	8 D. H.	9 F. M.	10 G. S.	11 J. S.	12 B. T.
Age, yr	24	21	22	21	44	55	45	60	39	21	22	21
Vital capacity, liters	5.7	5.2	5.5	5.2	6.2	4.1	4.6	4.3	5.4	6.1	5.7	6.0
Total lung capacity, liters	7.1	7.1	7.7	6.5	8.2	4.9	6.5	5.6	7.2	7.8	7.8	7.8
Functional residual capacity, liters	3.9	4.1	4.7	2.9	4.0	2.2	2.8	1.9	2.6	3.8	4.2	3.6
Residual volume, liters	1.4	1.9	2.2	1.3	2.0	0.8	1.9	1.3	1.8	1.7	2.1	1.8
RV/TLC, %	20	26	28	20	24	16	29	23	25	22	27	23
Closing capacity (sitting), %	23	30	30	28	33	29	38	33	27	24	30	28
FEV ₁ , %	90	87	80	77	73	78	81	77	79	81	79	80
Height, cm	175	183	193	183	178	166	170	180	178	194	193	192
Weight, kg	80	79	91	68	89	71	70	82	84	82	80	72

via a suitable antecubital vein to the region of the shoulder. This line served only as the site for injection of dye for cardiac output measurements. All three lines were placed percutaneously, and, as a precaution, under continuous electrocardiographic monitoring.

The subject was then placed in the body position chosen for the study and connected to the appropriate inspired gas mixture. For all measurements, the same mouthpiece and valve box (Collins pulmonary function laboratory breathing valve P-316, Warren E. Collins, Inc., Braintree, Mass.) was used. While breathing air, subjects were connected to the mouthpiece 5–10 min before the initial sampling, whereas during 100% O₂ breathing, they were connected by necessity for the duration of the study.

Experimental groups. Four of the seven young subjects formed group I and all of the five older subjects formed group II. These were studied both while breathing room air and 100% oxygen. Six (three young and three older) were studied first breathing room air and then oxygen, while in the remainder, the measurements were made in the reverse order. In all cases, the subjects were semirecumbent at an angle of between 30 and 40 degrees to the horizontal throughout the measurements. In any one subject, body position remained unaltered for the duration of the study.

The three remaining young subjects formed group III. Each was studied breathing room air only, but in the supine and erect (sitting) positions. In two, the measurements were made first erect and then supine, while in the third subject, the reverse order was used.

Method of solution of the six test gases. Gas from a tank containing approximately 20% SF₆, 20% cyclopropane, and 60% ethane was passed through a 0.22- μ m Millipore filter (Swinnex-25, Millipore Corp., Bedford, Mass.) and then bubbled via sterile tubing into a 500-ml bottle of sterile 5% dextrose (or saline) so as to replace the air in the bottle with the gas mixture. The tank was turned off, and the bottle shaken vigorously for several seconds. The gas in the bottle was then replaced by further bubbling of the tank mixture, and the process repeated twice more.

With the above gas mixture bubbling very slowly into the bottle, 1 ml of liquid diethyl ether, analytical reagent grade, was next injected directly into the bottle with a sterile needle

and syringe. This was followed by 5 ml of similar-grade acetone. No shaking of the bottle was needed, since both substances, being very water-soluble, disperse rapidly. Shaking at this stage could have resulted in loss of the poorly soluble gases already in solution, since due to the presence of ether and acetone, the gas above the dextrose must have reduced partial pressures of the poorly soluble gases.

Five of the six gases were now in solution, and at this stage the dextrose was transferred into sterile, pyrogen-free, ungreased 200-ml glass syringes (Becton-Dickinson & Co., Rutherford, N. J.). We found these the most convenient form of reservoir, since their volume was readily reduced as the infusion took place without exposure of the solution of gases to air. This transfer was accomplished anaerobically and with sterile technique.

The final gas, halothane, was added directly to the syringes, rather than together with ether and acetone, because it is relatively insoluble in water and would require considerable agitation for even dispersion. As pointed out, such agitation is undesirable. 1 ml of liquid halothane was injected into each 200-ml syringe of dextrose, after which the syringe, free of all bubbles, was inverted several times to dissolve the halothane. Some, however, remained undissolved, but since halothane is much denser than water, it lay in the dependent part of the syringe and therefore could not be infused because the syringe was kept horizontal at all times. The solution was now ready for infusion into the subject.

Several points may be made concerning the technique for preparing the infusate. The concentrations of the gases in the tank need not be known accurately since the distribution of \dot{V}_A/\dot{Q} is obtained only from measurements of concentrations in arterial blood and expired gas; the concentrations of the gases in the infusate do not enter the calculations. Equilibration of the gases with dextrose need not be complete for the same reason. The relative proportion of each gas in the infusate has been selected so as to result in approximately uniform concentrations in the arterial blood and so increase the accuracy of measurement. All major receptacles of the infusate (and expired gas and arterial blood samples) must be of grease-free glass or metal, since some of the gases are soluble in plastic and grease and would therefore be partly lost from the solution.

The infusate was examined on several occasions for both sterility and freedom from pyrogens. Neither organisms nor pyrogens have ever been detected.

When infusing at the usual rate of 5 ml/min, systemic arterial concentrations of each gas never reach more than one part per 100,000 and are usually an order of magnitude less than that. Their presence was not usually noticed by the subjects.

Infusion of the solution of the six gases. With the subject in the desired position and breathing the appropriate inspired gas mixture, the infusion was begun after assurance of steady-state conditions, criteria of which were a stable pulse rate, blood pressure, and respiratory frequency. Closer to the time of measurements, additional information regarding the steady state was collected. This included measurements of cardiac output, minute ventilation, and both end-tidal and mixed expired P_{O_2} and P_{CO_2} , measured continuously by mass spectrometer.

The solution was infused into the peripheral venous cannula through a 0.22- μ m Millipore filter as a precaution against bacterial contamination. Both infusion and roller pumps were used on different occasions to introduce the material at a rate of 5 ml/min. After 15 min of infusion, subjects not breathing 100% O_2 (and hence not on a mouthpiece) were connected to the mouthpiece and valve box. This permitted continuous measurements of minute ventilation, collection of expired gases, and monitoring of tidal fluctuation in P_{O_2} and P_{CO_2} . After a further 5 min to allow for any change in breathing pattern (which was always small), and with the infusion continuing, an initial set of measurements was made (described below). 5 min later, a duplicate set of measurements was made while the infusion continued.

When both sets of data had been collected, the infusion was stopped, the mouthpiece removed, and the subject allowed to rest (in the same body position in groups I and II) for some 15 min.

A second study was then performed, exactly as above, under a new set of physiological conditions as set out in the section of experimental groups. At least 15 min were allowed for each subject to reach a new steady state before the infusion was begun, so that by the time the measurements were made, the subject had been exposed to the new conditions for at least 35 min. In the case of 100% O_2 breathing, a nitrogen washout was obtained and the level of expired nitrogen at the time of measurement was also available, confirming virtually complete denitrogenation (end-tidal N_2 concentrations of less than 1%).

Measurements. In temporal sequence, the following steps made up one set of measurements, as referred to above:

(a) A heparinized 15-ml blood sample from the radial artery, for determination of the concentrations of the six gases. The blood was withdrawn steadily over 30 s to damp respiratory oscillations in gas concentration. Sterile ungreased glass syringes were used.

(b) A simultaneous sample of mixed expired gas also collected in an ungreased glass syringe for measurement of the six gases. Leakage of gas from these syringes was minimized by the use of syringes with matched barrel and plunger. Simultaneous samples of blood and gas were taken because of the steady rise in concentrations of the gases during the infusion. Mixed expired gas was required rather than end-tidal, because the latter is not representative of all alveoli, and this required a mixing system. Further, the mixing system had to be made of either metal or glass to avoid absorption of gases such as halothane, ether, and acetone, and heated above body temperature to avoid the loss of the water-soluble gases in condensed water vapor.

Our solution was to build a long coil of copper pipe (diameter, 1.5 in; approximate length, 30 ft into a heated insulated box). The subject's expiratory line was connected to one end, and by the time expired gas had traveled the length of the pipe, sufficient mixing had occurred to completely eliminate tidal fluctuations in gas concentration. Thus, mixed expired gas could be sampled at the effluent end of the pipe. In order to make physiologically simultaneous collections of arterial blood and expired gas with this system, a delay period was required between the arterial blood sample and the mixed expired gas sample. This delay represents the finite time for travel of the expired gas through the copper pipe, and was calculated in the following way. First, the entire pipe and connections were filled with room air. Then a subject was connected to the valve box and asked to breathe normally and regularly. Cumulative expired volume was measured from the time of collection, and with a mass spectrometer, the P_{CO_2} at the effluent end of the system was measured continuously. For a period of time approximately equal to the volume of the collection system (about 12 liters) divided by minute ventilation, the P_{CO_2} remained equal to that in room air, but then began to rise over the next three breaths until a plateau concentration was reached. By the same principle as that employed in the measurement of anatomic dead space by the Fowler single-breath method, the effective volume of the entire collection system could thus be measured. This volume was 12.5 liter, and was independent of the level of minute ventilation over the range tested, namely, 8–40 liter/min.

(c) A 3-ml Heparinized radial artery sample for P_{O_2} , P_{CO_2} , and pH. Analysis was performed within 5 min, with the samples kept in glass syringes on ice before measurement. Radiometer blood gas electrodes were used. The oxygen electrode was calibrated with low and high O_2 mixtures containing 5% CO_2 before blood measurements were made. The blood-gas correction factor was determined by tonometry of blood samples with these O_2 mixtures on several occasions.

(d) Minute ventilation and respiratory frequency were measured minute-to-minute over the 4 min bracketing the blood sampling. Ventilation was measured with a calibrated Wright respirometer.

(e) Cardiac output was measured by dye dilution. 2 ml of indocyanine green (5 mg) were injected into the venous cannula placed near the shoulder, and arterial blood was sampled from the radial artery. A Gilford densitometer (Gilford Instrument Laboratories, Inc., Oberlin, Ohio) was used to measure dye concentration, and the curves were recorded on a Brush recorder (Series 200, Gould Inc., Instruments System Div., Cleveland, Ohio). Replotting of the downslopes was done by hand, and the areas of the curves planimetered. A four-point calibration of the densitometer was performed.

(f) Continuous measurements of both tidal and mixed expired P_{O_2} and P_{CO_2} were obtained with a Perkin-Elmer respiratory mass spectrometer (Perkin-Elmer Corporation, Pomona, Calif.) whenever subjects were on the mouthpiece. In addition, tidal nitrogen concentrations were measured during oxygen breathing.

On the day of the study, hemoglobin concentration and hematocrit were measured in the hospital laboratory. In addition, plasma hemoglobin estimations were performed before and after the study. The purpose of these measurements was to monitor possible hemolytic effects of the solution of gases. Halothane in high concentration is known to hemolyze blood, but in preliminary in vitro tests, no hemolysis was found to occur at concentrations 100 times greater than those present in the subjects. Plasma hemoglobin values rose by a

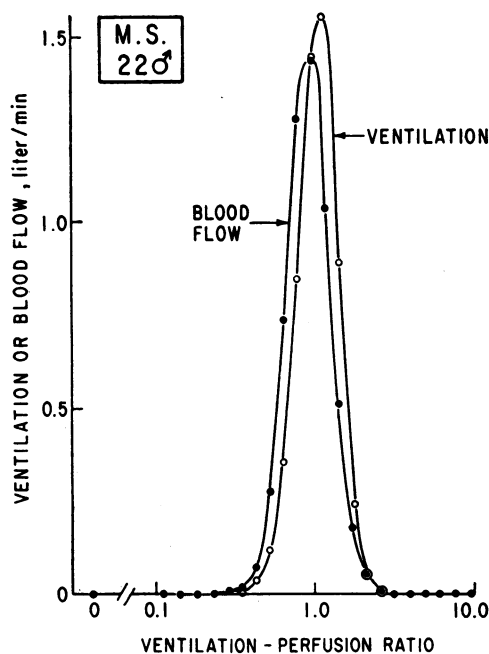


FIGURE 1 The distribution of ventilation and blood flow in a young subject, M. S., breathing room air. There is very little dispersion in either curve with no areas of high or low \dot{V}_A/\dot{Q} . There is no shunt. Both distributions are appropriately positioned about a \dot{V}_A/\dot{Q} close to 1.0, and are symmetrical on a log scale.

mean of 5 mg/100 ml over the course of the study, equivalent to less than 2 ml of blood being hemolyzed. We ascribe this minor hemolysis to the reinfusion of blood withdrawn during the cardiac output determinations.

Gas chromatography. The concentrations of the six test gases in both mixed expired gas and arterial blood were determined by gas chromatography. A Beckman gas chromatograph (GC)¹ model GC 72-5 with both flame ionization detector (FID) and electron capture detector (ECD) was used (Beckman Instruments, Inc., Fullerton, Calif.). SF_6 was measured with the ECD, while the remaining five gases were detected by the FID.

Because only ratios of concentrations were needed, absolute calibration of the GC was unnecessary. Since the FID is linear over a wide range with respect to peak height, raw peak height data were sufficient for computation of the gas concentration ratios. However, the ECD is inherently a linear, so that a relative calibration curve was necessary for SF_6 . This was readily obtained by means of serial dilutions of the most concentrated sample of SF_6 .

Expired gas samples were introduced into the GC directly via a 2-ml constant volume inlet loop. To measure the gases in arterial blood, they were first extracted into helium which was then introduced as above into the GC. The method of extraction and measurements is described elsewhere in detail (16) and is similar in principle to that originally described by Hamilton (17). It consists of equilibrating known volumes of arterial blood and helium at the temperature of the subject for a period of 40 min. The once-equilibrated blood is then

¹ Abbreviations used in this paper: ECD, electron capture detector; FID, flame ionization detector; GC, gas chromatograph.

re-equilibrated with a second volume of helium as before, and from the ratio of the two peak heights obtained at each equilibration, the solubility of each gas may be calculated. This enables the original blood concentration and solubility to be computed for each gas.

For the FID, the carrier gas (helium) flow rate was 50 ml/min, and column temperature 170°C. For the ECD, helium flow rate was 25 ml/min and temperature 80°C. In both cases, the same column was used, namely, Poropak-T 80/100 mesh, 6 ft long, and $\frac{1}{8}$ th in diameter (stainless steel). The column was obtained prepacked from Beckman Instruments, Inc.

Computer analysis. From the ratio of mixed expired to arterial concentrations for each gas, the solubility of each gas, and minute ventilation and cardiac output, the arterial-to-venous ratio and expired-to-venous ratio of concentrations for each gas were calculated by means of the Fick principle.

As described in the general outline, these ratios, together with the measurements of solubility, constitute all the necessary data for the determination of both the distribution of ventilation and of blood flow with respect to \dot{V}_A/\dot{Q} . These distributions are not unique in a strict mathematical sense, because they are calculated in terms of a large number (50) of compartments. However, all possible distributions that can be derived from a given set of data can be shown to be virtually indistinguishable, so that a single useful solution can be obtained. This concept is considered in detail elsewhere (12), where the principles of the numerical analysis that transform the data into the distributions are also described. The computer program for this analysis is written in Fortran and is directly executable on most large computers, including the Control Data 3600 and Burroughs 6700 digital computers. Execution time on such a computer varies between 1 and 3 min depending on the complexity of the distribution, since the iterative methods take longer to converge upon a complex shape than upon a simple one. The computer program is available from the authors.

RESULTS

Distributions of \dot{V}_A/\dot{Q} in semirecumbent subjects breathing air

Group 1: young subjects aged 21–24 yr. Fig. 1 shows typical distributions of ventilation and blood flow against \dot{V}_A/\dot{Q} in a young normal subject (M.S.). \dot{V}_A/\dot{Q} is shown on a log scale and the individual points showing blood flow and ventilation add up to the total cardiac output and ventilation, respectively. The line joining the individual points is for clarity only. Note how little dispersion there is in either curve. A useful index of the dispersion is the standard deviation of the distribution calculated with a natural log scale for the abscissa (log SD). In this case, log SD was 0.32 for blood flow and 0.29 for ventilation. The values in Table II are the means of two measurements made 5 min apart.

Although an attenuated scale for \dot{V}_A/\dot{Q} is used in Fig. 1 (only the region of \dot{V}_A/\dot{Q} from 0.1 to 10.0 is plotted) the analysis of this subject's data was performed routinely, namely, by obtaining the solution over the entire working \dot{V}_A/\dot{Q} range of from 0.005 to 100.0. The reason for using this attenuation was that all the points for blood flow and ventilation outside the

range in Fig. 1 had a value of zero. In fact, it can be seen that all the blood flow and ventilation was confined to the \dot{V}_A/\dot{Q} range, 0.3–3.0.

The positioning of the two curves is appropriate to the ratio of total alveolar ventilation (5.3 liter/min) to cardiac output (5.8 liter/min) in this subject. The \dot{V}_A/\dot{Q} ratio at the mean of the blood flow distribution was 0.87, while that at the mean of the ventilation distribution was 1.0. The ratio of total alveolar ventilation to cardiac output was 0.91, very close to the geometric mean of 1.0 and 0.87, namely, 0.93. Logarithmically normal distributions with similar degrees of dispersion behave so that the geometric average of the mean \dot{V}_A/\dot{Q} of blood flow and ventilation coincides with the ratio of total alveolar ventilation to cardiac output. As may be seen from Fig. 1, both distributions are virtually symmetrical on the logarithmic scale, making them logarithmically normal.

Another striking feature was the absence of shunt. None of the subjects in this group had any shunt while breathing air, Table II. As will be discussed later, the present method measures only intrapulmonary and intracardiac shunt, in contrast to standard methods based on 100% oxygen breathing, which also include the shunt due to bronchial and Thebesian venous admixture. Thus, in the semirecumbent young subjects, there were no perfused regions of the lung that were completely unventilated. It should be noted that the present method is very sensitive at detecting the degree of shunt. This is because of the behavior of SF₆, the least soluble gas. In a normal subject, the arterial concentration of SF₆ is about 0.5% of the venous level, but if a shunt of 1% developed, this value would rise to 1.5%, or three times the previous level. As a result, small shunts can be detected with considerable accuracy.

The summarized results for the young subjects (group 1) breathing air are shown in Table II. The average dispersion, estimated by the mean log SD for the group, was 0.43 for the blood flow distributions and 0.35 for ventilation. As a guide to the physiological effects of this degree of dispersion, it is useful to examine the ideal alveolar-arterial oxygen difference produced by log-normal distributions with similar dispersion. A log SD of 0.3 is associated with an O₂ difference of approximately 5 mm Hg; one of 0.4 with 9 mm Hg, and one of 0.5 with 14 mm Hg. These values are for lungs with normal overall \dot{V}_A/\dot{Q} .

The \dot{V}_A/\dot{Q} at the mean of the blood flow distribution averaged 0.78, and that at the mean of the ventilation distribution 1.03. The points on the \dot{V}_A/\dot{Q} axis two log SD above and below the means are, for blood flow, 1.84 and 0.33, respectively, and for ventilation 2.07 and 0.51, respectively. Thus, more than 95% of both ventilation and blood flow are confined between \dot{V}_A/\dot{Q} ratios of 0.3 and 2.1, and these limits form a convenient

definition of the range of \dot{V}_A/\dot{Q} in normal young subjects in the semirecumbent position.

In all subjects in this group there was no skewness to the curves so that the distributions were virtually symmetrical along the \dot{V}_A/\dot{Q} axis. This was assessed quantitatively by calculating the third moment of the distributions about the mean (again on a log scale). If the third moment is zero, the distribution is perfectly symmetrical; a negative value indicates the presence of a tail (of ventilation or blood flow) in areas of low \dot{V}_A/\dot{Q} but not in high \dot{V}_A/\dot{Q} areas, and vice versa. The mean third moment of the blood flow distributions was +0.01, and that for ventilation –0.03, confirming the virtual lack of skewness. Values for individual subjects are shown in Table II.

It is of interest to compare the dead space calculated by the present method with physiologic dead space computed from the Bohr formula with the arterial and mixed expired P_{CO₂} values. In both cases, the methods give a value that includes instrumental dead space, anatomic dead space, and ventilation to unperfused alveoli. In addition, the Bohr dead space includes dead-spacelike effects of all regions whose alveolar P_{CO₂} are less than the arterial level. By contrast, the present method only includes the dead-spacelike effect of units with a \dot{V}_A/\dot{Q} over 100. As a result, when the Bohr dead space is due in part to the presence of high \dot{V}_A/\dot{Q} areas with \dot{V}_A/\dot{Q} less than 100, the value given by CO₂ should exceed that given by the inert gas analysis.

These considerations may be applied to the data from the young subjects. Since there are very few areas with \dot{V}_A/\dot{Q} above 2 (mean less than 2% of the total ventilation), we would expect the results from each method of calculation to be similar. For the young subjects, there is fairly close agreement (Table II). The slope of the regression line is 1.08, the intercept is –3.2, and correlation coefficient is 0.76.

Group II: older subjects aged 39–60 yr. Fig. 2 shows the distribution in one older subject breathing room air (E.L.). Comparison of this figure with that for the young subject (Fig. 1) shows a little more dispersion of both ventilation and blood flow (log SD of blood flow 0.57, and that for ventilation 0.48). The range of \dot{V}_A/\dot{Q} is correspondingly greater, namely, from 0.07 to 3.0, but is still under two decades of \dot{V}_A/\dot{Q} . 7.4% of the blood flow and 0.3% of the ventilation lie below the lower limit of normal for young subjects as defined above, while 0.5% of the blood flow and 1.0% of the ventilation lie above the upper normal limit given above. Thus, although there is more dispersion in this subject than in the average young subject, there are no areas of very high or very low \dot{V}_A/\dot{Q} . There was no shunt in this subject. In the older subjects as a group, mean shunt was only 0.08%.

TABLE II
Summary

Subject	Group I								Group II	
	R. D.		M. H.		M. S.		P. B.		W. C.	
	Air	O ₂	Air	O ₂	Air	O ₂	O ₂	Air	Air	O ₂
Conditions studied§										
Minute ventilation, liter/min	7.0	8.1	6.3	7.5	9.3	11.0	8.6	8.0	7.7	9.4
Frequency, min ⁻¹	9.5	11.5	11	11	14	14	15	15	12	20
Tidal volume, ml	740	700	570	680	660	790	570	530	640	470
Cardiac output, liter/min	5.8	5.8	4.9	5.2	5.8	5.6	5.4	6.3	6.0	6.3
Pao ₂ , mm Hg	91	590	87	600	97	600	600	93	75	506
Paco ₂ , mm Hg	38	35	41	39	39	35	38	40	38	39
PEO ₂ , mm Hg	120	—	117	—	119	—	—	123	124	—
PECO ₂ , mm Hg	25	23	25	21	24	21	22	22	24	17
\dot{V}_{O_2} , ml/min	245	260	250	240	340	360	260	250	220	200
\dot{V}_{CO_2} , ml/min	200	215	185	180	260	270	215	205	210	190
AaDo ₂ , mm Hg	15	83	11	75	2	73	73	9	35	167
O ₂ shunt, %	—	5.2	—	4.4	—	3.0	4.4	—	—	13.5
Shunt, present method, %	0	0.9	0	0	0	0.8	0.6	0	0	10.7
Bohr deadspace, %	41	41	38	48	40	35	45	45	40	57
Deadspace, present method, %	38	40	—	—	43	34	42	44	32	48
Mean V _A /Q blood flow	0.89	0.91	0.67	1.0	0.87	1.14	0.70	0.68	0.61	0.75
Log SD, blood flow	0.33	0.28	0.39	0.34	0.37	0.38	0.69	0.64	1.05	0.50
Skew, blood flow	0	0	-0.01	0	0	+0.01	+0.05	+0.06	-2.04	-0.02
Mean V _A /Q ventilation	1.10	1.20	—†	—	1.0	1.40	1.20	1.00	1.13	0.90
Log SD, ventilation	0.28	0.29	—	—	0.33	0.32	0.49	0.40	0.76	0.33
Skew, ventilation	0	0	—	—	-0.02	0	-0.10	-0.07	+0.11	0.0

* All values are means of two measurements made under the same conditions. Because of inaccuracy in the measurement of expired Po₂ when breathing 100% O₂, \dot{V}_{O_2} under these conditions is calculated from the measured \dot{V}_{CO_2} and the respiratory exchange ratio breathing air.

† Ventilation data on subject 2 were invalid due to errors in measurement.

§ In each subject, the conditions are shown in chronological order.

There was little skewness in the distributions in this subject (third moments being -0.12 for blood flow and $+0.01$ for ventilation). Another subject (A.H.), had very similar results (Table II) but it is of interest that in the remaining three in this group (W.C., D.H., and F.M.) there was considerable maldistribution of ventilation and blood flow. The results for subject W.C. are presented in Fig. 3, where it can be seen that 15.5% of the blood flow and 2.4% of the ventilation lie below the lower limit of normal in the young group (V_A/Q of 0.3) and that 15.3% of the ventilation and 3.9% of the blood flow lie above the upper limit of 2.1. The log SD of the blood flow distribution is 1.05 and that for ventilation 0.76. The V_A/Q ratio at the mean of the blood flow curve is 0.61 while that for ventilation is 1.13. In addition, the blood flow curve has considerable negative skewness (third moment, -2.04) due to the areas of V_A/Q ratio between 0.01 and 0.1. However, even in this subject, whose distributions contained the greatest dispersion seen in the entire study, there was no shunt while breathing air.

Another feature in this subject was that his minute ventilation changed between one measurement and the next. In Fig. 3, minute ventilation was 7.7 liter/min, while in a subsequent measurement it had risen to 11.3 liter/min, due to an increase in frequency at the same

tidal volume. There was no change in cardiac output. The effect on the resulting \dot{V}_A/Q distribution was only to shift the curves along the V_A/Q axis en masse by increasing all values by approximately 50% toward the direction of higher V_A/Q . In particular, the shape and dispersion of the distributions was not significantly affected.

Taken as a group, the five older subjects had a mean log SD for the blood flow distribution of 0.76, while that for ventilation was 0.44. The average V_A/Q at the mean of the blood flow distribution was 0.78, and that for ventilation was 0.92, while the mean third moment was -0.90 for blood flow and $+0.02$ for ventilation. Thus in summary, the distributions were broader in the older subjects, both with respect to ventilation and blood flow, and the blood flow curve was skewed due to the presence of areas of low V_A/Q . The distribution of ventilation was essentially log-normal. Individual results are given in Table II.

The total dead spaces computed by the present method and from the arterial and mixed expired Pco₂ were compared just as for the young subjects. As explained previously, a discrepancy between the two would be expected when regions of high V_A/Q are present. Since there was more inequality of ventilation and blood flow in the older subjects, the Bohr dead

of Results*

Group II								Group III					
A. H.		E. L.		D. H.		F. M.		G. S.		J. S.		B. T.	
Air	O ₂	Air	O ₂	O ₂	Air	O ₂	Air	Supine	Erect	Supine	Erect	Erect	Supine
6.1	8.4	7.6	8.9	7.3	9.4	7.3	6.2	7.5	6.9	7.7	8.3	7.7	8.0
10.5	11.5	16	16	11	11	10	9.5	8	12	10.5	12	11.5	14
580	730	480	560	660	850	730	650	940	580	730	690	670	570
5.5	5.1	4.8	5.0	4.5	4.7	4.6	5.4	8.0	6.3	6.2	5.8	6.5	6.9
86	560	79	550	540	82	550	76	89	87	98	102	86	91
40	37	39	37	35	34	36	39	42	41	36	35	43	41
122	—	126	—	—	128	—	119	125	122	122	124	122	124
24	20	19	16	22	20	22	26	22	23	24	22	25	24
200	220	210	210	225	240	240	230	220	220	250	250	250	235
170	190	170	170	190	215	190	185	195	185	210	210	220	220
13	113	24	123	135	30	125	26	14	16	9	6	15	15
—	7.3	—	8.1	7.5	—	6.9	—	—	—	—	—	—	—
0	2.5	0.04	1.8	0.8	0	1.9	0.35	0.7	0	0	0	0	0
41	46	50	57	37	42	37	39	32	44	36	41	43	41
37	41	45	44	37	45	40	38	22	36	39	37	41	41
0.69	0.83	0.73	0.90	0.85	0.97	0.90	0.69	0.73	0.60	0.77	0.76	0.60	0.66
0.48	0.90	0.57	0.48	1.00	0.84	1.12	0.86	0.30	0.56	0.69	0.38	0.57	0.47
-0.03	-1.1	-0.12	-0.11	-3.0	-1.29	-3.28	-1.02	0	+0.02	-0.31	0	-0.05	-0.03
0.73	1.08	0.78	1.01	1.13	1.23	0.98	0.74	0.82	0.77	1.0	1.17	0.71	0.75
0.34	0.32	0.36	0.30	0.40	0.48	0.21	0.24	0.59	0.52	0.39	0.85	0.50	0.21
0	0	0.01	0.00	0	0	0	0	+0.03	+0.06	-0.02	-0.45	+0.08	0

spaces exceeded those measured by the present method in several cases, as expected (Table II). Mean Bohr dead space was 43.8%, while the dead space by the present method was 40.1%, the difference being significant at the 0.05 level.

Distributions in semirecumbent subjects breathing 100% oxygen

Group I: young subjects aged 21–24. Irrespective of the order of the studies (i.e., whether the measurements on oxygen preceded or followed those on room air), two differences were noted between the results during air breathing and those during oxygen breathing.

First, as a consequence of mild hyperventilation while breathing O₂, there was a shift in both the ventilation and blood flow curves towards higher \dot{V}_A/\dot{Q} , by an amount appropriate to the change in the ratio of alveolar ventilation to cardiac output. As a group, the average \dot{V}_A/\dot{Q} ratio at the mean of the blood flow distribution increased from 0.78 to 0.94 and that for ventilation from 1.03 to 1.27. This was not associated with significant changes in the shape or dispersion of the distributions. The mean log SD was 0.43 on air and 0.44 on O₂ for blood flow; the values were 0.35 to 0.37 for ventilation. Both distributions remained unskewed.

The change of greater interest, however, was the development of blood flow to unventilated areas (shunt), in spite of the hyperventilation. Three of the four subjects in this group showed this change, resulting in a mean shunt of 0.5% ($P < 0.05$). These changes occurred within 30 min of breathing oxygen. It should be pointed out that the subjects were all asked to breathe "normally", and that occasional sighs and deep breaths were observed in all. In the subject (P.B.) in whom the measurements were made with O₂ breathing first, the shunt was no longer present subsequently during air breathing, indicating its ready reversibility.

The distributions of blood flow for the subject shown in Fig. 1 are plotted in Fig. 4 (upper panel) to demonstrate these effects of oxygen.

Group II: old subjects aged 39–60. The changes with oxygen breathing in this group were more complex. While the cardiac output fell insignificantly (mean fall of 3%), minute ventilation increased by 14%, like the changes in the young subjects. However, the distributions did not simply shift towards areas of higher \dot{V}_A/\dot{Q} , since in addition there was an increase in the blood flow to low \dot{V}_A/\dot{Q} areas and the development of shunts. The result was only a small rise in average \dot{V}_A/\dot{Q} at the mean (from 0.78 to 0.84 for blood flow and 0.92 to 1.02 for ventilation), since the effect of

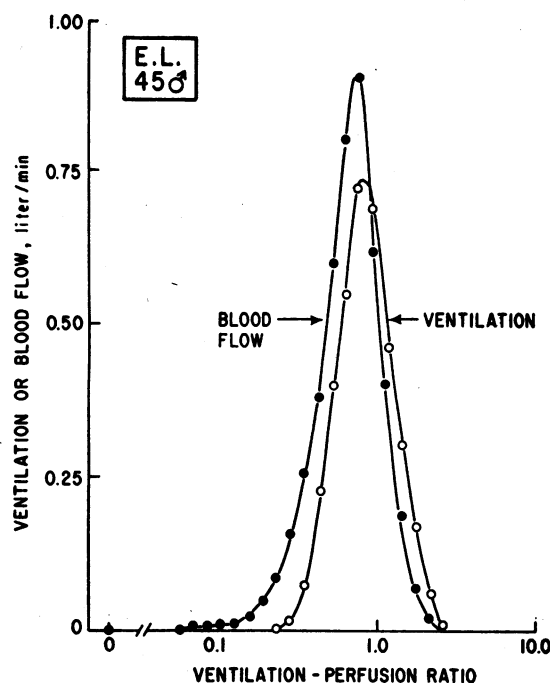


FIGURE 2 The distribution of ventilation and blood flow in an older subject (E. L.) breathing room air. Compared with the young subject (Fig. 1), there is more dispersion in both curves, and a small tail of blood flow in low \dot{V}_A/\dot{Q} areas, so that the blood flow distribution is not log-normal. There is still no shunt, and there are no areas of very high or low \dot{V}_A/\dot{Q} .

hyperventilation was partly offset by the increase in low \dot{V}_A/\dot{Q} areas. There was little change in the dispersion of the distributions (from log SD 0.76 to 0.80 for

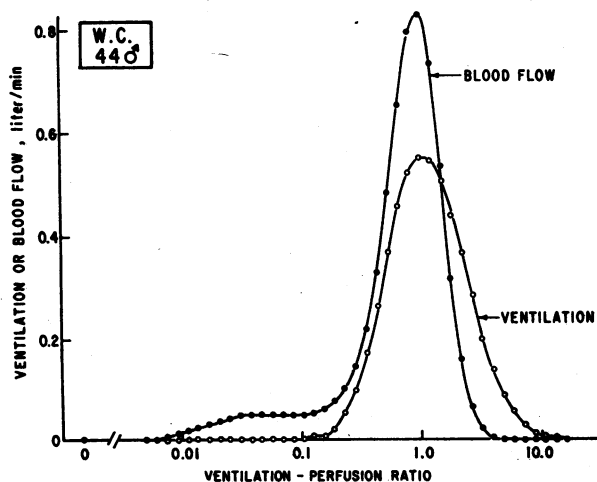


FIGURE 3 The distribution of ventilation and blood flow in subject W. C. breathing room air. As distinct from the subject in Fig. 2, this man demonstrated areas of low \dot{V}_A/\dot{Q} , with units as low as 0.01. However, there was still no shunt, and although the main body of the distributions showed more dispersion than those in Fig. 2, there were no areas with \dot{V}_A/\dot{Q} greater than 10.

blood flow and 0.44 to 0.31 for ventilation) or in the skewness of ventilation (third moment, 0.02 to 0.00) but the blood flow distributions became more negatively skewed (third moment, -0.90 to -1.50) due to the increased blood flow in low \dot{V}_A/\dot{Q} areas.

In all subjects, a shunt appeared (mean value 3.2%) after breathing oxygen for 30 min. As for the young subjects, this shunt was present only during oxygen breathing, whether before or after air breathing. In on subject (W.C.), shown in Fig. 4 (lower panel), the shunt reached a value of 10.7%. Note that the main body of the distribution in this case was virtually unaltered while the blood perfusing units in the \dot{V}_A/\dot{Q} range 0.005-0.1 (amounting to 9.6% of the cardiac output) disappeared. Hypotheses consistent with the

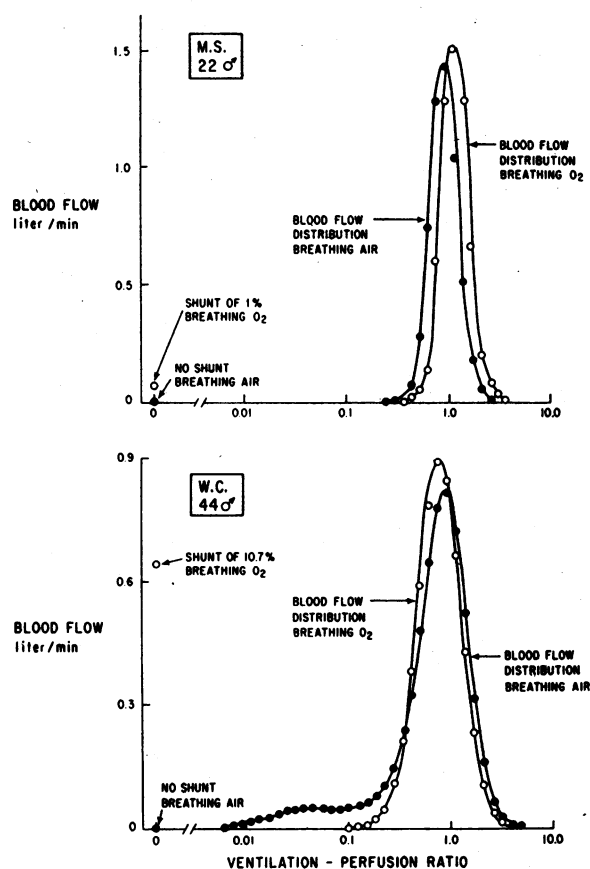


FIGURE 4 Distributions of blood flow breathing both air and 100% oxygen in one young subject and one older subject. In the young man, (M. S.) there was an overall shift due to hyperventilation, and a shunt of 1% appeared. The older subject, (W. C.) demonstrated major changes. The shoulder of blood flow in low \dot{V}_A/\dot{Q} areas breathing room air has disappeared on breathing oxygen, while at the same time a shunt of 10.7% developed. Quantitatively, the amount of blood flow in the low \dot{V}_A/\dot{Q} regions breathing room air closely matched the degree of shunt on oxygen. The main body of the distribution was unaltered.

conversion of areas of low \dot{V}_A/\dot{Q} into shunt during oxygen breathing are discussed later.

Direct sampling of mixed venous blood was not done in these studies, but since arterial P_{O_2} , oxygen uptake, and cardiac output were measured, the arteriovenous oxygen difference breathing oxygen, and hence the shunt fraction, could be calculated. This "O₂" shunt and that given by the inert gas measurements are shown in Table II. In every case the O₂ shunt exceeded the inert gas shunt, but there was an almost constant difference between the two over the range studied. This difference averaged 4.5% of the cardiac output.

There are two reasons for this consistent discrepancy. First, the venous admixture effect produced by emptying of the bronchial and Thebesian veins into the left side of the circulation is detected as shunt by the oxygen method. This is not the case in the inert gas method, because the inert gas concentrations are virtually unaltered in these circulations. This explanation probably accounts for up to half of the difference between the methods. The remainder of the discrepancy is probably explained by the errors in measurements of P_{O_2} when the P_{O_2} exceeds 400 mm Hg. Metabolic consumption of oxygen by the blood awaiting analysis and uptake of oxygen by the blood gas electrodes both lead to underestimates of P_{O_2} . That this is the most likely explanation is suggested by the close correlation between the two estimates of shunt when the shunt is larger (of the order of 20% or more), in experimental dog studies.

Effects of change of posture on the distributions: group III

Fig. 5 shows the distributions in one of the three subjects (J.S.) in this group both supine and erect. Note the increased ventilation and decreased blood flow in areas with \dot{V}_A/\dot{Q} ratios above 1, as the erect posture is assumed. These changes are consistent with the known effects of gravity, which causes underperfusion of the apex of the upright lung and thus increased ventilation to high \dot{V}_A/\dot{Q} areas. In addition, in the supine position, there is more blood flow to moderately low \dot{V}_A/\dot{Q} regions, caused perhaps by intermittent ventilation in the dependent zones due to a higher closing capacity.

Note that the blood flow distribution in the erect position is narrower than in the supine position. At first sight this might be thought to be paradoxical in view of the greater topographical differences in blood flow when the subject is erect. However, in this posture, blood flow is more closely matched to \dot{V}_A/\dot{Q} than is ventilation because of the appreciable ventilation to the apex with its very high \dot{V}_A/\dot{Q} . As a result, the plot of blood flow against \dot{V}_A/\dot{Q} becomes narrower as the topographical differences increase.

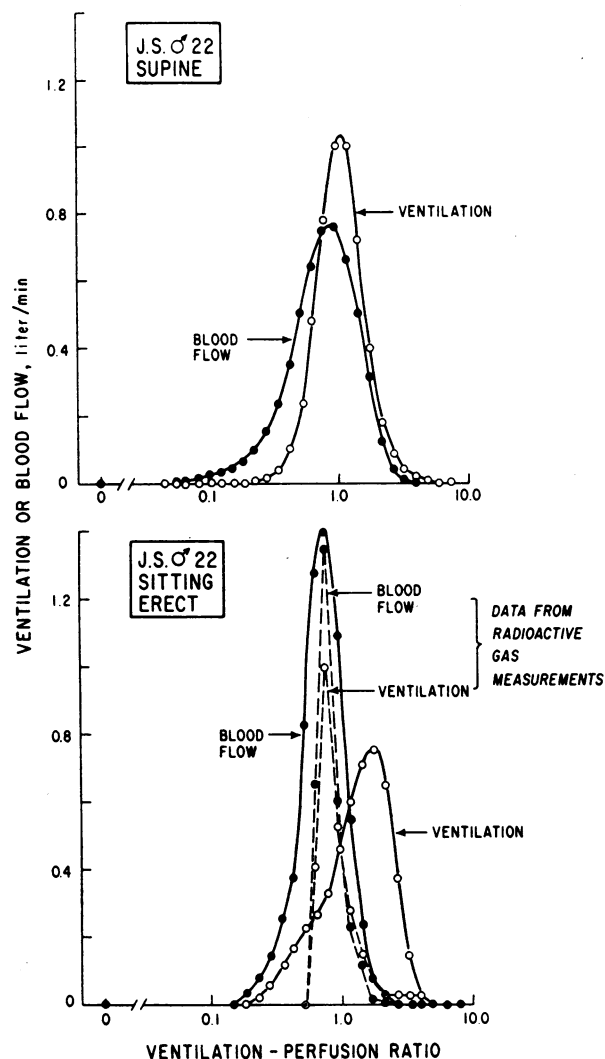


FIGURE 5 Distributions of ventilation and blood flow in subject J. S. determined first supine and then erect. In the erect position there were fewer low, and more high \dot{V}_A/\dot{Q} regions. These results are compatible with known differences in topographical distributions of ventilation and blood flow and functional residual capacity, between the two positions. The distributions derived from topographical data in erect subjects are plotted in the lower panel (interrupted lines), showing considerably less dispersion than in the present study.

Also plotted in Fig. 5 are the distributions of ventilation and blood flow derived from the topographical data obtained with radioactive CO₂ in upright normal subjects (3). This original data described the blood flow, ventilation, and \dot{V}_A/\dot{Q} in nine slices of lung. However, the \dot{V}_A/\dot{Q} of these slices are not equally spaced logarithmically, so that a simple plot of blood flow or ventilation versus \dot{V}_A/\dot{Q} slice by slice is not comparable with the present distributions. This difficulty was overcome by plotting blood flow first and then ventilation cumulatively against \dot{V}_A/\dot{Q} , and

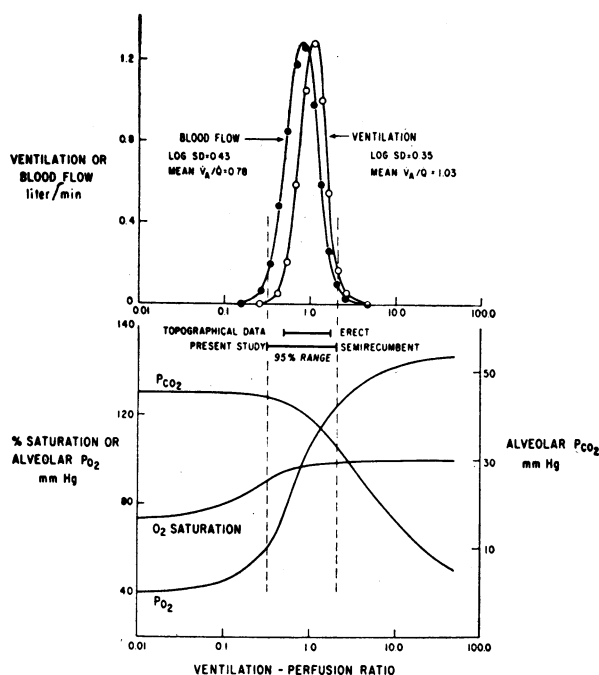


FIGURE 6 The average distribution in young, semirecumbent subjects (upper panel). Lower panel shows alveolar P_{O_2} , P_{CO_2} , and O_2 saturation as a function of \dot{V}_A/\dot{Q} . 95% ranges for blood flow and ventilation are shown and indicate a range of alveolar P_{O_2} of from 60 to 123 and one of P_{CO_2} from 44 to 43 mm Hg. Note that the range determined from the present method exceeds that derived from topographical data in erect subjects.

then reading off values at \dot{V}_A/\dot{Q} ratios equally logarithmically spaced. In this manner, frequency distributions of ventilation and blood flow were derived and compared in Fig. 5 with the present data.

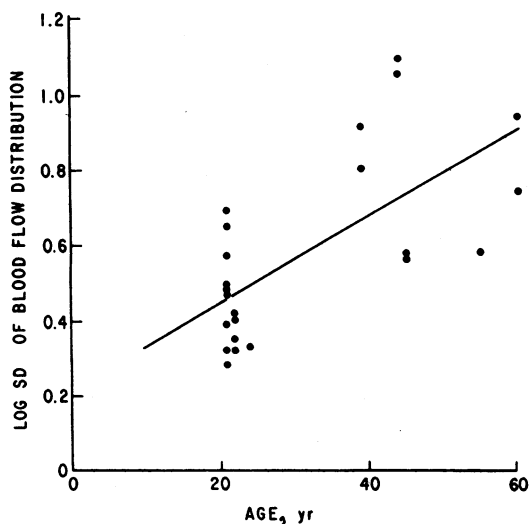


FIGURE 7 Increase in log SD with age. Despite considerable scatter, the dispersion of the distributions increases with age. This is probably responsible for the gradual fall in arterial P_{O_2} known to occur with age.

There is considerably less dispersion in the distributions derived from the topographical data than in the present case. From Fig. 5 this is seen to be due to less ventilation and blood flow in both high and low \dot{V}_A/\dot{Q} units (rather than to a truncation of the curves at only one end). These differences are readily explained by the lack of resolution of the radioactive gas method and its inability to sample to entire lung.

Of the other two subjects in this group, one, (G.S.) showed similar changes with an increase in high \dot{V}_A/\dot{Q} areas in the erect position, but the final subject (B.I.) showed only a small difference between the supine and erect positions, with slightly more inequality in the erect position.

Average distributions of ventilation and blood flow in young subjects

Fig. 6 shows the average distributions of the semirecumbent young subjects (group 1) breathing air. These were calculated from the observed mean log SD and \dot{V}_A/\dot{Q} at the mean, independently for both blood flow and ventilation by assuming a logarithmically normal shape. The 95% limits are drawn, the lower limit being 2 SD below the mean for blood flow (\dot{V}_A/\dot{Q} of 0.3) and the upper 2 SD above the mean for ventilation (\dot{V}_A/\dot{Q} of 2.1). In the lower panel of Fig. 6, alveolar P_{O_2} , O_2 saturation, and alveolar P_{CO_2} are shown as a function of \dot{V}_A/\dot{Q} (mixed venous P_{O_2} 40 and P_{CO_2} 45 mm Hg). It can be seen that the 95% range of P_{O_2} is from 60 to 123 mm Hg, considerably more than predicted by the topographical distributions (76–120).

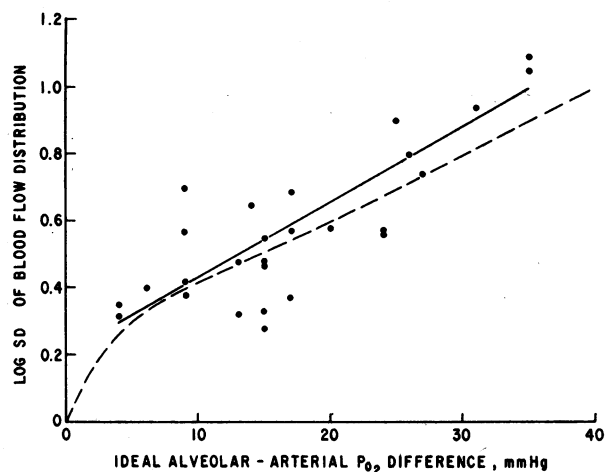


FIGURE 8 Relationship between the alveolar-arterial oxygen difference and log SD of blood flow in all subjects breathing room air. There is a good correlation, indicating that the distributions are consistent with independent measurements of oxygen and carbon dioxide exchange. Further, the relationship between these parameters for theoretical log-normal distributions is shown by the interrupted line, and demonstrates a very similar relationship.

Note that the 95% range of \dot{V}_A/d in the erect position according to the topographical \dot{Q}_{ata} is also less than the range indicated in the semirecumbent position for the present study.

Changes in the distributions with age

Fig. 7 shows the increasing dispersion of the blood flow distributions with age in the nine subjects. There is considerable scatter, so that a precise definition of the relationship between log SD and age is not possible, but log SD in the older group was significantly higher than in the younger group (P less than 0.05). On the other hand, there was no clear relationship between age and log SD of the ventilation distributions. These findings are explained by the changes with age observed in the measured distributions, namely, the development of regions of low \dot{V}_A/\dot{Q} (< 0.1) without the appearance of areas of high \dot{V}_A/\dot{Q} (> 10) as in Figs. 2 and 3.

DISCUSSION

Comparison with previous work. There is little previous information concerning distributions of \dot{V}_A/\dot{Q} for comparison with the present studies. However, Lenfant and Okubo (8, 9) reported distributions measured during nitrogen washout and showed that in their two young normal subjects, the distributions of ventilation and blood flow were very narrow. In addition, they studied three older subjects, who each had broader distributions, as found in this study.

In our studies there are several features consistent with the present limited knowledge of \dot{V}_A/\dot{Q} distributions. We have pointed out that the position of the distributions in both young and old subjects is appropriate to the ratio of total ventilation to total blood flow, and that the mean of the blood flow curve is always less than that of the ventilation curve. It is reasonable, especially in the young subjects, that there are no areas of very high or very low \dot{V}_A/\dot{Q} .

It is well known that the arterial P_{O_2} falls with age in the normal population. Whatever the pathological mechanism, functionally this is most likely to be associated with increasing \dot{V}_A/\dot{Q} inequality. We have shown that the dispersion of the distribution increases with age.

Several indices of oxygen and carbon dioxide exchange were measured in the present studies and may be related to the distributions. For example, the ideal alveolar-to-arterial P_{O_2} difference increased with the log SD of blood flow (Fig. 8). In this figure we also show the relationship between the alveolar-arterial difference and log SD for theoretical, log-normal distributions. This theoretical relationship is remarkably similar to the measured relationship and it shows an abrupt inflection towards the origin for low values of A-a difference, which were beyond our range of measure-

ment. Other indices are the Bohr dead space for CO_2 and the dead space measured by the inert gas method. The two values were very similar except when areas of high \dot{V}_A/\dot{Q} were present, when, as previously mentioned, the Bohr dead space for CO_2 exceeded that of the inert gas method, because of contributions from units with high \dot{V}_A/\dot{Q} . A third point of comparison is the shunt measured by the present method and that obtained while breathing 100% oxygen by standard methods. Although there was a previously explained systematic difference between the two measurements, they ran parallel to one another. Finally, the changes in the distributions with posture were consistent with the known effects of gravity, in that areas of higher \dot{V}_A/\dot{Q} appeared as the subjects moved from the supine to the erect positions.

Effects of breathing 100% oxygen on the distributions. In eight of the nine subjects studied while breathing oxygen, a shunt developed within 30 min of commencing oxygen breathing. This was true irrespective of the order of the study, implying ready reversibility of the shunt on breathing room air again. The magnitude of the shunt was minimal in subjects with very narrow distributions, and greatest when blood flow was present in low \dot{V}_A/\dot{Q} areas (less than 0.1) while breathing room air. In subject W.C., in whom the shunt increased from zero breathing air to 10.7% breathing oxygen, an approximately equivalent (9.6% of blood flow) region of low \dot{V}_A/\dot{Q} disappeared without significant change in the main body of the distribution (Fig. 4, lower panel).

Such behavior would be expected to result from atelectasis after denitrogenation as predicted by Briscoe, Cree, Filler, Houssay, and Cournard (18) in 1960. They argued that as the alveolar P_{O_2} rose in low \dot{V}_A/\dot{Q} units from near mixed venous levels to near one atmosphere as the inspired P_{O_2} was raised, there would be an increase in the flux of oxygen from alveolar gas into capillary blood. It would then be possible for this flux to exceed the rate of delivery of fresh gas into the alveoli, thus resulting in a progressive loss of alveolar volume and eventually in atelectasis. We suggest that a second, synergistic mechanism may act to cause further atelectasis as the alveolar P_{O_2} rises. This mechanism is the release of hypoxic vasoconstriction, which would result in an increase in the blood flow and hence reduction in \dot{V}_A/\dot{Q} in these same units of low \dot{V}_A/\dot{Q} . As the \dot{V}_A/\dot{Q} falls by this mechanism, the likelihood of atelectasis on the basis of the first mechanism increases. Calculations indicate that both these effects will also result in the lowering of the \dot{V}_A/\dot{Q} in areas whose initial \dot{V}_A/\dot{Q} breathing room air is high enough (about 0.1–0.7) that atelectasis during oxygen breathing does not occur, but whose $P_{A_{O_2}}$ is still fairly low during air breathing. When the \dot{V}_A/\dot{Q} ratio exceeds about 0.7, there is virtually no change

with oxygen, since the PA_{O_2} breathing air is high enough that there is little change in vasoconstriction or flux of O_2 during O_2 breathing. Thus in addition to the development of shunt, oxygen breathing would be expected to increase blood flow to low \dot{V}_A/\dot{Q} areas and thus result in a skewing of the blood flow distribution. In the older group of subjects, this was in fact observed, while in the younger subjects very little change was seen because during room-air breathing the distributions contained very little blood flow in low \dot{V}_A/\dot{Q} regions.

Whatever the mechanisms, these results have important clinical implications. If a measurable shunt develops within 30 min in normal, nonsmoking volunteers breathing oxygen spontaneously, then hypoxic patients, who presumably have more areas with reduced \dot{V}_A/\dot{Q} , probably run a greater risk of developing shunt when given oxygen to breathe. This may be especially true after operations where poor lung expansion compounds the issue.

Limitations of the method. The ability of the method to distinguish between shunt and regions of low \dot{V}_A/\dot{Q} depends on the low solubility of the least soluble gas (SF_6) used in the method. In practice, units with \dot{V}_A/\dot{Q} less than 0.005 cannot be separated from shunt when SF_6 is the least soluble gas. If, for example, a gas existed that was 10 times less soluble than SF_6 , it would be possible to distinguish between shunt and units with \dot{V}_A/\dot{Q} of 0.0005.

In a similar manner, the resolution between totally unperfused areas and those with high \dot{V}_A/\dot{Q} depends on the solubility of the most soluble gas, acetone. With this gas, the method can separate areas whose \dot{V}_A/\dot{Q} ratio is 100 from unperfused regions. As a result, the working range of \dot{V}_A/\dot{Q} is from 0.005 to 100. Over this range, distributions with up to three separate modes can be accurately described.

When only one mode is present, its position, shape, and dispersion are accurately measured except for the extreme case of a truly homogeneous lung. When the computer program used in the method is fed data corresponding to such a lung, the result is a very narrow distribution centered at the exact \dot{V}_A/\dot{Q} of the given homogeneous lung. In other words, when there is zero dispersion in the real lung, the analysis returns a distribution that contains a small amount of dispersion, but which is otherwise accurate. As an indication of the error this will cause, the narrowest distribution that can be accurately recovered is one in which the log SD of blood flow is 0.25 and the alveolar-to-arterial PO_2 difference is 5 mm Hg. Even in the present study, in which normal subjects have been studied, this limit, although approached, has not been exceeded.

Repeatability of the distributions. The log SD for both blood flow and ventilation distributions was measured

from the first and second measurements separated by 5 min (see Methods). In most cases there was close correspondence, and the correlation coefficient from all points in the table was 0.91, the slope of the regression line was 0.95, and its intercept 0.03. Correspondence was equally good over the entire range of log SD measured.

Errors in cardiac output, ventilation, and inert gas measurements. The information required for measurement of the distributions consists of cardiac output, minute ventilation, and the concentrations of the six inert gases, in both arterial blood and mixed expired gas.

Errors in the inert gas measurements have been discussed elsewhere in detail (16) and are small. The standard deviation of the measurement of these gases is less than 3% of the concentration in both gas and blood for all gases except SF_6 , for which the standard deviation is 5.7%. The effects of such errors on the resulting distributions can be shown to be small.

Errors in the measurement of cardiac output and minute ventilation may be larger, so that it is important to assess the effects of such errors on the results. This was done in the following way. The data for the distributions shown in Figs. 1 and 3 were reprocessed by the computer program with cardiac outputs of $\pm 20\%$ of the measured value, but with the original inert gas concentrations in arterial blood and expired gas. The resulting distributions were not significantly different from the actual curves in either the shape or dispersion (log SD). The only significant difference was the positioning of the distributions along the \dot{V}_A/\dot{Q} axis. For a 20% underestimate in cardiac output, the distributions were shifted to the right (i.e., towards higher \dot{V}_A/\dot{Q} by about 20%. For example, if the \dot{V}_A/\dot{Q} at the mean of the distribution was 0.8, an error of this size would increase that mean \dot{V}_A/\dot{Q} value to 0.96. Such a shift is relatively small, compared with the range of \dot{V}_A/\dot{Q} ratios encountered. In the analysis, cardiac output and ventilation are used as ratios of one another, so that a 20% overestimate in ventilation will produce an identical effect. Errors in the opposite direction will shift the distributions correspondingly in the opposite direction.

Assumptions. A requirement of the method is that a steady state of gas exchange exists. There is considerable evidence for a steady state in the present studies. During the duplicate sampling procedures, end-tidal and mixed expired PO_2 and PCO_2 were monitored continuously and found to be stable. Arterial blood gases were constant to within 3 mm Hg over this period, and the duplicate measurements of cardiac output and minute ventilation were very similar. The mean absolute difference between the duplicate cardiac output measurements was 7.7% and that for venti-

lation 4.8%. Pulse rate was constant to within 5 beats/min in each subject.

The lack of systematic difference between the distributions obtained from the first and duplicate samples is evidence that the six inert gases were also in a steady state of gas exchange. Had a steady state not been in effect due to slow change of gas concentrations in areas of the lung with high volume perfusion ratios but low \dot{V}_A/\dot{Q} , the ratio of arterial to venous concentration would have risen between the initial and duplicate samples, and this was never seen. This would have affected particularly the poorly soluble gases, thereby resulting in an artificially low allocation of blood flow to areas of low \dot{V}_A/\dot{Q} in the distributions derived from the initial samples. Finally the fact that the results were physiological and well correlated with independent measurements such as the alveolar to arterial oxygen difference suggests that a steady state had been reached during the infusions.

Another assumption is that for the six test gases, alveolar and end capillary concentrations in any gas exchange unit are identical. This implies complete diffusion equilibration along the capillary, which, as Forster (19) pointed out, is almost certainly the case in the normal lung, since the equilibration time is calculated to be only a few hundredths of a second. Therefore, even if considerable diffusion impairment existed for oxygen and carbon dioxide, it is still likely that diffusion equilibrium would exist for the inert gases. This method would then allow the distribution of \dot{V}_A/\dot{Q} to be measured in the presence of diffusion impairment and allow separation of the effects of the two phenomena on gas exchange.

In the present studies, there is evidence that the assumption of inert gas diffusion equilibration is correct. There is also evidence that all of the inequality of ventilation and blood flow is due to differences between units arranged in parallel, and not due to series or stratified inhomogeneity. The basis of both these statements lies in a comparison of the blood flow and ventilation distributions in each subject. Under conditions of diffusion equilibrium and purely parallel \dot{V}_A/\dot{Q} inequality, the ventilation and blood flow curves could be calculated one from the other, since ventilation is the product of \dot{V}_A/\dot{Q} and blood flow in every compartment. If either of the above conditions were not met, then in any gas exchange unit, the alveolar and end capillary concentrations of the inert gas would be different. As a result, the effective \dot{V}_A/\dot{Q} of the unit would be different, depending on whether the arterial or the alveolar concentration was being considered, and the computation of ventilation from the product of blood flow and \dot{V}_A/\dot{Q} would not be possible. Within the limits of experimental accuracy, ventilation can be calculated from blood flow (this may be seen from Figs.

1, 2, and 3), indicating that incomplete diffusion equilibration or stratified inhomogeneity in normal subjects is not detectable, or if present, has insignificant effects on steady-state gas exchange.

There is additional information concerning rates of diffusion of the inert gases in the lungs. The six gases range in molecular weight from 30 (ethane) to 197.5 (halothane). If diffusion rates were sufficiently slow to produce noticeable effects on gas exchange, halothane should be affected most. In a homogeneous lung, the arterial and alveolar to venous concentration ratios of an inert gas are simple functions of the partition coefficient of the gas and \dot{V}_A/\dot{Q} of the lung. This relationship has been given by several authors (13, 20) and is:

$$\frac{P_a}{P_v} = \frac{P_A}{P_v} = \frac{\lambda}{\lambda + \dot{V}_A/\dot{Q}}$$

where λ is the blood: gas partition coefficient. It may be seen from this equation that the inverse of both P_a/P_v and P_A/P_v are linear functions of the inverse of partition coefficient. This equation is derived assuming that diffusion equilibrium exists. If this relationship is incorrect for halothane because of slow diffusion rates, it will not conform to the straight line predicted from the other gases of much lower molecular weight. In this manner, impaired diffusion of the inert gases may be detected. Even if the lung contains some \dot{V}_A/\dot{Q} inequality, the inverse relationship still appears smooth and close to linear so that the same conclusions may be made. In the present studies, this analysis always indicated complete diffusion equilibration.

ACKNOWLEDGMENTS

We would like to acknowledge with thanks the expert technical assistance of Mr. Peter Naumann, Mr. Richard Gaines, Miss Lee Durand, Mr. George Ozaki, and Miss Nancy Reppeto, and the generous provision of facilities by Dr. Eric Wahrenbrock.

This work was supported by U.S.P.H.S. Grants HL 13867-03, HL 05931 and HL 14169-03 and NASA Grant NGL 05-009-109.

REFERENCES

1. Martin, C. J., F. Cline, Jr., and H. Marshall. 1953. Lobar alveolar gas concentrations: effect of body position. *J. Clin. Invest.* **32**: 617-621.
2. Mattson, S. B., and E. Carlens. 1955. Lobar ventilation and oxygen uptake in man: influence of body position. *J. Thorac. Cardiovas. Surg.* **30**: 676-682.
3. West, J. B., and C. T. Dollery. 1960. Distribution of blood flow and ventilation-perfusion ratio in the lung, measured with radioactive CO_2 . *J. Appl. Physiol.* **15**: 405-410.
4. Riley, R. L., and A. Cournand. 1951. Analysis of factors affecting partial pressures of oxygen and carbon dioxide in gas and blood of lungs: theory. *J. Appl. Physiol.* **4**: 77-101.
5. Riley, R. L., A. Cournand, and K. W. Donald. 1951. Analysis of factors affecting partial pressures of oxygen

- and carbon dioxide in gas and blood of lungs: methods *J. Appl. Physiol.* **4**: 102-120.
6. Briscoe, W. A. 1959. A method for dealing with data concerning uneven ventilation of the lung and its effect on blood gas transfer. *J. Appl. Physiol.* **14**: 291-298.
 7. Rochester, D. F., R. A. Brown, Jr., W. A. Wichern, Jr., and H. W. Fritts, Jr. 1967. Comparison of alveolar and arterial concentrations of ^{85}Kr and ^{133}Xe infused intravenously in man. *J. Appl. Physiol.* **22**: 423-430.
 8. Okubo, T., and C. Lenfant. 1968. Distribution function of lung volume and ventilation determined by lung N_2 washout. *J. Appl. Physiol.* **24**: 658-667.
 9. Lenfant, C., and T. Okubo. 1968. Distribution function of pulmonary blood flow and ventilation-perfusion ratio in man. *J. Appl. Physiol.* **24**: 668-677.
 10. Lenfant, C. 1965. Effect of high FI_{O_2} on measurement of ventilation/perfusion distribution in man at sea level. *Ann. N. Y. Acad. Sci.* **121**: 797-808.
 11. Peslin, R., S. Dawson, and J. Mead. 1971. Analysis of multicomponent exponential curves by the Post-Widder's equation. *J. Appl. Physiol.* **30**: 462-472.
 12. Wagner, P. D., H. A. Saltzman, and J. B. West. 1974. Measurement of continuous distributions of ventilation-perfusion ratios: theory. *J. Appl. Physiol.* **36**: 588-599.
 13. Farhi, L. E. 1967. Elimination of inert gas by the lung. *Respir. Physiol.* **3**: 1-20.
 14. Klocke, R. A., and L. E. Farhi. 1964. Simple method for determination of perfusion and ventilation-perfusion ratio of the underventilated elements (the slow compartment) of the lung. *J. Clin. Invest.* **43**: 2227-2232.
 15. Yokoyama, T., and L. E. Farhi. 1967. Study of ventilation-perfusion ratio distribution in the anesthetized dog by multiple inert gas washout. *Respir. Physiol.* **3**: 166-176.
 16. Wagner, P. D., P. F. Naumann, and R. B. Laravuso. Simultaneous measurement of eight foreign gases in blood by gas chromatography. *J. Appl. Physiol.* **36**: 600-605.
 17. Hamilton, L. H. 1962. Gas chromatography for respiratory and blood gas analysis. *Ann. N. Y. Acad. Sci.* **102**: 15-28.
 18. Briscoe, W. A., E. M. Cree, J. Filler, H. E. J. Houssay, and A. Cournand. 1960. Lung volume, alveolar ventilation and perfusion interrelationships in chronic pulmonary emphysema. *J. Appl. Physiol.* **15**: 785-795.
 19. Forster, R. E. 1964. Diffusion of gases. *Handb. Physiol.* **33**: 845.
 20. Kety, S. S. 1951. The theory and applications of the exchange of inert gas at the lungs and tissues. *Pharmacol. Rev.* **3**: 1-41.