

Altered Distribution of Pulmonary Ventilation and Blood Flow Following Induction of Inhalational Anesthesia

Ronald Dueck, M.D.,* Iven Young, M.D.,† Jack Clausen, M.D.,‡ Peter D. Wagner, M.D.§

The development of impairment of pulmonary gas exchange during inhalational anesthesia was studied in ten patients (ages 52-75 years) by use of the multiple-inert-gas elimination method. Preoperative pulmonary function tests indicated a wide range of abnormal pulmonary function. Control gas-exchange studies with the subjects awake (supine position) demonstrated modest increases in pulmonary ventilation-blood flow (\dot{V}_A/\dot{Q}) distribution in all subjects (mean log SD = 0.96), but the shunt was minimal (mean 1.3 per cent). Inhalational anesthesia was either 1) halothane, 0.4 per cent (end-tidal) in N_2O , 50-60 per cent, balance oxygen, for eight subjects, or 2) halothane, 0.6 per cent, in nitrogen, 50-60 per cent, balance oxygen, for two subjects. Striking increases in retention of the least soluble tracer gases (SF_6 and ethane) were seen in all patients after a minimum of 35 min of anesthesia, during mechanical ventilation with both anesthetic regimens. This was due to one of three different patterns of responses. Three subjects showed primarily increased intrapulmonary shunt (mean shunt = 23 per cent of cardiac output). Three subjects showed primarily increases in low- \dot{V}_A/\dot{Q} units (mean = 32 per cent of cardiac output), with little or no shunt, while the remaining four had both intrapulmonary shunt and units of low \dot{V}_A/\dot{Q} . Arterial blood P_{O_2} measurements suggested substantially greater impairment of oxygenation when the pattern of response was primarily an increase in shunt. This difference was accentuated by the concentrating effect of N_2O uptake on alveolar P_{O_2} in low- \dot{V}_A/\dot{Q} units. As a consequence, arterial blood P_{O_2} values grossly underestimated the \dot{V}_A/\dot{Q} inequality in patients in whom low- \dot{V}_A/\dot{Q} regions developed. An alternative index, the development of CO_2 retention at constant alveolar ventilation, more reliably identified patients in whom severe \dot{V}_A/\dot{Q} inequality developed during inhalational anesthesia. (Key words: Anesthetics; volatile; halothane. Lung: function; perfusion; shunting; washout. Ventilation: carbon dioxide tension; distribution; oxygen tension; perfusion (ventilation-perfusion); shunting.)

GENERAL ANESTHESIA is known to impair pulmonary gas exchange.¹⁻⁴ This impairment occurs in patients who have either healthy^{4,5} or diseased⁶ lungs, as well as in the young^{4,5} and the elderly.^{1,2,3,6} The extent of impairment, however, is unpredictable, probably because it is the result of many interacting factors.^{7,8}

* Assistant Professor, Department of Anesthesiology.

† Research Fellow, Department of Medicine.

‡ Assistant Professor, Department of Medicine.

§ Associate Professor, Department of Medicine.

Received from the Department of Anesthesiology and Medicine, University of California, San Diego, and the Anesthesia Research Laboratory, Veterans Administration Hospital, San Diego, California 92161. Accepted for publication June 8, 1979. Supported by a Veterans Administration Research Grant. Presented in part at the Annual Meeting of the American Society of Anesthesiologists, October 1977.

Address reprint requests to Dr. Dueck: Veterans Administration Hospital, 3350 La Jolla Village Drive, San Diego, California 92161.

Analysis of the relative importances of various pathophysiologic mechanisms has been limited by previous inability to quantitate the relative roles of various possible gas-exchange mechanisms.⁸ For example, studies of the relative contributions of intrapulmonary shunt and regions with low ventilation-perfusion (\dot{V}_A/\dot{Q}) ratios by use of the Riley method of analysis⁹ have produced conflicting results.²⁻⁴ This may be due in part to the fact that changes in cardiac output, oxygen uptake, and alveolar gas tensions (due to uptake of soluble anesthetic gases) complicate the interpretation of changes in arterial blood P_{O_2} . Recent introduction by Wagner *et al.*¹⁰⁻¹² of the multiple-inert-gas method for determining estimates of the distribution of ventilation-perfusion ratios has enabled substantially improved resolution of the shunt and \dot{V}_A/\dot{Q} inequality components of venous admixture, independent of the inspired oxygen concentration. Further modifications by Dueck *et al.*¹³ have made feasible analysis of multiple-inert-gas elimination during inhalational anesthesia with both nitrous oxide and halothane in the usual combined clinical concentrations.

This modified inert-gas analysis technique was utilized in a series of patients with known pre-existing pulmonary disease to demonstrate that: 1) \dot{V}_A/\dot{Q} inequality has an important role in the gas-exchange impairment induced by anesthesia, especially in patients with pulmonary disease; 2) the extent of arterial hypoxemia during anesthesia depends primarily on the pattern of \dot{V}_A/\dot{Q} inequality, and this relationship is significantly complicated by continuing uptake of soluble anesthetic gases present in high inspired concentrations; 3) measured arterial blood P_{O_2} (and therefore $P(A'-a)O_2$) is not a consistently reliable index of the severity of gas-exchange impairment during anesthesia; 4) when alveolar ventilation is held constant, an increase in arterial blood P_{CO_2} following induction of anesthesia indicates the development of major \dot{V}_A/\dot{Q} inequality.

Methods

Ten patients scheduled for major elective surgical procedures at our Veterans Administration Hospital were selected for study. Selection of patients was based on the presence of one or more of three criteria: 1) more than 50 years of age; 2) more than 50 pack-

TABLE 1. Pulmonary Function Data

	Age (Years)	Ht. (cm)	Wt. (kg)	VC (% Pred.)	TLC (% Pred.)	FRC (% Pred.)	RV (% Pred.)	FEV ₁ (% VC)	FEF 25-75%	Pst TLC (cm H ₂ O)	RV/TLC (Per Cent)	Slope III (% N ₂ /l)	CV (% VC)
Subject 1	70	163	57	96	108	103	99	67	0.9	26	38	—	—
Subject 2	55	188	85	—	—	—	—	—	—	—	—	—	—
Subject 3	59	180	61	93	106	108	120	54	1.0	25	40	3.6	15
Subject 4	65	168	74	130	141	128	133	69	1.9	25	36	2.9	10
Subject 5	52	180	88	87	85	75	71	88	5.6	41	27	1.1	20
Subject 6	62	165	54	83	110	115	134	62	0.9	21	46	3.6	26
Subject 7	68	178	100	75	83	89	83	43	0.4	—	39	—	—
Subject 8	54	180	56	111	139	162	180	35	0.4	13	44	8.9	*
Subject 9	75	180	96	82	96	120	105	71	1.5	35	44	2.2	32
Subject 10	65	170	70	63	124	158	209	69	0.9	20	65	22.0	*

VC = vital capacity, TLC = total lung capacity, FRC = functional residual capacity, RV = residual volume, all obtained by body plethysmography, all at BTPS (% Pred. = per cent of value predicted for weight, height and age).^{19,20} FEV₁ = forced expiratory volume in 1 second, FEF 25-75% = forced expiratory flow rate

(l/sec) at 25-75% VC.¹⁹ Pst TLC = elastic recoil at total lung capacity, Slope III = slope of phase III during single-breath N₂ washout.²¹ CV = the lung volume above RV at the onset of phase IV (single-breath N₂ washout) as a percentage of VC.²²

* CV indeterminate because of the high slope of phase III.

year smoking history; 3) symptomatic pulmonary disease. None of the patients had unstable angina, arrhythmias, or congestive heart failure. All patients gave informed consent prior to the study in accordance with the protocol approved by the local committee on investigation of human subjects.

Preoperative pulmonary function testing of seven of the patients was performed with the patients seated the day before operation. Variables measured included vital capacity, residual volume, functional residual capacity, and total lung capacity by body plethysmography. A flow-volume loop was recorded and, where possible, lung elastic recoil and closing volume were measured (table 1). For Subjects 1 and 7, both of whom had long-standing and stable chronic obstructive pulmonary disease, results of pulmonary function tests conducted 30 to 60 days before operation were used. Pulmonary function testing of Subject 2 was not done because of scheduling limitations.

Preoperative lung volume measurements showed hyperinflation in Subjects 4 and 6 and severe hyperinflation in Subjects 8 and 10. Subjects 6 and 10 had lung elastic recoil values at total lung capacity that were near the lower limits of normal (elastic recoil pressure <15 cm H₂O at total lung capacity); the elastic recoil in Subject 8 was significantly less than normal, consistent with severe emphysema. The lung volumes of Subjects 5 and 7, on the other hand, were borderline low, suggestive of a restrictive pulmonary disorder. Both subjects had modest chronic hypertension, but no clinical evidence of congestive heart failure as a cause of restrictive pulmonary disease. Closing capacity was indeterminate in Subjects 8 and 10 due to a very high slope of phase III of the single-breath nitrogen test, and was demonstrated to be greater than functional residual capacity in the supine position only for Subject 9. Expiratory flow rates

ranged from normal (Subject 5) to moderately severe airway obstruction (Subjects 7 and 8).

On the day of the anesthetic study, subjects arrived without premedication in the operating room suite, having received nothing by mouth for a minimum of eight hours. Electrodes were placed for electrocardiographic monitoring and three catheters were inserted percutaneously, during infiltration anesthesia, into a peripheral vein, radial artery and pulmonary artery (Swan-Ganz #7 catheter via the internal jugular vein). A mixture of six inert gases (SF₆, ethane, cyclopropane, enflurane, ether, acetone) dissolved in tracer concentrations in lactated Ringer's solution with 5 per cent dextrose solution was then infused through a peripheral intravenous catheter at 2.4 ml/min.

Measurements of the distribution of \dot{V}_A/\dot{Q} ratios were made in duplicate during steady-state breathing of room air with the patients in the supine position. Steady-state conditions were checked by monitoring systemic and pulmonary vascular pressures, heart rate, respiratory frequency, tidal volume (calibrated Wright respirometer) and end-tidal CO₂ concentration (Beckman LB-2 CO₂ analyzer). Samples for inert-gas analysis were obtained following a minimum of 50 min of infusion of the solution containing the inert gases, including at least 30 min of steady-state conditions. These samples were 10 ml each of mixed venous blood and arterial blood in heparinized 30-ml matched-barrel glass syringes and 15 ml of mixed expired gas in a matched-barrel glass syringe (collected after passing expired gas through a heated mixing box¹¹ via a mouthpiece). In addition, 4-ml samples of mixed venous blood and arterial blood were taken for measurements of P_{O₂}, P_{CO₂}, and pH (Radiometer electrodes). Inert-gas concentration measurements were performed with Hewlett-Packard

Model 5711 FID and Model 5713 ECD gas chromatographs.¹³ Samples intended for blood-gas analysis were stored (on ice) for no more than 20 min prior to measurement of P_{O_2} , P_{CO_2} , and pH .

Anesthesia was induced via mask in all subjects. In Subjects 1 to 8 the inspired concentrations of N_2O and halothane were sufficient to maintain an end-tidal halothane concentration of 0.4 to 0.6 per cent, and an inspired oxygen concentration of 37 to 47 per cent (table 2). Subjects 9 and 10 received anesthesia with halothane vaporized in nitrogen and oxygen, maintaining halothane at an end-tidal concentration of 0.6 per cent with inspired oxygen concentrations of 39 and 47 per cent, respectively. The purpose of excluding N_2O in the study of these two patients was to test the hypothesis that the changes in measured distribution of \dot{V}_A/\dot{Q} ratios for Subjects 1 to 8 were primarily due to continuing uptake of N_2O , especially in regions of relatively low \dot{V}_A/\dot{Q} , creating a concentrating effect on tracer inert gases.¹⁴ Such a concentrating effect would decrease expired ventilation, especially in low- \dot{V}_A/\dot{Q} regions, and would thereby worsen \dot{V}_A/\dot{Q} inequality.

Studies of the distribution of ventilation-perfusion ratios were performed prior to operation during mechanical ventilation via an endotracheal tube. Tidal volumes were set at 12 ml/kg and frequency adjusted to provide minute volume values equal to those awake. Sampling times during anesthesia were varied, for two reasons. First, steady-state conditions were difficult to reproduce at a predictable point in time because of the need to proceed more cautiously in patients with concurrent cardiovascular disease. Second, we tested the hypothesis that continuing uptake of relatively large amounts of soluble anesthetic gas in low- \dot{V}_A/\dot{Q} regions was the primary cause

of the observed large amounts of blood flow to regions in the lung with very low \dot{V}_A/\dot{Q} ratios and shunt. We assumed that on the basis of such a phenomenon early measurements would show higher retention values than later measurements, due to progressive decreases in anesthetic gas uptake. Hence, our shortest induction-to-sampling-time interval was 35 min, and the longest, 255 min (Subject 8 was studied three and four hours after induction, intraoperatively). The mean interval from induction to first sampling time was 60 min, with another 5–15-min interval for duplicate or triplicate measurements.

Physiologic variables were again monitored and recorded, and blood and expired gas samples obtained, as in the preoperative awake study. In addition, inspired gas samples were obtained for chromatographic analysis of inspired oxygen (thermal conductivity detector), N_2O , and halothane (flame ionization detector) concentration. Arterial and venous blood N_2O and halothane tensions, as well as rates of uptake of these gases, were determined for Subjects 6 to 10.

Gas chromatographic analysis of inert-gas concentrations was performed as described earlier.^{10,13} Calculation of the solubilities of the inert gases and of excretion (mixed expired/mixed venous blood partial pressure ratio) and retention (mixed arterial blood/mixed venous blood partial pressure ratio) was also performed as described earlier.¹⁰ Determination of representative distributions of ventilation-perfusion ratios was done with the form of Ridge regression analysis described recently by Evans and Wagner.¹² Typical data sets were also analyzed to determine the range of distributions compatible with the data. All computations were performed with a PDP 11-V03 Mini-Computer.

TABLE 2. Gas-exchange Data during Studies with the Subjects Awake

	P_{IO_2} (torr)	Arterial Blood P_{O_2} (torr)	Venous Blood P_{O_2} (torr)	Arterial Blood P_{CO_2} (torr)	Cardiac Output (l/min)	Low \dot{V}_A/\dot{Q} (% \dot{Q}_t)	Shunt (% \dot{Q}_t)	Mean \dot{V}_A/\dot{Q} Blood Flow	Log SD Blood Flow	\dot{V}_E (l/min)	V_D (% \dot{V}_E)
Subject 1	149	54	30	44	4.3	2.5	3.9	0.65	0.86	7.9	55
Subject 2	149	70	27	38	5.8	4.2	3.4	0.73	1.06	7.7	28
Subject 3	149	66	35	40	9.0	1.9	0.9	0.43	0.81	8.6	42
Subject 4	147	69	37	40	5.2	1.4	0.6	0.69	0.78	7.9	48
Subject 5	148	69	35	32	8.4	5.8	0.0	0.60	0.93	10.7	41
Subject 6	148	57	32	36	6.0	1.6	3.0	0.50	0.86	9.1	53
Subject 7	148	56	30	47	6.7	15.8	1.3	0.39	1.42	7.1	34
Subject 8	148	58	35	40	4.4	7.8	5.6	0.59	1.17	6.5	26
Subject 9	148	67	37	38	7.2	2.7	1.7	0.54	0.80	7.5	34
Subject 10	149	64	36	43	5.5	0.9	0.1	0.53	0.94	8.0	40

P_{IO_2} = inspired P_{O_2} ; low \dot{V}_A/\dot{Q} = percentage of cardiac output distributed to areas with $0.005 > \dot{V}_A/\dot{Q} < 0.1$; mean \dot{V}_A/\dot{Q} and log SD blood flow are statistical analyses of the blood flow distribu-

tion with respect to \dot{V}_A/\dot{Q} ; \dot{V}_E = minute ventilation, BTPS; V_D = dead space, percentage of minute ventilation, as determined by inert-gas analysis. The data shown are mean values.

FRACTIONAL RETENTION (R) AND EXCRETION (E)
..... DATA ——— HOMOGENEOUS LUNG

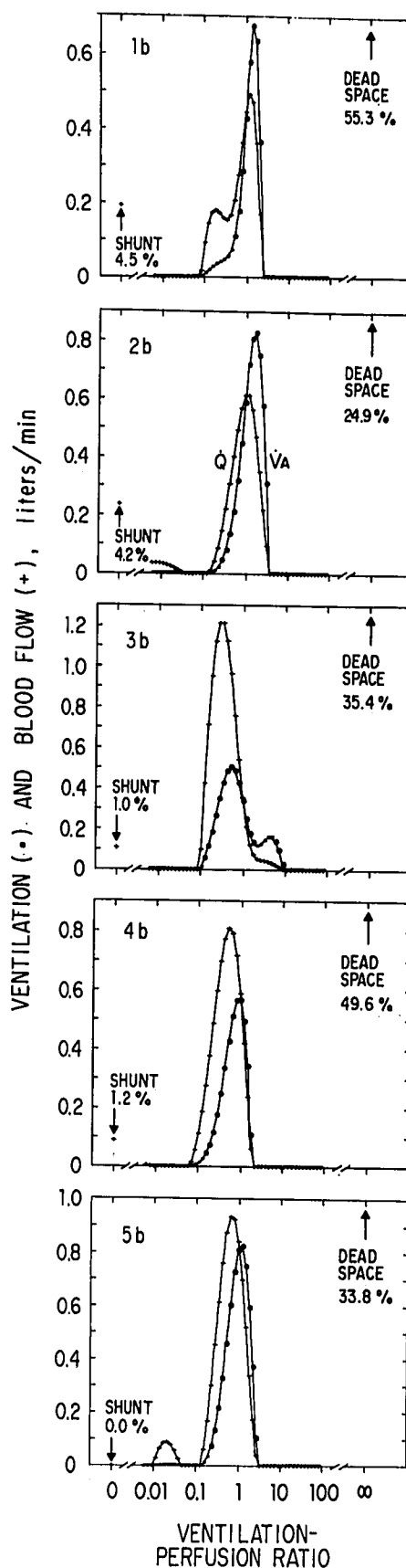
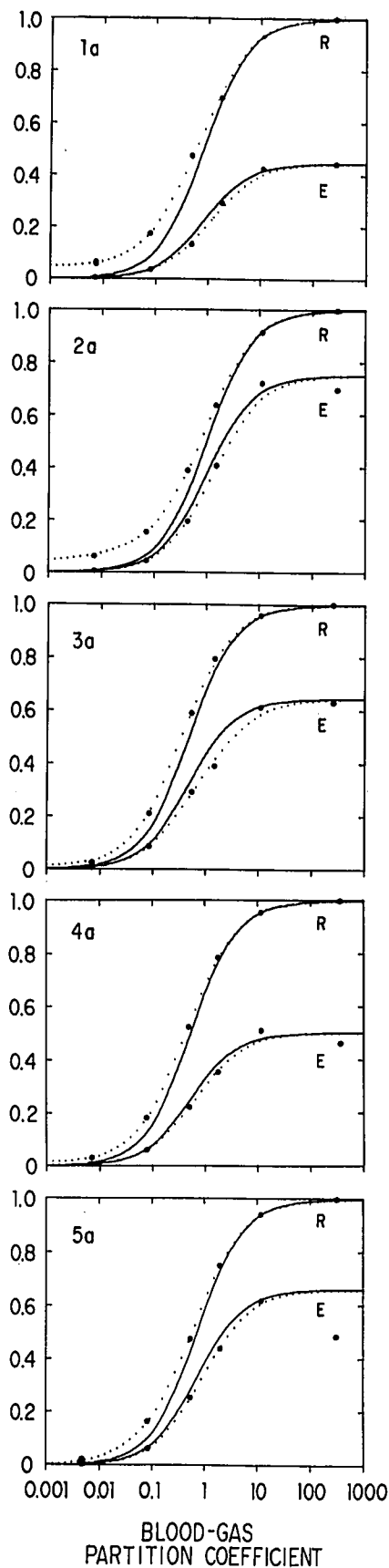
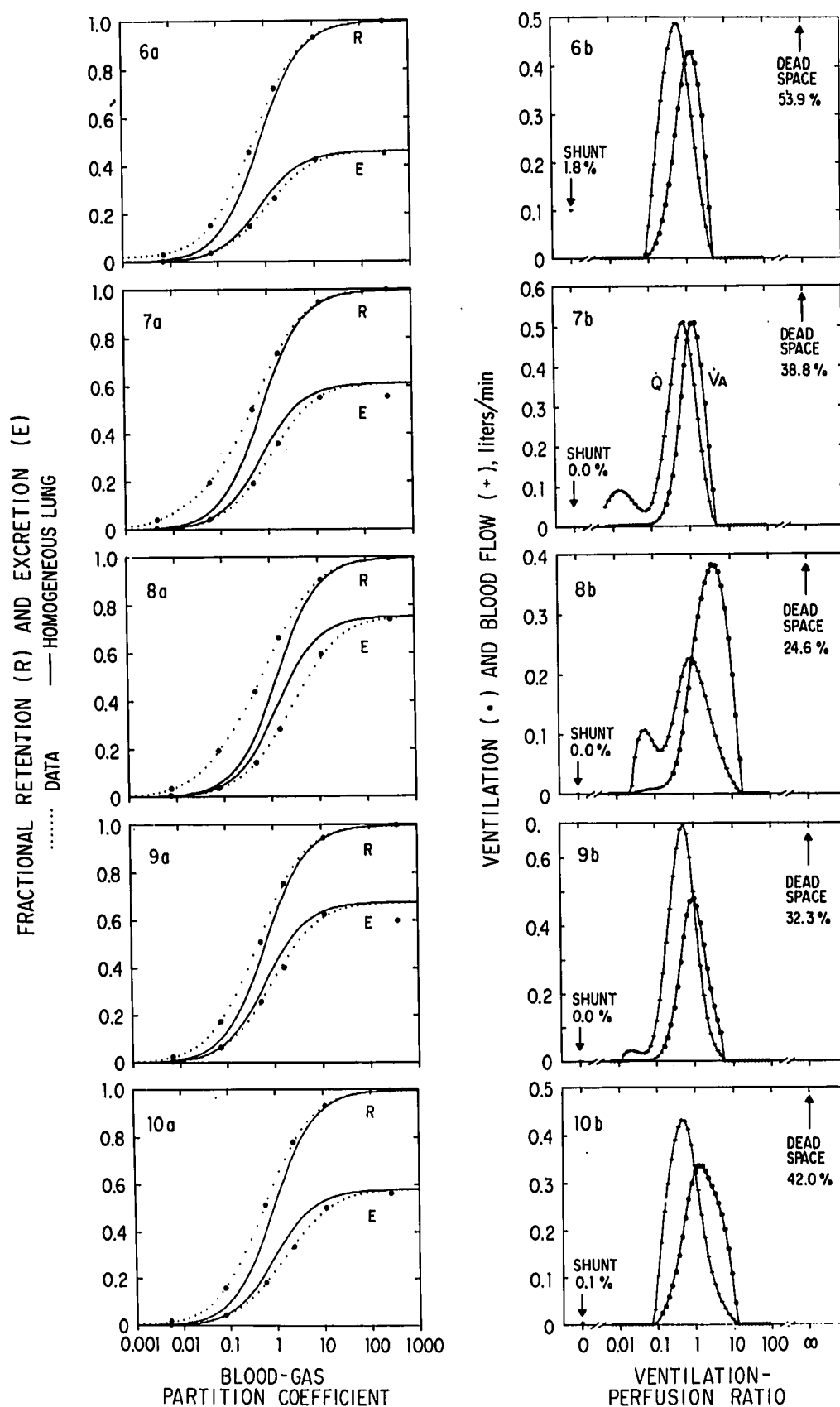


FIG. 1. Examples of retention-solubility (R) curves and excretion-solubility (E) curves for Subjects 1 to 5, obtained with the subjects awake, are plotted on the left (a). Dotted lines (.....) are the "best-fit" curves through the measured retention and excretion data. Each heavy dot (•••••) represents one test gas (SF_6 , ethane, cyclopropane, enflurane, ether, acetone, left to right), while solid lines represent the curves that would have been obtained in a homogeneous lung with the same minute ventilation (same dead space) and cardiac output (no shunt). The representative distribution of \dot{V}_A/\dot{Q} ratios from the measured inert-gas data are plotted on the right (b), with blood flow (—+—+—) and ventilation (—•—•—) in l/min , and \dot{V}_A/\dot{Q} on a log scale. All five subjects whose values are shown had widened distributions of \dot{V}_A/\dot{Q} ratios, when compared with findings in healthy younger subjects.

FIG. 2. Measured retention-solubility and excretion-solubility curves obtained from Subjects 6 to 10, while awake, are plotted on the left (a), with the associated representative distributions of \dot{V}_A/\dot{Q} ratios on the right (b). All five of these patients also showed considerably increased inhomogeneity or "maldistribution" of \dot{V}_A/\dot{Q} ratios, when compared with young healthy subjects. A considerable amount of blood flow to low \dot{V}_A/\dot{Q} ($0.005 > \dot{V}_A/\dot{Q} < 0.1$) regions is evident in the values for Subjects 7 and 8.



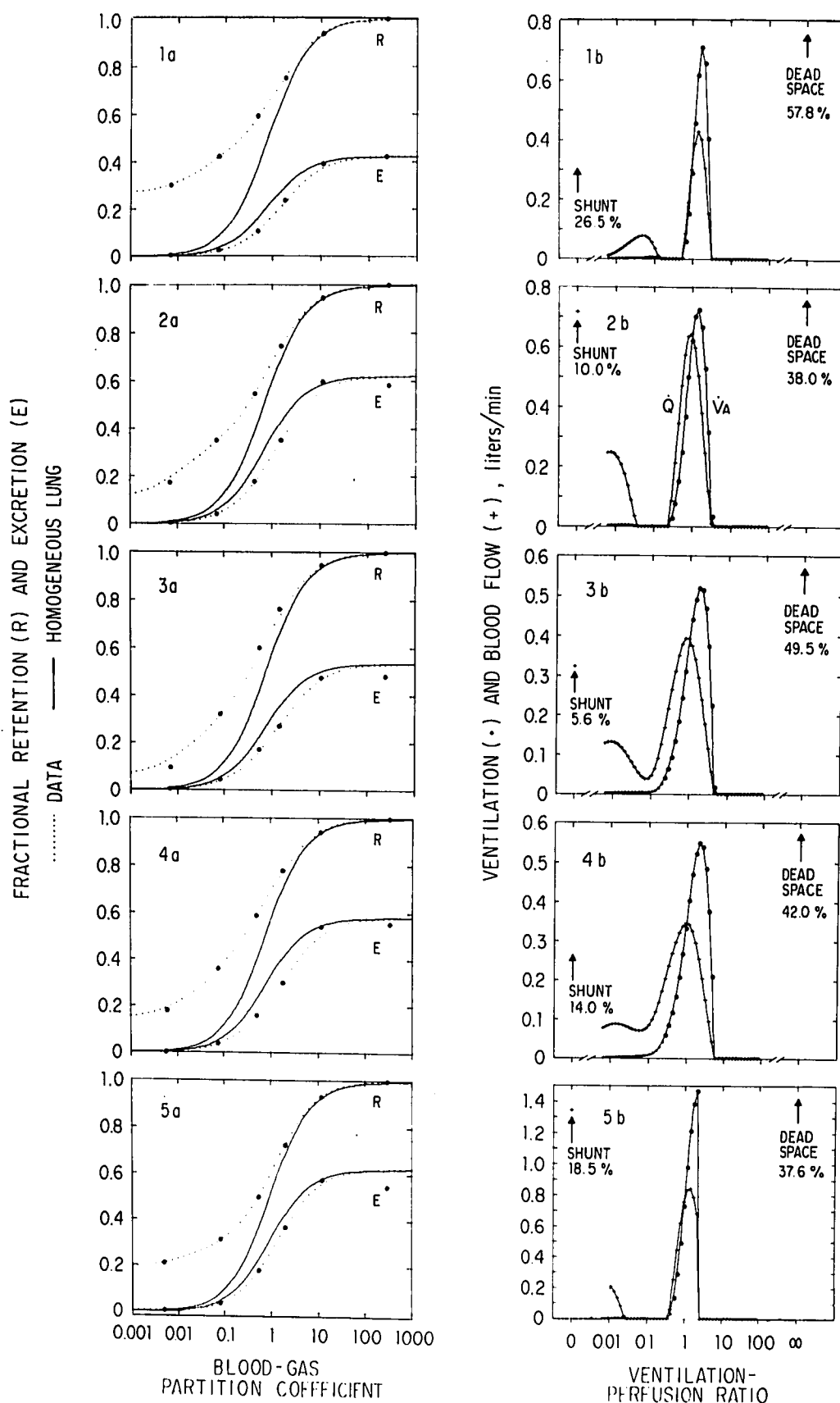
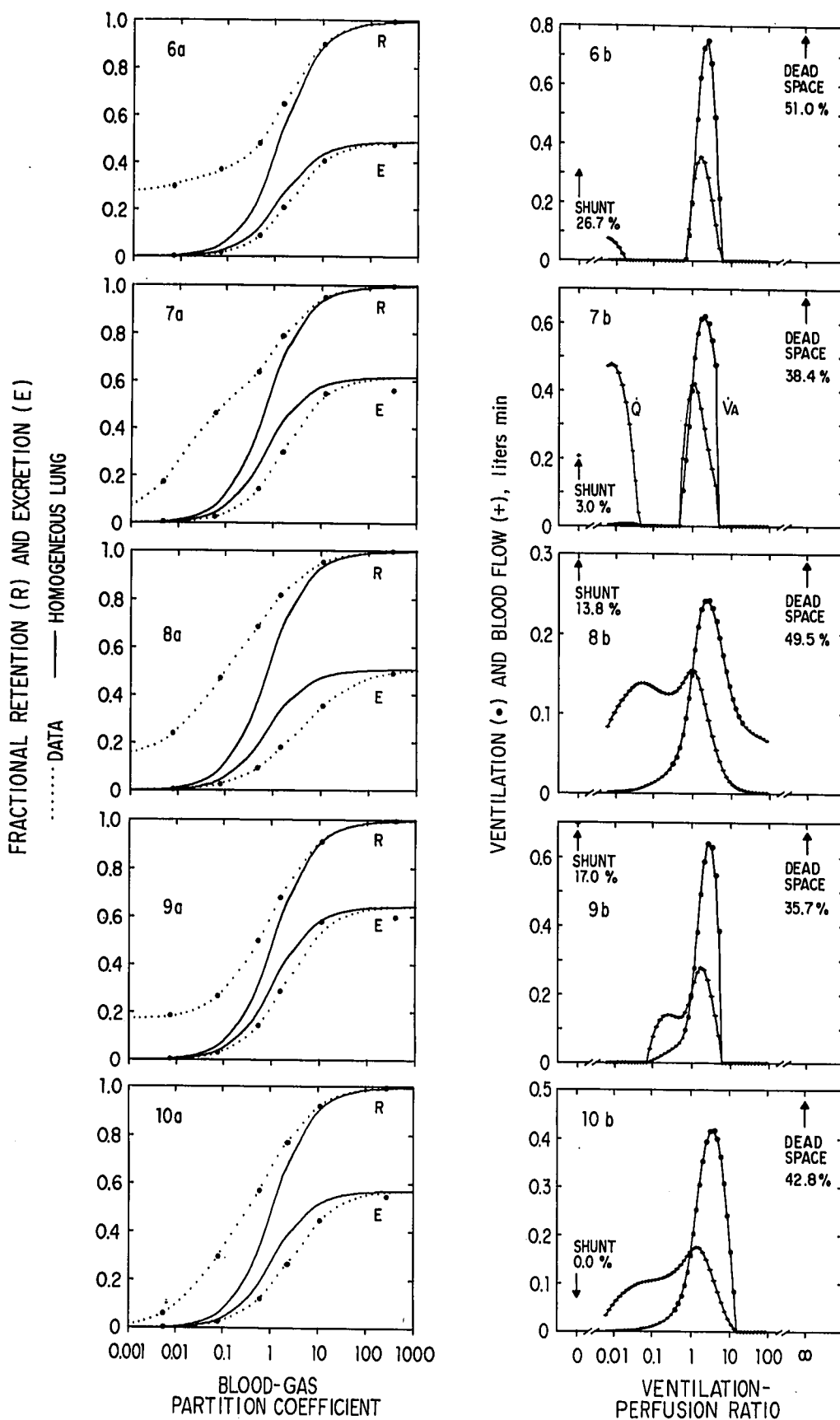


FIG. 3. Retention-solubility and excretion-solubility curves for Subjects 1 to 5 during anesthesia are shown on the left (a), with the representative distributions of \dot{V}_A/\dot{Q} ratios on the right (b). The pattern of responses of Subjects 1 and 5 is compatible with large increases in shunt ($\dot{V}_A/\dot{Q} < 0.005$), as indicated in the representative \dot{V}_A/\dot{Q} distributions, whereas Subjects 2 and 4 had responses compatible with both an increase in shunt and development of low- \dot{V}_A/\dot{Q} units. Subject 3 showed a development of regions of low \dot{V}_A/\dot{Q} , with a relatively small amount of shunt.

FIG. 4. Retention-solubility and excretion-solubility curves for Subjects 6 to 10 (during anesthesia) are plotted on the left (a), and the representative distributions of \dot{V}_A/\dot{Q} ratios on the right (b). The pattern of responses of Subjects 6 and 9 is compatible with relatively large increases in shunt and relatively small increase in low \dot{V}_A/\dot{Q} regions. Subjects 7 and 10 showed a distinctly different pattern, which was the result of development of regions of low \dot{V}_A/\dot{Q} but not shunt. Subject 8 again showed a response indicative of both an increase in shunt and development of low- \dot{V}_A/\dot{Q} units. The patterns for Subjects 9 and 10, receiving halothane anesthesia without nitrous oxide, demonstrate development of each of the two distinctly different patterns of \dot{V}_A/\dot{Q} . These were both associated with very definite increases in retention of the lower-solubility gases (SF_6 , ethane, cyclopropane), in spite of the absence of nitrous oxide.



Results

Studies of inert-gas elimination while the patients were awake showed a range of mild to moderate impairment generally consistent with the results of preoperative pulmonary function tests. The retention-solubility curves, with the corresponding representative distributions of \dot{V}_A/\dot{Q} ratios, are shown for Subjects 1 to 5 in figure 1 and for Subjects 6 to 10 in figure 2. An interrupted line (least-squares best-fit retention-solubility and excretion-solubility curve) has been drawn through the patient data points and is compared with a solid line that indicates where the points would have been positioned for each patient if there had been no \dot{V}_A/\dot{Q} inhomogeneity or shunt, but the same dead space, minute ventilation, and cardiac output. Dead-space ventilation in this case is defined by the fractional amount of ventilation to regions with $\dot{V}_A/\dot{Q} > 100$, as determined by analysis of inert-gas excretion data. This includes both anatomic and instrumental dead spaces, as well as any regions in the lung with $\dot{V}_A/\dot{Q} > 100$. Compared with volunteer subjects with normal lungs,⁹ Subjects 1, 2, 3, 4, and 6 showed small increases in the retention of the least soluble gases (SF_6 and ethane) suggestive of small amounts of intrapulmonary shunt while awake. Subjects 5 and 9 showed small, but physiologically significant, increases in ethane retention (but not retention of SF_6), suggestive of relatively small regions with low \dot{V}_A/\dot{Q} ratios. Subject 8, especially, and Subject 10 showed decreased enflurane and ether excretion, suggestive of areas with higher \dot{V}_A/\dot{Q} ratios and consistent with the interpretation of the results of their pulmonary function testing, which indicated some emphysema.¹⁵ All subjects showed considerable increases in the widths of both blood flow and ventilation distributions with respect to ventilation-perfusion ratios; that is, increased \dot{V}_A/\dot{Q} inequality (mean log SD 0.96, 0.77 respectively), compared with values obtained for healthy volunteer subjects (mean log SD < 0.5).¹¹ Dead-space ventilation was generally increased, though variable from subject to subject, due in part to the additive effect of instrumental dead space (70 ml) and in part to variable tidal volumes as a consequence of the small increase in air-flow resistance ($< 2 \text{ cm H}_2\text{O/l/sec}$) through the one-way valve and expired gas-mixing tubing.

Studies during anesthesia showed a striking increase in impairment of inert-gas elimination. There was an average sixfold increase in SF_6 retention, with a fivefold increase in ethane retention (figs. 3 and 4) from awake control values. However, there was considerable variability in the magnitudes of the increased retention, as well as in the relative increases in retention of SF_6 as compared with ethane. Relatively greater increases in SF_6 retention were seen in

Subjects 5, 6, and 9, and this response was reflected in the associated \dot{V}_A/\dot{Q} distributions by substantial increases in shunt, with a mean value of 23 per cent of the cardiac output (mean awake value = 2 per cent in the same subjects). Considerably greater increases in ethane retention were seen in Subjects 3, 7 and 10, and were reflected in the associated \dot{V}_A/\dot{Q} distributions by an average of 32 per cent of the cardiac output distributed to areas with low \dot{V}_A/\dot{Q} ratios (mean awake value = 6 per cent). Subjects 1, 2, 4, and 8 showed an intermediate pattern of response, associated with mean values of 17 per cent shunt and 23 per cent of the cardiac output distributed to areas with low \dot{V}_A/\dot{Q} ratios during anesthesia. It is important to note that the two distinct patterns, a predominant increase in intrapulmonary shunt, and a predominant increase in low \dot{V}_A/\dot{Q} ratios, were also seen in patients not receiving N_2O , that is, Subjects 9 and 10.

Only Subjects 8 and 10 showed increases in amounts of ventilation to areas with high \dot{V}_A/\dot{Q} ratios ($10 < \dot{V}_A/\dot{Q} < 100$), as indicated by decreases in enflurane and ether excretion during anesthesia. These amounted to 12 and 3 per cent of minute ventilation, respectively.

Variable changes in dead space ($\dot{V}_A/\dot{Q} > 100$) were seen following induction of anesthesia, with no directional change for the group as a whole. This may have been related in part to the combined effects of variable changes in anatomic dead space with tracheal intubation¹⁶ and mechanical ventilation.

The reliability of the representative patterns of responses to anesthesia indicated by the levels of tracer inert-gas retention data was tested in two ways. First, the retention-solubility data obtained during anesthesia in Subjects 4, 6, and 7 were compared with retention-solubility curves that would have been seen if all \dot{V}_A/\dot{Q} inequality had been in 10 per cent increments of either pure shunt, or a low- \dot{V}_A/\dot{Q} mode ($\dot{V}_A/\dot{Q} = 0.005$) (fig. 5, A, B, and C). These shunt and low- \dot{V}_A/\dot{Q} isopleths represent two-compartment models of either shunt of areas of low \dot{V}_A/\dot{Q} (same cardiac output and minute ventilation), with the second compartment having a $\dot{V}_A/\dot{Q} \approx 1$ (the exact values being determined by the above variables). The choice of a low- \dot{V}_A/\dot{Q} mode of 0.005 was made as a matter of convenience, to compare the shapes of retention-solubility curves produced by shunt and by \dot{V}_A/\dot{Q} inequality. Other choices of a low \dot{V}_A/\dot{Q} ratio could equally well have been made. Subject 6 (fig. 5A) had primarily an increase in intrapulmonary shunt following induction of anesthesia, with the best-fit line being closer in shape and position to the 30 per cent shunt line than to any other isopleth. Some additional increase in ethane retention (fig. 5A) does suggest additional blood flow to a region with low \dot{V}_A/\dot{Q} ratios. In contrast, the retention-solubility curve for Subject 7 (fig. 5B) sharply transects all of the iso-shunt curves,

and more closely resembles the low \dot{V}_A/\dot{Q} isopleths. This indicated why the representative distribution of \dot{V}_A/\dot{Q} ratios for Subject 7 (fig. 4) showed so much of the cardiac output in regions with \dot{V}_A/\dot{Q} ratios considerably less than 0.1 but greater than zero. For Subject 4 (fig. 5C), the retention-solubility curve was dissimilar from both of the illustrated pure forms of \dot{V}_A/\dot{Q} inequality. This must be due to a combination of both an increase in shunt and areas with low \dot{V}_A/\dot{Q} ratios.

Our second method of testing these three representative patterns of \dot{V}_A/\dot{Q} inequality was by the use of linear programming.¹² This test indicated that the majority of blood flow to poorly ventilated regions in figure 5A had to have a \dot{V}_A/\dot{Q} ratio of less than 0.005 (shunt), and that the majority of blood flow to poorly ventilated regions in figure 5B had to have a \dot{V}_A/\dot{Q} ratio >0.005 and <0.05 , that is, very low \dot{V}_A/\dot{Q} . For Subject 4 (fig. 5C), it was impossible to account entirely for the increased retention of SF₆ and ethane with either shunt or a low \dot{V}_A/\dot{Q} region alone, indicating that both types of lung units had to be present.

We did not attempt to predict arterial blood P_{O₂} values from the derived \dot{V}_A/\dot{Q} distributions, as has been done previously,¹⁵ for two reasons. First, the increased inspired P_{O₂} during anesthesia substantially magnifies small errors in apportioning of regions with the lowest \dot{V}_A/\dot{Q} to either shunt or very low \dot{V}_A/\dot{Q} ratios. Ongoing anesthetic gas uptake, especially of N₂O, could further magnify this effect. Second, such a prediction requires measurement of mixed venous blood and inspired N₂O and halothane concentrations, which were not available for all subjects. The problem is of sufficient complexity to warrant extensive theoretical study in its own right prior to clinical application.

On the basis of our findings of high retention values for the least soluble tracer gases during anesthesia in all ten subjects, regardless of the sampling interval from time of induction or the presence of nitrogen as the balance gas, we conclude that the magnitude of \dot{V}_A/\dot{Q} inequality (shunt and low- \dot{V}_A/\dot{Q} regions) demonstrated in this study was not primarily due to continuing anesthetic gas uptake in regions of low \dot{V}_A/\dot{Q} (fig. 6). The underlying assumption of highly variable rates of anesthetic gas uptake was supported by evidence obtained in Subjects 6 to 10 by gas chromatographic analysis, as described previously.¹³ Mean values (duplicate samples) of anesthetic gas uptake were 125 ml/min at 42 min for Subject 6, 325 ml/min at 85 min for Subject 7, and 28 ml/min at 230 min for Subject 8. Subjects 9 and 10, not receiving N₂O, each had a mean value of 9 ml/min halothane uptake. In spite of an almost threefold greater anesthetic gas uptake in Subject 7 as compared with Subject 6, and a twelvefold greater uptake than

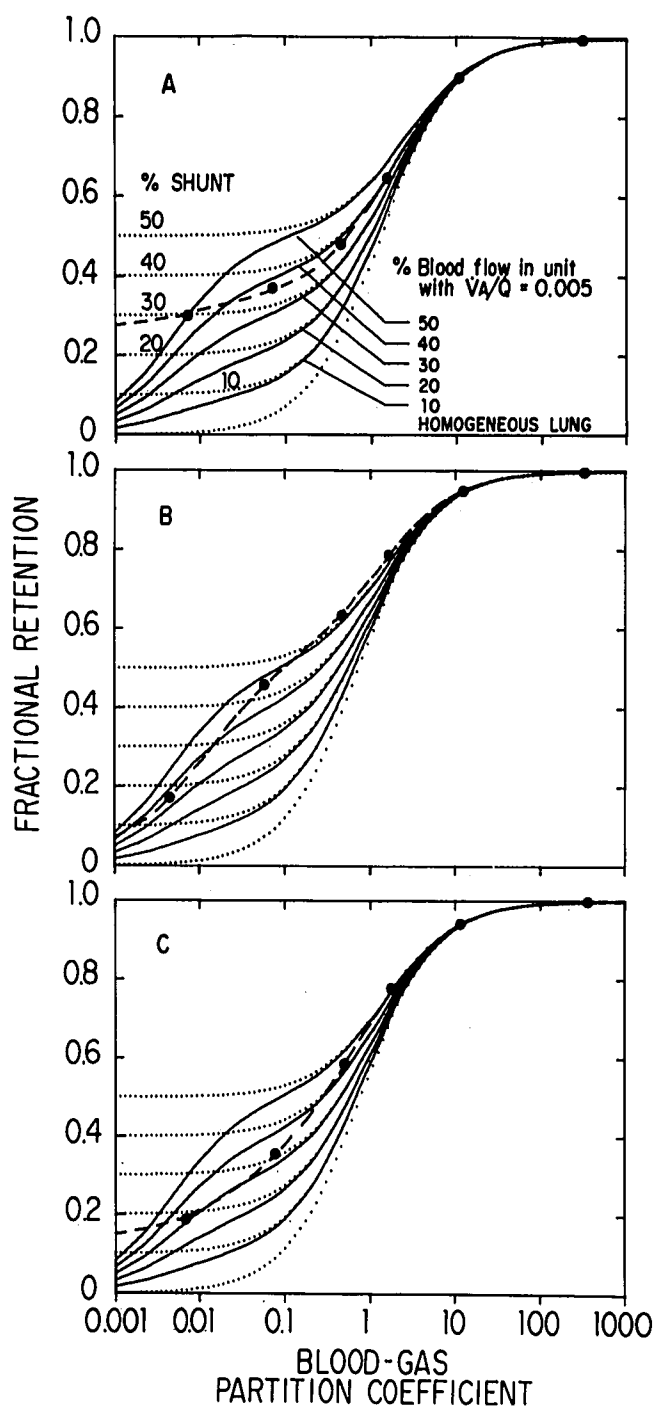


FIG. 5. The retention-solubility curves of Subjects 6, 7, and 10 during anesthesia are plotted in panels A, B, and C, respectively, with comparative curves (same minute ventilation and cardiac output) for 10 per cent increments in shunt (-----) or a very low \dot{V}_A/\dot{Q} ($\dot{V}_A/\dot{Q} = 0.005$) mode (—). These isopleths from a "two-compartment" model (second compartment \dot{V}_A/\dot{Q} approximately equal to 1) suggest that the \dot{V}_A/\dot{Q} abnormality for A is predominantly shunt, that for B is almost completely due to a very-low- \dot{V}_A/\dot{Q} region, and C is probably a combination pattern.

that of Subject 8, the levels of SF₆ and ethane retention were very similar (fig. 6). In fact, SF₆ retention was greater for Subject 6 than for Subject 7, in spite of

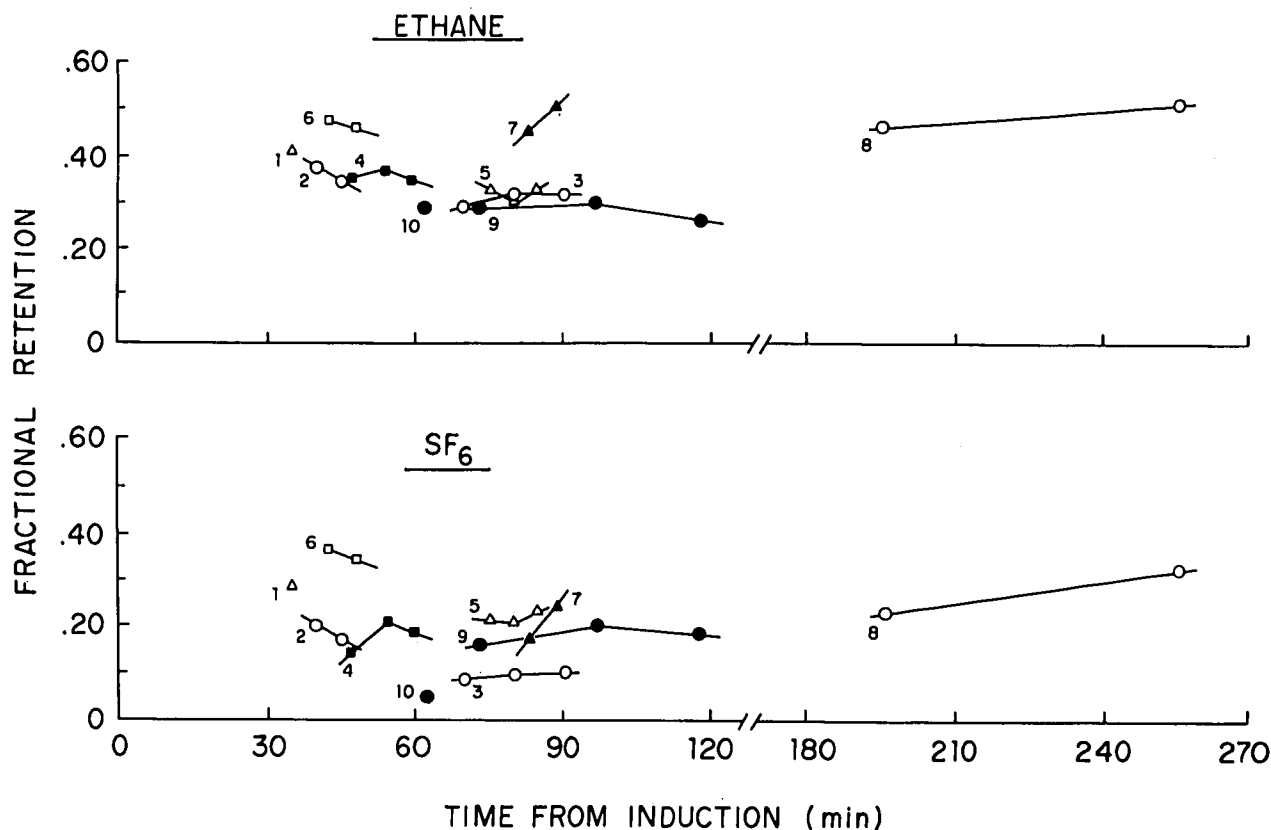


FIG. 6. Fractional retention of ethane (upper panel) and SF₆ (lower panel) plotted against sampling time interval from the time of induction for each analysis (single, duplicate, triplicate) in each subject during anesthesia. Notice that there is no consistent pattern of either increase or decrease of fractional retention of the least soluble tracer gases with respect to time, in spite of the known progressive decline of soluble anesthetic gas uptake.

the difference in anesthetic gas uptakes. The levels of retention of SF₆ and ethane for Subjects 9 and 10 were comparable to levels seen in subjects receiving N₂O in addition to halothane. Finally, no consistent change in the magnitude of retention of the least soluble gases (SF₆ and ethane) was seen with increasing times of sampling from the time of induction of anesthesia.

Arterial blood P_{O₂} values in awake subjects reflected both the variability of the preoperative extent of ventilation-perfusion mismatching and variability in mixed venous blood P_{O₂} values due to differences in cardiac output. The lowest arterial blood P_{O₂} was seen in Subject 1 (table 2), in spite of relatively modest \dot{V}_A/\dot{Q} inequality (log SD of the blood flow distribution 0.85). This was due to a relatively low cardiac output, 4.3 l/min, for the rate of O₂ consumption, 240 ml/min, resulting in a mixed venous blood P_{O₂} of 30 torr. Subject 2, in contrast, with a log SD of the blood flow distribution of 1.1, had a cardiac output of 9.5 l/min, and his arterial blood P_{O₂} was 70 torr, the highest awake value for all subjects. The severity of hypoxemia in Subjects 7 and 8, on the other hand, was that expected on the basis of \dot{V}_A/\dot{Q} inequality (log SDs of blood flow distributions = 1.4 and 1.2, respectively) and normal cardiac output.

Blood-gas values found during anesthesia were consistent with the physiologic implications of the described patterns of \dot{V}_A/\dot{Q} distribution (table 2). The arterial blood P_{O₂} was lowest for Subject 1, in spite of the fact that Subject 7 had almost twice the amount of blood flow to poorly ventilated lung (compared with the amount of blood flow to unventilated lung for Subject 1). The difference in oxygenation for these two patterns was accentuated not only by the increased inspired oxygen concentration but also by the presence of N₂O. Comparing Subjects 8 and 10, both of whom had inspired oxygen concentrations of 47 per cent, the presence of N₂O in Subject 8 resulted in an arterial blood P_{O₂} higher than that of Subject 10 (no N₂O used). This occurred in spite of the presence of 19 per cent shunt in Subject 8 (mean of two determinations) and comparable amounts of low- \dot{V}_A/\dot{Q} units (31 per cent for Subject 8; 28 per cent for Subject 10). Similarly, Subject 7 had an arterial blood P_{O₂} only 12 torr lower than that of Subject 10, in spite of breathing oxygen, 40 per cent, and having both a substantially greater amount of blood flow to regions of very low \dot{V}_A/\dot{Q} and an 8.5 per cent shunt.

This accentuation of the difference in arterial oxygenation in patients with low- \dot{V}_A/\dot{Q} rather than shunt

regions was probably due to a concentrating effect of N_2O uptake on alveolar P_{O_2} .¹⁷ This effect persisted for an extended period, as illustrated by the findings in Subject 8, whose measured arterial N_2O tensions were 10 and 20 torr higher than inspired N_2O tensions three and four hours following induction of anesthesia, respectively. Measured values of uptake of N_2O were 28 and 15 ml/min, respectively, in spite of the fact that at the three-hour sampling time mixed venous blood N_2O tension had already reached a value equal to the inspired N_2O tension.

Theoretical considerations based on the derived \dot{V}_A/\dot{Q} distributions for Subject 8 indicated that this uptake occurred in lung units with \dot{V}_A/\dot{Q} ratios between 0.005 and 0.5, whereas excretion of N_2O occurred in units with \dot{V}_A/\dot{Q} ratios greater than 0.5 (but less than 100).

Arterial blood P_{CO_2} values increased (mean increase 5 torr) during anesthesia in Subjects 2, 3, 4, 6, 7, and 8, in spite of no significant change in alveolar ventilation (minute ventilation minus dead space ventilation), with mean ± 1 SD values of 4.7 ± 0.5 l/min while the patients were awake and 4.5 ± 0.6 l/min during anesthesia. This increase in P_{CO_2} could not have been due to increased CO_2 production, since there was an average 27 per cent decrease ($P < 0.05$, paired t analysis) as determined by the Fick principle from

mixed venous blood and arterial blood P_{CO_2} differences and cardiac output. Therefore, the most likely cause of CO_2 retention was the increased \dot{V}_A/\dot{Q} inequality. This is supported by the linear relationship shown for arterial blood P_{CO_2} and log SD of the blood flow distribution during anesthetic studies ($r = 0.66$) (fig. 8).

Discussion

This study has confirmed that inhalational anesthesia leads to both ventilation-perfusion inequality and shunting, as suggested earlier by Nunn *et al.*² and Price *et al.*⁴ on the basis of findings obtained by use of the Riley method of analysis.⁹ However, the changes we observed were considerably greater than those seen in patients or volunteer subjects without symptomatic pulmonary disease.²⁻⁴ Moderate amounts of perfusion to low- \dot{V}_A/\dot{Q} lung units were suggested under conditions of hypoventilation during spontaneous breathing in Nunn's² patients receiving nitrous oxide and halothane, but this could not be demonstrated during mechanical ventilation in a similar group of patients also receiving nitrous oxide and halothane.³ In Price's⁴ study, replacement of nitrogen with nitrous oxide during halothane anesthesia in healthy young volunteer subjects again resulted in inability to demonstrate the presence of low- \dot{V}_A/\dot{Q} regions seen with nitrogen as the balance gas.

We believe the variability in these reported find-

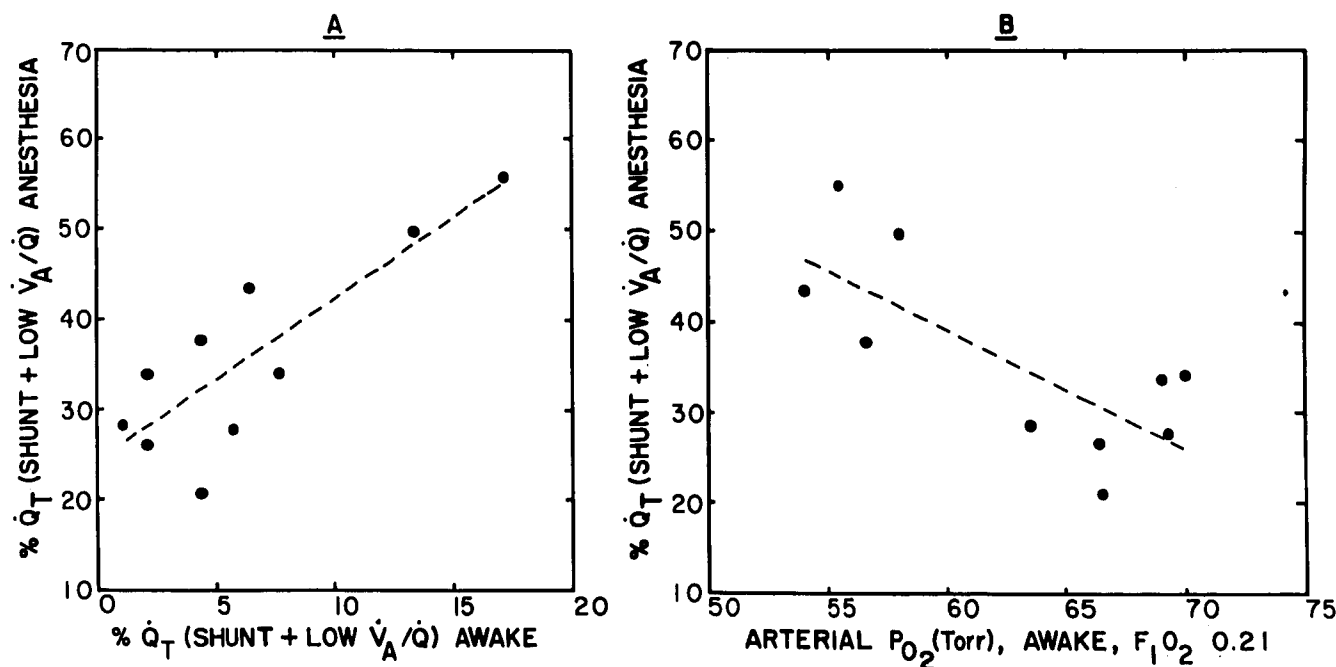


FIG. 7. The amount of \dot{V}_A/\dot{Q} inequality (shunt + low- \dot{V}_A/\dot{Q} units) as a percentage of cardiac output produced by anesthesia is plotted on the ordinate in A, against the amount of inequality for each subject while awake (correlation coefficient = 0.69). In B, the amount of \dot{V}_A/\dot{Q} inequality produced by anesthesia for each subject is again plotted on the ordinate, against the arterial blood P_{O_2} (torr) value obtained for the awake subject breathing room air (correlation coefficient = 0.56). Notice that both comparisons indicate that gas-exchange impairment while awake was related to some extent to impairment during anesthesia.

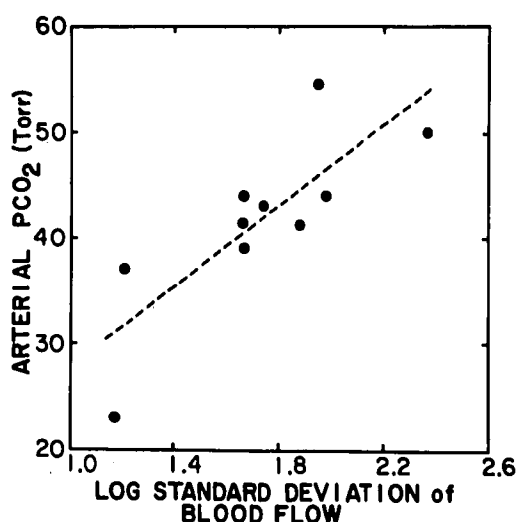


FIG. 8. Arterial blood P_{CO_2} (torr) values during anesthesia are plotted on the ordinate with respect to a statistical measure of \dot{V}_A/\dot{Q} inequality, log standard deviation of the distribution of blood flow. A reasonably good correlation ($r = 0.66$) is evident.

ings is in large part accounted for by limitations of the Riley approach in this setting. First, inspired oxygen concentration must be sufficiently low to demonstrate a contribution of low- \dot{V}_A/\dot{Q} units to venous admixture, and this oxygen concentration must be held at a consistent level to enable comparison both among different subjects and among different studies. The increased inspired oxygen concentrations (greater than room air) used in all of the above-mentioned studies placed serious limitations on their interpretation. Second, the concentrating effect of N_2O uptake on alveolar P_{O_2} ¹⁷ may have greatly increased alveolar P_{O_2} values, especially in regions of very low \dot{V}_A/\dot{Q} , and thus prevented those regions from contributing to venous admixture at relatively low inspired oxygen concentrations. The findings in our present study suggest that this phenomenon may persist for an ex-

tended period, well beyond the first few minutes of rapid N_2O uptake during induction of anesthesia.

The related hypothesis that the magnitude of \dot{V}_A/\dot{Q} inequality demonstrated by the multiple-inert-gas method was inordinately large due to a concentrating effect of continuing anesthetic gas uptake in low- \dot{V}_A/\dot{Q} regions was not supported by our finding that comparable levels of tracer inert gas retention were demonstrated both early and late following induction. Indeed, it is more likely that the highly variable rates of anesthetic gas uptake at given intervals from the time of induction (also seen by Nunn *et al.*³) were in large part due to variations in patterns and degrees of \dot{V}_A/\dot{Q} inequality produced by anesthesia. This was best exemplified by the high rate of uptake in Subject 7 (323 ml/min) 85 min following induction, in contrast to the rate for Subject 6 (125 ml/min) at 42 min. Subject 7 had 47 per cent of his cardiac output distributed to low- \dot{V}_A/\dot{Q} regions, compared with 8 per cent for Subject 6. Therefore, we conclude that the magnitude of \dot{V}_A/\dot{Q} inequality demonstrated in our study was an appropriate representation of the extent of ventilation and blood flow mismatching and shunt produced by inhalational anesthesia.

An additional finding with the multiple-inert-gas method of analysis was that the magnitude of \dot{V}_A/\dot{Q} inequality (that is, blood flow to low- \dot{V}_A/\dot{Q} units and shunt) produced by anesthesia was related to the amount of \dot{V}_A/\dot{Q} inequality present when the subjects were awake prior to anesthesia (fig. 7A, $r = 0.69$). This, again, could not be corroborated with blood-gas analysis, for the reasons stated above. It may be useful to note that subjects whose arterial blood P_{O_2} values during breathing of room air prior to anesthesia were less than 65 torr had the greatest ventilation-perfusion inequalities during anesthesia (fig. 7B, $r = 0.56$).

Arterial blood P_{O_2} values during anesthesia in the present study were highly variable at similar levels of

TABLE 3. Gas-exchange Data during Studies of Anesthesia

	P_{IO_2} (torr)	Arterial Blood P_{O_2} (torr)	Venous Blood P_{O_2} (torr)	Arterial Blood P_{CO_2} (torr)	Cardiac Output (l/min)	Low \dot{V}_A/\dot{Q} (% \dot{Q}_t)	Shunt (% \dot{Q}_t)	Mean \dot{V}_A/\dot{Q} Blood Flow	Log SD Blood Flow	\dot{V}_E (l/min)	\dot{V}_D (% \dot{V}_E)
Subject 1	269	58	51	44	4.1	17	27	0.55	1.66	8.0	58
Subject 2	263	82	48	44	7.3	23	12	0.30	1.98	8.0	38
Subject 3	275	123	36	41	6.1	21	5.3	0.33	1.66	8.5	49
Subject 4	267	114	47	43	6.5	21	13	0.33	1.74	8.2	46
Subject 5	275	66	33	23	7.9	6.2	21	0.77	1.17	10.7	33
Subject 6	283	56	35	39	4.8	7.5	30	0.87	1.67	9.4	50
Subject 7	283	90	40	50	7.3	47	7.5	0.12	2.37	8.0	38
Subject 8	334*	116	49	55	4.8	31	19	0.19	1.95	7.4	51
Subject 9	278	78	38	37	5.4	4.4	16	0.67	1.20	7.2	26
Subject 10	336*	102	40	41	3.9	29	0	0.33	1.88	8.0	43

P_{IO_2} = inspired P_{O_2} ; low \dot{V}_A/\dot{Q} = percentage of cardiac output distributed to areas with $0.005 > \dot{V}_A/\dot{Q} < 0.1$; mean \dot{V}_A/\dot{Q} and log SD blood flow are statistical analyses of the blood flow distribution with respect to \dot{V}_A/\dot{Q} ; \dot{V}_E = minute ventilation, BTPS; \dot{V}_D

= dead space, percentage of minute ventilation, as determined by inert-gas analysis. The data shown are mean values.

* Note: Subjects 8 and 10 received 47 per cent oxygen.

inspired P_{O_2} . Patients with predominantly shunt had much lower arterial blood P_{O_2} values than did patients whose \dot{V}_A/\dot{Q} abnormalities were predominantly on the basis of areas of low \dot{V}_A/\dot{Q} . This difference was in large part due to the increased inspired P_{O_2} , which decreased the hypoxemic effect of poorly ventilated lung units but not that of unventilated lung units. In addition, comparison of the arterial blood P_{O_2} values during anesthesia in Subjects 7, 8, and 10 (table 3) indicated that in the presence of a large amount of blood flow to low- \dot{V}_A/\dot{Q} units, replacement of nitrogen with the relatively soluble gas, nitrous oxide, resulted in significantly greater arterial blood P_{O_2} values for a given inspired P_{O_2} . This demonstration of the concentrating effect of nitrous oxide on alveolar P_{O_2} in low- \dot{V}_A/\dot{Q} units suggests that arterial blood P_{O_2} values (and hence, $P(A-a)O_2$ calculations) may not be reliable indications of the extent of gas-exchange impairment due to anesthesia.

Arterial blood P_{CO_2} during anesthesia in the present study was also highly variable at similar levels of alveolar ventilation. Although this may have been due in part to variations in levels of CO_2 production, it is more likely to have been related to differences in the pattern and degree of \dot{V}_A/\dot{Q} inequality (fig. 8). This finding suggests that the development of CO_2 retention during anesthesia at constant alveolar ventilation (equal to awake), in spite of the use of large tidal volumes and no increase in CO_2 production, should be viewed as indicating development of a potentially harmful \dot{V}_A/\dot{Q} inequality,¹⁸ even when the arterial blood P_{O_2} remains above 100 torr at inspired oxygen concentrations of 40 to 50 per cent.

No single index of pulmonary mechanics was consistently indicative of severe gas-exchange impairment during anesthesia. When all tests are considered, however, it is clear that patients with moderate to severe preoperative abnormalities of either lung volumes or expiratory flow rates also had moderate to severe gas-exchange impairment produced by anesthesia. The best predictor of the severity of \dot{V}_A/\dot{Q} inequality (shunt and low- \dot{V}_A/\dot{Q} regions) due to anesthesia was the severity of \dot{V}_A/\dot{Q} inequality while awake. A rough prediction could also be obtained from the awake arterial blood P_{O_2} value during breathing of room air. An arterial blood P_{O_2} of less than 65 torr in the awake subject was always associated with a large \dot{V}_A/\dot{Q} inequality during anesthesia.

References

1. Bendixen HH, Hedley-Whyte J, Laver MB: Impaired oxygenation in surgical patients during general anesthesia with controlled ventilation. *N Engl J Med* 269:991-996, 1963
2. Nunn JF: Factors influencing the arterial oxygen tension during halothane anesthesia with spontaneous ventilation. *Br J Anaesth* 36:327-341, 1964
3. Nunn JF, Bergman NA, Coleman AJ: Factors affecting the arterial oxygen tension during anesthesia with artificial ventilation. *Br J Anaesth* 37:898-914, 1965
4. Price HL, Cooperman LH, Warden JC, et al: Pulmonary hemodynamics during general anesthesia in man. *ANESTHESIOLOGY* 30:629-636, 1969
5. Marshall BE, Cohen PJ, Klingermaier CH, et al: Pulmonary venous admixture before, during and after halothane: oxygen anesthesia in man. *J Appl Physiol* 27:653-667, 1973
6. Weenig CS, Pietak S, Hickey RF, et al: Relationship of preoperative closing volume to functional residual capacity and alveolar-arterial oxygen difference during anesthesia with controlled ventilation. *ANESTHESIOLOGY* 41:3-7, 1974
7. Rehder K, Sessler AD, Marsh HM: General anesthesia and the lung. *Am Rev Resp Dis* 112:541-563, 1975
8. Wagner PD: Recent advances in pulmonary gas exchange. *Int Anesthesiol Clin* 15:81-111, 1977
9. Riley RL, Cournand A: "Ideal" alveolar air and the analysis of ventilation perfusion relationships in the lungs. *J Appl Physiol* 1:825-847, 1949
10. Wagner PD, Naumann PF, Laravuso RB: Simultaneous measurement of eight foreign gases in blood by gas chromatography. *J Appl Physiol* 36:600-605, 1974
11. Wagner PD, Laravuso RB, Uhl RR, et al: Continuous distributions of ventilation-perfusion ratios in normal subjects breathing air and 100% O_2 . *J Clin Invest* 54:54-68, 1974
12. Evans JW, Wagner PD: Limits on \dot{V}_A/\dot{Q} distributions from analysis of experimental inert gas elimination. *J Appl Physiol* 42:889-898, 1977
13. Dueck R, Rathbun M, Wagner PD: Chromatographic analysis of multiple tracer inert gases in the presence of anesthetic gases. *ANESTHESIOLOGY* 49:31-36, 1978
14. Stoelting RK, Eger EI, II: An additional explanation for the second-gas effect: A concentrating effect. *ANESTHESIOLOGY* 30:273-277, 1969
15. Wagner PD, Dantzker DR, Dueck R, et al: Ventilation-perfusion inequality in chronic obstructive pulmonary disease. *J Clin Invest* 59:203-216, 1977
16. Kain ML, Panday J, Nunn JF: The effect of intubation on the deadspace during halothane anaesthesia. *Br J Anaesth* 41:94-101, 1969
17. Farhi LE, Olszowska AJ: Analysis of alveolar gas exchange in the presence of soluble inert gases. *Resp Physiol* 5:53-67, 1968
18. West JB: Ventilation-perfusion inequality and overall gas exchange in computer models of the lung. *Resp Physiol* 7:88-110, 1969
19. Morris JF, Kofki AA, Johnson LC: Spirometric standards for healthy nonsmoking adults. *Am Rev Resp Dis* 103:57-67, 1971
20. Goldman HI, Becklake MR: Respiratory function tests, normal values at median altitudes, and prediction of normal results. *Am Rev Tuberc* 79:547-566, 1959
21. Buist AF, Ross BB: Quantitative analysis of the alveolar plateau in the diagnosis of early airway obstruction. *Am Rev Resp Dis* 108:1078-1087, 1973
22. Buist AF, Ross BB: Predicted values for closing volumes using a modified single breath nitrogen test. *Am Rev Resp Dis* 107:744-752, 1973