

# Canine $\dot{V}_A/\dot{Q}$ Distribution Responses to Inhalation Anesthesia and Mechanical Ventilation

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The effects of anesthesia produced by halothane (0.7–1.5 per cent end-tidal concentration) vaporized in oxygen (21 per cent), balance nitrous oxide (N<sub>2</sub>O) on distribution of ventilation-perfusion ( $\dot{V}_A/\dot{Q}$ ) ratios, and pulmonary gas exchange were studied in five healthy mongrel dogs during both spontaneous (SV) and mechanical (MV) ventilation. Awake control studies (via chronic tracheostomy) with room air breathing in the left or right lateral decubitus position demonstrated normal values for arterial blood P<sub>O<sub>2</sub></sub> (98.1 ± 4.5 torr, mean ± SD) and P<sub>CO<sub>2</sub></sub> (37.1 ± 3.8 torr). Representative distributions derived from multiple tracer inert gas analysis demonstrated minimal or no areas of very low (0.005 <  $\dot{V}_A/\dot{Q}$  < 0.1) or very high (10.0 <  $\dot{V}_A/\dot{Q}$  < 100.0)  $\dot{V}_A/\dot{Q}$  ratios. Shunt ( $\dot{V}_A/\dot{Q}$  < 0.005) was 0.2 ± 0.3 per cent of cardiac output, and dead space ( $\dot{V}_A/\dot{Q}$  > 100.0) was 40.3 ± 4.3 per cent of minute ventilation. Studies during anesthesia in the same body position showed no significant development of either low  $\dot{V}_A/\dot{Q}$  areas or shunt. The dispersion of the distribution of blood flow with respect to  $\dot{V}_A/\dot{Q}$  ratios (represented by standard deviation calculated on a logarithmic scale, log SD) increased from 0.351 ± 0.132 awake to 0.449 ± 0.033 during anesthesia with SV, and 0.609 ± 0.147 with MV. Anesthesia consistently produced either very high  $\dot{V}_A/\dot{Q}$  areas, increased dead space ventilation, or both. Since high  $\dot{V}_A/\dot{Q}$  areas were seen only at the upper extremes (near  $\dot{V}_A/\dot{Q}$  = 100), they were effectively similar to dead space. Hence, dead space increased to 62.2 ± 11.1 per cent of minute ventilation for SV, and 55.2 ± 7.0 per cent for MV. This difference was due to smaller tidal volumes during SV. Linear regression of dead space (plus high  $\dot{V}_A/\dot{Q}$  area) ventilation with respect to tidal volume showed  $r = -0.777$  for SV, and  $r = -0.693$  for MV. In contrast,  $\dot{V}_A/\dot{Q}$  inequality (log SD blood flow) in the intermediate range (0.1 <  $\dot{V}_A/\dot{Q}$  < 10.0) showed a positive correlation with tidal volume during anesthesia MV,  $r = 0.919$ , but not for either awake or anesthesia SV conditions.

Arterial P<sub>O<sub>2</sub></sub> values increased significantly during anesthesia, to 114 ± 12.4 torr for SV, and 112 ± 7.8 torr for MV,  $P < 0.005$  for both, due to reduced oxygen consumption rate,  $r = -0.586$ ,  $P < 0.01$ . The authors propose that  $\dot{V}_A/\dot{Q}$  inequality in the

intermediate range was produced by altered chest cage and diaphragm motion. In dogs with healthy lungs, this mechanism did not result in impaired arterial oxygenation. Areas of very high  $\dot{V}_A/\dot{Q}$  and increased dead space ventilation, however, were probably due to redistribution of pulmonary blood flow leading to the presence of essentially unperfused but ventilated lung regions. The authors believe that this was induced through a pharmacologic mechanism of one of the inhalation anesthetic agents, most likely halothane. (Key words: Anesthetics, volatile: halothane. Anesthetics, gases: nitrous oxide. Lung: function; gas exchange; perfusion, shunting. Ventilation: carbon dioxide tension; distribution; oxygen tension, perfusion [ventilation-perfusion ratio]; shunting).

INVESTIGATION of the mechanisms of impaired pulmonary gas exchange during anesthesia has been frustrated in part by the large number of inter-active variables. In addition to the inherent difficulty in independent control of these variables, there has been the problem of quantifying the contribution of individual variables in the inhalation anesthesia environment. For example, the relative contributions of shunt and of areas with low ventilation-perfusion ratios could not be assessed in the presence of relatively high inspired concentrations of nitrous oxide.

Two recent developments have enabled us to address these problems in a systematic fashion. First was the introduction of the multiple tracer inert gas elimination method for assessment of ventilation-perfusion inequality.<sup>1-3</sup> Second was the development of a chronic animal model to permit awake control measurements and thus differentiate the effects of inhalation anesthesia from those of mechanical ventilation. The dog was used as this animal model because earlier acute experiments using pentobarbital anesthesia<sup>4,5</sup> and preliminary acute studies in this laboratory with nitrous oxide and halothane§ demonstrated that dogs frequently have a moderate amount of intrapulmonary shunting during anesthesia. It could not be ruled out that preexisting lung disease might have been responsible for such abnormalities in the acute studies. Therefore, the purpose of the present investigation was to determine whether intrapulmonary shunting and  $\dot{V}_A/\dot{Q}$  inequality are produced by anesthesia in dogs with healthy lungs, due to either the pharmacologic effects of anesthetic agents on the lung, or to the indirect effect of altered

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§ Unpublished observations.

motion of the chest wall and diaphragm during anesthesia.

## Methods

### AWAKE STUDIES

Five healthy mongrel dogs, 25–30 kg in weight, were each surgically prepared with a chronic tracheostomy and an exteriorized carotid artery (subcutaneous tunnel) at least two weeks prior to anesthesia studies. Preparation for awake control studies was performed after inducing mild sedation using acetyl promazine maleate (Acepromazine®), 0.5 mg/kg, im, (with a repeat injection of 0.25 mg/kg, im, if needed to provide a steady breathing pattern). Subcutaneous infiltration and topical application of Xylocaine® to place a peripheral iv (Abbocath 18-gauge), a flow-directed pulmonary artery (Swan-Ganz #7) catheter via the external jugular vein, an arterial catheter (Abbocath 18-gauge) in the exteriorized carotid artery, and a 9.5-mm (ID) cuffed endotracheal tube in the tracheostomy site were also used. A mixture of six inert gases (sulfur hexafluoride (SF<sub>6</sub>), ethane, cyclopropane, enflurane, ether, and acetone) dissolved in tracer concentrations in 5 per cent dextrose in lactated Ringer's solution was infused continuously in the peripheral vein. All awake studies were performed in the lateral decubitus position. Two dogs were studied on two occasions at a two-week interval, hence a total of seven studies were performed. After a minimum of 50 min of tracer inert gas infusion and a minimum of 30 min of maintained stable conditions (as determined by constant end-tidal CO<sub>2</sub>, vascular pressures, heart rate, tidal volume and frequency), mixed venous and arterial blood and mixed expired gas samples were obtained as described previously for multiple tracer inert gas and blood-gas analysis.<sup>1</sup> Samples for blood-gas analysis were obtained in heparinized glass syringes, stored on ice, and analyzed with Radiometer blood-gas electrodes within 20 min. Tracer inert gas analysis was performed with Hewlett-Packard Model 5711® flame ionization detector and Hewlett-Packard Model 5710® electron capture detector gas chromatographs.<sup>3</sup> Minute ventilation was measured with a calibrated Wright spirometer.

### ANESTHESIA STUDIES

*Spontaneous breathing.* Anesthesia was induced and maintained with halothane, 0.7–1.5 per cent end-tidal concentration, vaporized in 21 per cent oxygen and balance nitrous oxide concentration. The halothane dose requirement was determined by the concentra-

tion needed to maintain a stable end-tidal CO<sub>2</sub> concentration during spontaneous breathing studies. The relatively wide range of concentrations was probably related to variable degrees of metabolism of the premedicant drug, Acepromazine®. (Dogs which received supplemental Acepromazine® following the catheterizations, because of unsteady breathing patterns prior to the awake control study, showed a tendency to require lower halothane concentrations to provide a stable respiratory pattern.) Blood samples and mixed expired gas samples for multiple inert gas analysis and blood-gas analysis were obtained at an average ( $\pm$ SD) 85.7  $\pm$  37.5 min following induction and repeated at an average 141.0  $\pm$  34.4 min following induction. The long initial sampling interval was caused by variability in the time at which stable respiratory patterns were achieved. Further delay for the repeat samples was designed to minimize loss of mixed expired tracer gases from the matched-barrel glass syringes (during the time required for chromatographic analysis of the first expired gas sample). All anesthesia studies were performed in the same lateral decubitus position used for the awake study.

*Mechanical ventilation with muscle paralysis.* Following the above study, pancuronium, 0.1 mg/kg, iv, was administered with further 1–2 mg increments as required to prevent spontaneous breathing. Mechanical ventilation was provided with a Harvard Model 613® ventilator at tidal volumes initially set at approximately 12 ml/kg (BTPS). Frequency was adjusted to provide minute ventilation values equal to awake values. In several instances this resulted in progressive CO<sub>2</sub> retention. Tidal volume was therefore increased in 25-ml increments sufficient to maintain an end-tidal CO<sub>2</sub> concentration similar to awake control values (the Beckman LB-2® infrared CO<sub>2</sub> analyzer signal was not corrected for the broadening effect of nitrous oxide on the CO<sub>2</sub> spectrum). The ventilator tubing was adapted with a T-piece on the inspired limb to enable identical endotracheal tube connections for spontaneous and mechanical ventilation, and an Ohio® one-way valve was utilized to assure a maximum instrumental dead space not greater than 70 ml. Samples for multiple inert gas and blood-gas analysis were again obtained following a minimum of 30 min of stable conditions (mean  $\pm$  SD, 167  $\pm$  49.5 min, and 190  $\pm$  49.7 min following induction for the first and second samples, respectively). Inspired oxygen and nitrous oxide and end-tidal halothane concentrations were maintained at a constant level (equal to the spontaneous ventilation study values) to enable comparison of anesthetic effects on  $\dot{V}_A/\dot{Q}$  distribution for spontaneous and mechanical ventilation at comparable anesthetic dose levels. The unpredictable

dose level required to produce stable end-tidal  $\text{CO}_2$  concentrations during spontaneous ventilation prevented reversal of the protocol sequence to examine for any possible time-related changes in  $\dot{V}_A/\dot{Q}$  distribution. However, sufficiently variable sampling times for both spontaneous and mechanical ventilation studies enabled both within-group and between-group (time overlap) comparison for any major time-related effects.

#### ANALYSIS AND COMPUTATIONS

Gas chromatographic data analysis was performed as described previously<sup>1</sup> using the Burroughs Model 6700<sup>®</sup> computer to calculate retention- and excretion-solubility values. A Control Data Model 3600<sup>®</sup> computer was used to obtain estimates of  $\dot{V}_A/\dot{Q}$  distributions using the modified form of ridge regression described by Evans and Wagner.<sup>2</sup> Dead space analysis from the inert gas elimination data was performed with the assumption that all dead space was personal, rather than in common.<sup>6</sup> Cardiac output ( $\dot{Q}_T$ ) was computed as a variance weighted mean of the six cardiac output values derived by the Fick method from each of the individual tracer inert gases analyzed for a given  $\dot{V}_A/\dot{Q}$  distribution:

from,

$$\dot{V}_E \times P_E = \lambda \times \dot{Q}_T(P_{\bar{V}} - P_a)$$

when,

$\dot{V}_E$  = minute ventilation;

$P_E$  = mixed expired partial pressure of a given tracer gas;

$\lambda$  = blood/gas partition coefficient of the tracer gas;

$\dot{Q}_T$  = cardiac output;

$P_{\bar{V}}$  = mixed venous partial pressure of the tracer gas; and

$P_a$  = arterial partial pressure of the tracer gas.

A simplified numerical measure of the degree of  $\dot{V}_A/\dot{Q}$  inequality represented by a given  $\dot{V}_A/\dot{Q}$  distribution was determined as the log standard deviation of the distribution of blood flow (or ventilation) with respect to  $\dot{V}_A/\dot{Q}$  ratios (log SD) from the 48 compartments of  $\dot{V}_A/\dot{Q} = 0.005$  to 100.0 equally spaced on a logarithmic scale, such that:

$$\log \text{SD} = \sum_{i=2}^{49} (\dot{Q}_i/\dot{Q}) \times [\log (\dot{V}_A/\dot{Q}_i) - m]^2$$

where

$$m = \sum_{i=2}^{49} (\dot{Q}_i/\dot{Q}) \times \log (\dot{V}_A/\dot{Q}_i)$$

and where  $\dot{Q}_i$  is the amount of blood flow to the  $i^{\text{th}}$

$\dot{V}_A/\dot{Q}$  compartment, and  $\dot{Q}$  is  $\dot{Q}_T$  minus blood flow to regions with  $\dot{V}_A/\dot{Q} > 0.005$ .

Arterial and venous oxygen contents were derived from measured values of blood  $\text{O}_2$  tension, pH, hemoglobin, hematocrit, and  $P_{50}$  (measured with the Radiometer<sup>®</sup> DSA continuous oxyhemoglobin-dissociation curve analyzer).<sup>7</sup> Oxygen consumption was estimated using the Fick principle from the calculated  $\text{O}_2$  contents and cardiac output determinations.

The null hypothesis that there were no significant differences between awake control values *vs.* either anesthesia spontaneous or mechanical ventilation values (using mean values for duplicate determinations) was tested by one-way analysis of variance (ANOVA).<sup>8</sup> Critical difference testing for multiple groups was performed with the Newman-Keuls multiple range test<sup>8</sup> for those findings in which the F statistic demonstrated rejection of the null hypothesis. In addition, linear regression analysis<sup>8</sup> was used to assess the relationship between tidal volume and dead-space ventilation, oxygen consumption, and blood oxygen tension (both venous and arterial), as well as between cardiac output and blood oxygen tension. Analysis of covariance<sup>8</sup> was utilized to test the significance level of the differences in slope of the linear regression of dead-space ventilation and of log standard deviation of blood flow distribution (in the range  $0.1 < \dot{V}_A/\dot{Q} < 10.0$ ) with respect to tidal volume comparing awake, anesthesia SV, and anesthesia MV.

## Results

### AWAKE STUDIES

Awake control studies (lateral decubitus position) of multiple tracer inert gas elimination demonstrated low levels of retention of the least soluble tracer gases and relatively high levels of excretion of the most soluble tracer gases, as shown in figure 1, awake panel. Representative distributions of  $\dot{V}_A/\dot{Q}$  ratios (see the example in fig. 2, awake panel) indicated minimal  $\dot{V}_A/\dot{Q}$  inequality. Statistical analysis of the degree of dispersion of blood flow in the lung with respect to  $\dot{V}_A/\dot{Q}$  ratios for all five dogs showed a mean  $\pm$  SD for log standard deviation of the distribution as  $0.351 \pm 0.132$  and the ventilation distribution as  $0.338 \pm 0.129$ . There was little or no shunt in any of the five dogs, no area of low  $\dot{V}_A/\dot{Q}$  ( $0.005 < \dot{V}_A/\dot{Q} < 0.1$ ) or high  $\dot{V}_A/\dot{Q}$  ( $10.0 < \dot{V}_A/\dot{Q} < 100.0$ ), and the mean  $\pm$  SD dead-space ventilation was  $40.3 \pm 4.3$  per cent of minute ventilation (see table 1). The latter includes any lung regions with  $\dot{V}_A/\dot{Q} > 100$ , as well as anatomical and mechanical (approximately 70 ml) dead space.

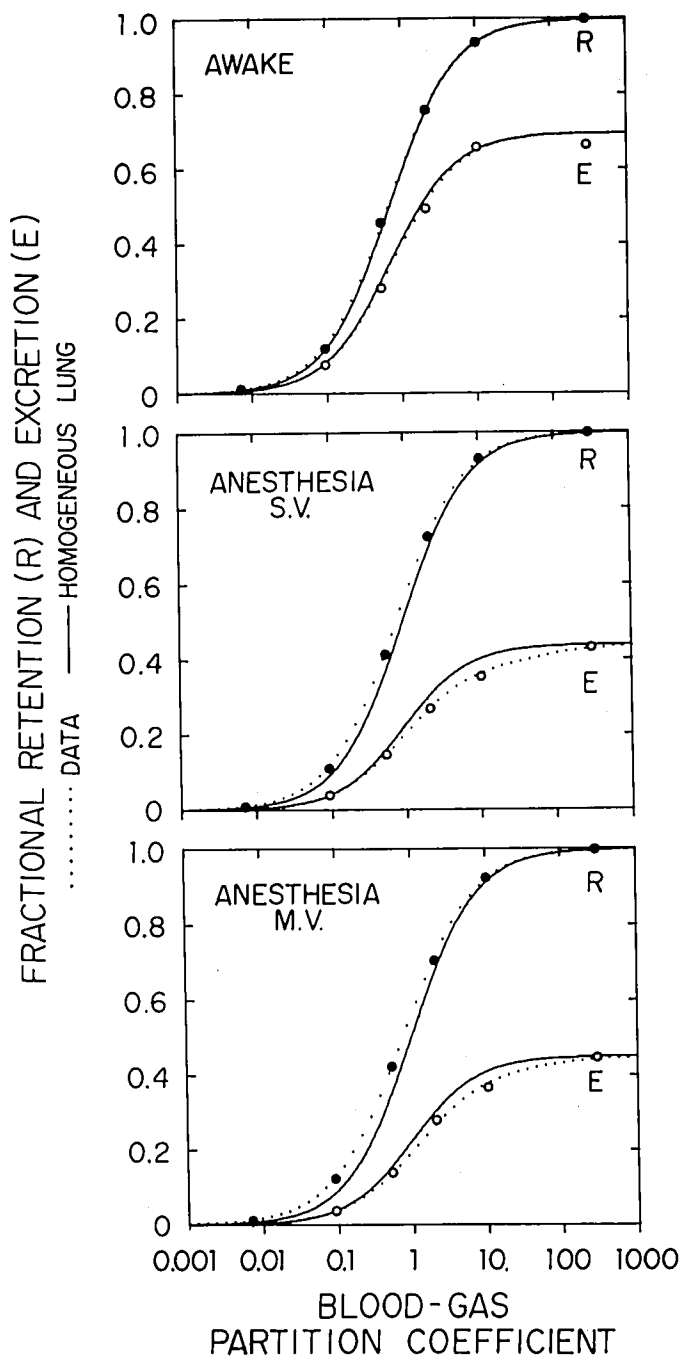


FIG. 1. Fractional retention (R) and excretion (E) of sulfur hexafluoride, ethane, cyclopropane, enflurane, ether, and acetone are plotted with respect to blood-gas partition coefficient from a typical example in one dog. Best fit lines through measured data points (.....●.....) are compared to the curves which would have obtained for the same cardiac output, minute ventilation and dead space, but with no shunt and no  $\dot{V}_A/\dot{Q}$  inequality (—). Note that there was little difference for these lines in the awake control study, but modest deviation during anesthesia SV and anesthesia MV. In addition, there was marked reduction in excretion of the more soluble gases, especially ether and acetone during both anesthesia conditions.

The corresponding awake control arterial  $P_{O_2}$  and  $P_{CO_2}$  values (see table 2) during room air breathing were  $98.1 \pm 4.5$  torr and  $37.1 \pm 3.8$  torr, respectively. Estimated awake oxygen consumption rate was  $160.8 \pm 44.9$  ml/min.

#### ANESTHESIA STUDIES

*Spontaneous breathing.* Studies during anesthesia demonstrated considerable reduction in elimination of intermediate- and high-solubility tracer gases, as seen in figure 1. Representative distributions of  $\dot{V}_A/\dot{Q}$  ratios (see fig. 2, anesthesia SV panel) indicated that these changes were due to relatively small increases in  $\dot{V}_A/\dot{Q}$  inequality in the intermediate range ( $0.1 < \dot{V}_A/\dot{Q} < 10.0$ ), and a more substantial though variable development of areas with high  $\dot{V}_A/\dot{Q}$  ( $10.0 < \dot{V}_A/\dot{Q} < 100.0$ ) ratios and especially areas with  $\dot{V}_A/\dot{Q} > 100$  (dead-space ventilation). Ventilation to areas with high  $\dot{V}_A/\dot{Q}$  ratios was always at the extreme upper range of high  $\dot{V}_A/\dot{Q}$ , very near  $\dot{V}_A/\dot{Q}$  values equal to 100.0. Dead-space ventilation (per cent minute volume) showed an inverse correlation with tidal volume,  $r = -0.619$ , which increased to  $r = -0.777$  if ventilation to high  $\dot{V}_A/\dot{Q}$  areas was combined with the dead-space values, as shown in table 1 and in the regression analysis in figure 3. In contrast to the intermediate and upper  $\dot{V}_A/\dot{Q}$  range changes, minimal or no areas of low  $\dot{V}_A/\dot{Q}$  were produced, and shunt did not change significantly.

Blood-gas analysis (see table 2) consistently demonstrated increased arterial  $P_{O_2}$  values ( $FI_{O_2} = 0.21$ ). This finding was associated with increased mixed venous  $P_{O_2}$  values, no consistent change in cardiac output, and therefore an estimated average 31 per cent decrease in the rate of oxygen consumption. In contrast, the average 2.1 torr increase in arterial  $P_{CO_2}$  was not statistically significant. This was due to an average 81.7 per cent increase in minute ventilation. The increase in minute ventilation occurred with a mean respiratory frequency 2.4 times the awake value and an average 25 per cent reduction in tidal volume.

*Mechanical ventilation with muscle paralysis.* These anesthesia studies (also performed in the lateral position) again demonstrated a moderate reduction in elimination of the intermediate- to high-solubility tracer gases, as compared to awake control findings (see fig. 1). Representative distributions of  $\dot{V}_A/\dot{Q}$  ratios demonstrated somewhat greater increases in  $\dot{V}_A/\dot{Q}$  inequality in the intermediate range ( $0.1 < \dot{V}_A/\dot{Q} < 10.0$ ), in comparison to the anesthesia studies during spontaneous breathing. This resulted in a mean log standard deviation for the blood flow dis-

tribution of  $0.609 \pm 0.147$  if the high  $\dot{V}_A/\dot{Q}$  area was included in the  $\dot{V}_A/\dot{Q}$  dispersion value, *vs.*  $0.557 \pm 0.179$  if it was not included. That is, the mean  $\pm$  SD value for  $\dot{V}_A/\dot{Q}$  inequality in the intermediate range ( $0.1 < \dot{V}_A/\dot{Q} < 10.0$ ) during anesthesia, muscle paralysis, and mechanical ventilation was significantly greater than the awake control value but not significantly different from anesthesia with spontaneous breathing when considered by analysis of variance techniques. Linear regression of log standard deviation of blood flow with respect to tidal volume, however, demonstrated significant positive correlation of  $\dot{V}_A/\dot{Q}$  inequality (intermediate range) with tidal volume during mechanical ventilation studies,  $r = 0.919$ . This was significantly different ( $P < 0.005$ ) from both the awake control and spontaneous breathing relationships (see fig. 4). Development of areas with high  $\dot{V}_A/\dot{Q}$  ratios showed the same degree of variability as seen in the anesthesia with spontaneous breathing studies, but dead-space ventilation was not as severe. The lesser increase in dead-space ventilation was primarily due to the larger tidal volumes as shown in figure 3.

Blood-gas analysis demonstrated consistently increased arterial  $P_{O_2}$  values in comparison to awake control findings; but no statistical difference was seen when comparing arterial  $P_{O_2}$  during spontaneous *vs.* mechanical ventilation (see table 2). A smaller increase in minute ventilation (average 42.7 per cent) was needed to maintain arterial  $P_{CO_2}$  at a level similar to awake control values.

No time-related effects of either anesthesia or muscle paralysis and mechanical ventilation could be seen for any of the  $\dot{V}_A/\dot{Q}$  inequality parameters, blood-gas findings, or oxygen consumption rate estimates described above. This was true whether evaluated by early and late comparisons within each group (spontaneous and mechanical ventilation studies), or by regression of these variables with respect to time (in minutes) from induction of anesthesia.

No significant differences were noted between the findings of the first and second study in the two dogs studied on more than one occasion. That is, the typical

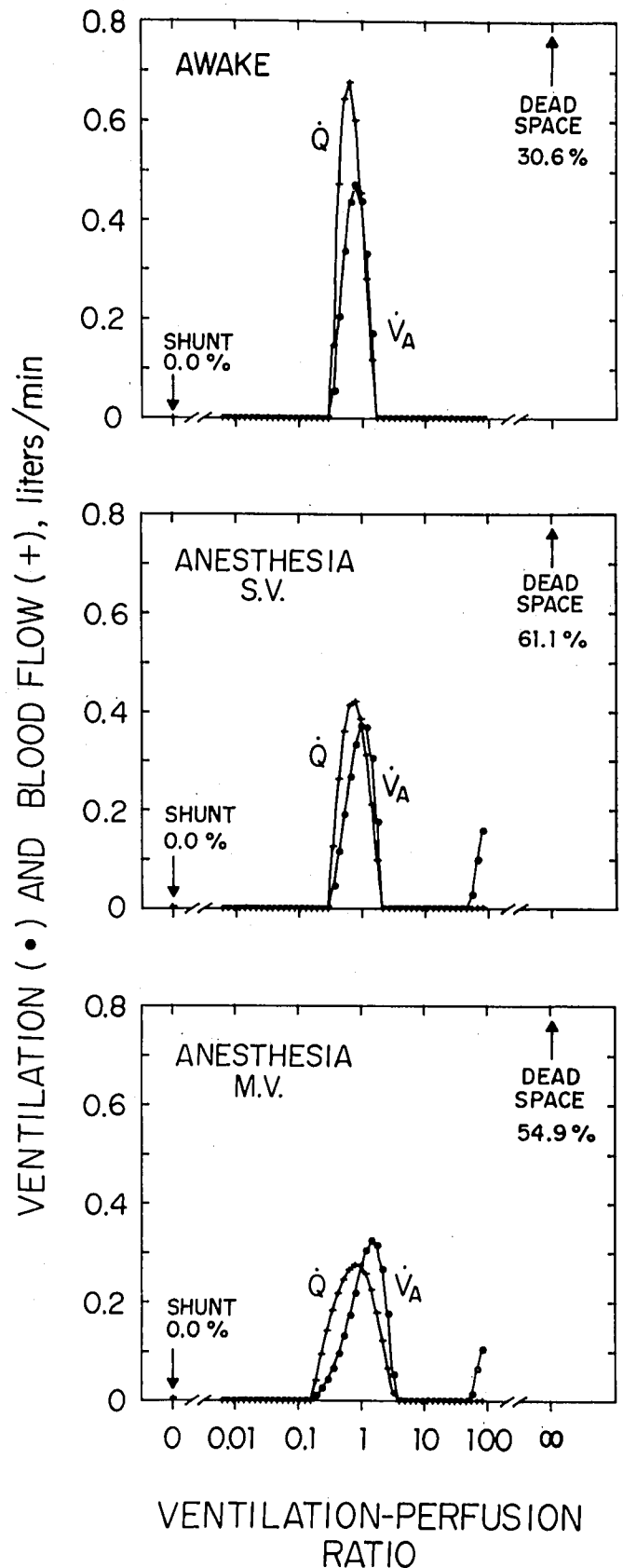


FIG. 2. Examples of the representative distributions of ventilation (—●—) and blood flow (—x—) in l/min (ordinate) with respect to  $\dot{V}_A/\dot{Q}$  ratio on a log scale (abscissa) were derived from the excretion- and retention-solubility data shown in figure 1. No shunt and no areas of low  $\dot{V}_A/\dot{Q}$  ratio were produced by either anesthesia or mechanical ventilation. There was more dead-space ventilation during SV, but more  $\dot{V}_A/\dot{Q}$  inequality in the intermediate range of  $\dot{V}_A/\dot{Q}$  ratios ( $0.1 < \dot{V}_A/\dot{Q} < 10.0$ ) during MV. Ventilation to high  $\dot{V}_A/\dot{Q}$  ( $10.0 < \dot{V}_A/\dot{Q} < 100.0$ ) areas occurred only at the extreme upper range during anesthesia studies.

TABLE 1. Distribution of Ventilation-Perfusion Ratios

Condition	N	Shunt Per Cent $\dot{Q}_T$ *	Low $\dot{V}_A/\dot{Q}$ Per Cent $\dot{Q}_T$ *	Dead Space Per Cent $\dot{V}_E$	Dead Space plus High $\dot{V}_A/\dot{Q}$ * Per Cent $\dot{V}_E$	Mean $\dot{V}_A/\dot{Q}$ Blood Flow†	Log SD† Blood Flow	Log SD Blood Flow 0.1 < $\dot{V}_A/\dot{Q}$ < 10.0†
Awake	7	0.16 ± 0.25	0.04 ± 0.11	40.33 ± 4.33	40.33 ± 4.33	0.648 ± 0.126	0.351 ± 0.132	0.351 ± 0.132
Anesthesia, SV	6	0.63 ± 0.54	0.0 ± 0.0	53.45 ± 8.70	62.18 ± 11.14	0.555 ± 0.130	0.449 ± 0.033	0.398 ± 0.096
Anesthesia, MV	7	0.36 ± 0.37	0.83 ± 2.10	47.34 ± 3.44	55.24 ± 7.00	0.583 ± 0.149	0.609 ± 0.147	0.557 ± 0.179
ANOV F Ratio‡		2.36 NS	0.49 NS	8.43 <i>P</i> < 0.005	13.64 <i>P</i> < 0.001	0.82 NS	8.38 <i>P</i> < 0.005	4.01 <i>P</i> < 0.05
Newman-Keuls Multiple Range Test§								
Awake vs. Anes, SV		—	—	<i>P</i> < 0.005	<i>P</i> < 0.001	—	NS	NS
Awake vs. Anes, MV		—	—	<i>P</i> < 0.05	<i>P</i> < 0.005	—	<i>P</i> < 0.005	<i>P</i> < 0.05
Anes, SV vs. Anes, MV		—	—	NS	NS	—	<i>P</i> < 0.05	NS

Mean ± SD values of the above parameters of  $\dot{V}_A/\dot{Q}$  inequality are shown from the seven studies in five dogs in the lateral decubitus position.

\* Shunt ( $\dot{V}_A/\dot{Q} < 0.005$ ) and the amount of blood flow to areas with low  $\dot{V}_A/\dot{Q}$  ratios ( $0.005 < \dot{V}_A/\dot{Q} < 0.1$ ) are represented as per cent of cardiac output ( $\dot{Q}_T$ ), and ventilation to areas with high  $\dot{V}_A/\dot{Q}$  ( $10.0 < \dot{V}_A/\dot{Q} < 100.0$ ) and dead space ( $\dot{V}_A/\dot{Q} > 100.0$ ) as per cent of minute ventilation ( $\dot{V}_E$ ).

† Mean  $\dot{V}_A/\dot{Q}$  values and log standard deviation (log SD) of the distribution of blood flow with respect to  $\dot{V}_A/\dot{Q}$  ratios are shown for the range of  $\dot{V}_A/\dot{Q}$  from 0.005 to 100.0. In addition standard

deviation of blood flow distribution is shown for the intermediate range,  $0.1 < \dot{V}_A/\dot{Q} < 10.0$ , i.e., without either low  $\dot{V}_A/\dot{Q}$  or high  $\dot{V}_A/\dot{Q}$  components.

‡ One-way analysis of variance, ANOV F Ratio, was used to test the null hypothesis ( $H_0$ ) that anesthesia values were not significantly different from awake control. This was accepted at *P* > 0.05, NS.

§ At *P* < 0.05 the Newman-Keuls multiple range test was used to determine whether the differences seen during anesthesia were specifically due to either spontaneous or mechanical ventilation conditions.

changes in  $\dot{V}_A/\dot{Q}$  distribution due to anesthesia and to muscle paralysis and mechanical ventilation were seen in each study and were similar in magnitude.

**Discussion**

This investigation of gas exchange impairment mechanisms of anesthesia has several important

features. First, awake control observations were obtained in a commonly used animal model, the dog. Second, the study protocol enabled considerable differentiation of the physical effects of altered breathing pattern from the pharmacologic effects of anesthetic agents on ventilation-perfusion ratios. In addition to these protocol features, our methods of

TABLE 2. Pulmonary Gas Exchange

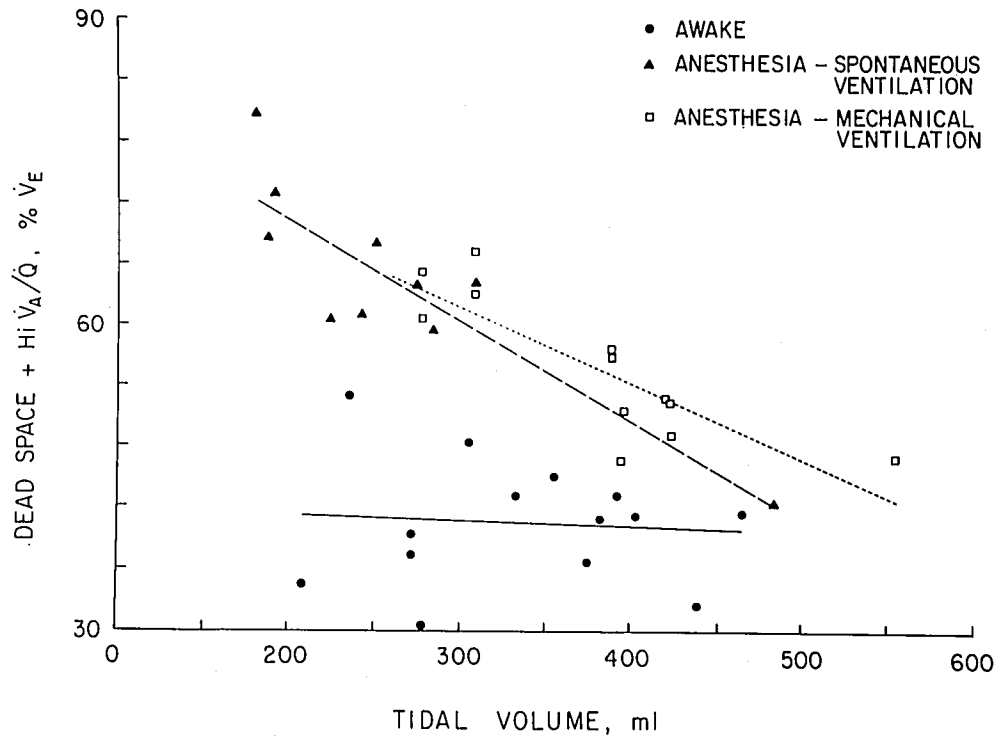
Condition	N	Arterial		Mixed Venous		Oxygen Consumption (ml/min)	Cardiac Output (l/min)	Minute Vent (l/min)	Respiratory Frequency
		$P_{O_2}$ (torr)	$P_{CO_2}$ (torr)	$P_{O_2}$ (torr)	$P_{CO_2}$ (torr)				
Awake	7	98.1 ± 4.5	37.1 ± 3.8	45.8 ± 3.9	41.5 ± 4.4	160.75 ± 44.85	3.30 ± 0.51	3.77 ± 0.76	10.7 ± 3.0
Anesthesia, SV	6	114.8 ± 12.4	39.2 ± 4.5	59.6 ± 11.6	43.1 ± 5.5	110.46 ± 19.62	4.35 ± 1.68	6.85 ± 2.84	25.9 ± 17.3
Anesthesia, MV	7	112.8 ± 7.8	37.1 ± 2.8	56.1 ± 6.7	40.37 ± 3.5	116.83 ± 39.08	3.93 ± 1.78	5.38 ± 0.78	12.7 ± 2.2
ANOV F Ratio†		7.63 <i>P</i> < 0.005	0.69 NS	5.88 <i>P</i> < 0.25	0.60 NS	3.72 <i>P</i> < 0.05	0.89 NS	5.51 <i>P</i> < 0.025	4.68 <i>P</i> < 0.025
Newman-Keuls Multiple Range Test‡									
Awake vs. Anes, SV		<i>P</i> < 0.01	—	<i>P</i> < 0.025	—	NS	—	<i>P</i> < 0.025	<i>P</i> < 0.05
Awake vs. Anes, MV		<i>P</i> < 0.01	—	<i>P</i> < 0.025	—	NS	—	NS	NS
Anes, SV vs. Anes, MV		NS	—	NS	—	NS	—	NS	<i>P</i> < 0.025

\* The parameters of pulmonary gas exchange reported here are mean ± SD values from seven studies in five dogs.

† Analysis of variance (ANOV F Ratio) was used to test for the presence of a significantly different subpopulation.

‡ The Newman-Keuls multiple range test was used to test for significance level of differences between those groups in which the ANOV F Ratio was significant at *P* < 0.05.

FIG. 3. Dead-space ( $\dot{V}_A/\dot{Q} > 100.0$ ) ventilation combined with ventilation to very high ( $10.0 < \dot{V}_A/\dot{Q} < 100.0$ )  $\dot{V}_A/\dot{Q}$  areas derived as per cent minute ventilation (per cent  $\dot{V}_E$ ) are plotted with respect to tidal volume, ml BTSP. Note that the inverse relationship of this dead-space ventilation with respect to tidal volume was seen only during anesthesia, with a correlation coefficient of  $-0.777$  for spontaneous and  $-0.693$  for mechanical ventilation (The regression slope was significantly different from awake,  $P < 0.005$  for spontaneous and  $P < 0.025$  for mechanical ventilation).



analysis enabled us to distinguish between the interacting variables of pulmonary gas exchange impairment (increased  $\dot{V}_A/\dot{Q}$  inequality) and reduced metabolic rate (oxygen consumption) for their effect on arterial oxygen tension.

Awake studies in healthy dogs in their normal recumbent (lateral decubitus) position showed a narrow range of ventilation-perfusion ratios, little or no intrapulmonary shunt, and dead-space values appropriate for the additional mechanical (70 ml) dead space needed for collection of expired gas. The essential absence of intrapulmonary shunting suggested that modest degrees of shunting seen in earlier acute "normal control" studies in dogs<sup>4,5</sup> may have been caused either by preexisting but undetected lung disease, or have been produced in the process of anesthesia induction and orotracheal intubation. The degree of  $\dot{V}_A/\dot{Q}$  inequality or dispersion in our awake study, when expressed as the log standard deviation of the blood flow distribution with respect to  $\dot{V}_A/\dot{Q}$  ratios, was essentially that seen in awake young healthy volunteers in the supine<sup>9</sup> and semi-Fowlers position,<sup>10</sup> and less than that seen for human subjects in the lateral decubitus position.<sup>9</sup> This latter finding supports the hypothesis that  $\dot{V}_A/\dot{Q}$  inequality in awake healthy subjects is primarily due to the effects of gravity on regional distribution of pulmonary blood flow and alveolar ventilation.<sup>11</sup> That is, since the distance from top to bottom of the lungs is less for dog lungs in the lateral position than for adult human

lungs, less regional disparity of blood flow or ventilation distribution would be expected either from the effect of gravity on the regional distribution of blood flow,<sup>12</sup> or from its effect on transdiaphragmatic pressure gradients, hence alveolar size and regional lung compliance.<sup>13</sup>

Blood-gas analysis demonstrated arterial  $P_{O_2}$  values consistent with the narrow range of ventilation-perfusion ratios, essential absence of shunting, and with room air breathing. These  $P_{O_2}$  values were well within the range of findings reported for awake healthy dogs reported by Wise,<sup>14</sup>  $90.0 \pm 5.7$  torr, and Clark, *et al.*,<sup>15</sup>  $101.3 \pm 5.6$  torr. Their corresponding arterial  $P_{CO_2}$  values were  $35.9 \pm 2.4$  torr and  $34.0 \pm 3.9$  torr, respectively. The somewhat higher mean arterial  $P_{CO_2}$  value seen in the present study suggests that Acepromazine® premedication may have produced a mild respiratory depressant effect. In addition, a small reduction in metabolic rate (oxygen consumption) may have been produced as suggested by a study of the effects of chlorpromazine in dogs by Bourgeois-Gavardin *et al.*<sup>16</sup> This was also supported by the high mean oxygen consumption rate,  $176 \pm 27$  ml/min, reported by Nahas *et al.*<sup>17</sup> in smaller (average 16 kg) unpremedicated dogs.

The most important change in the distribution of ventilation-perfusion ratios produced by inhalation anesthesia was the consistent development of increased dead-space ( $\dot{V}_A/\dot{Q} > 100.0$ ) ventilation. An additional but more variable development of high

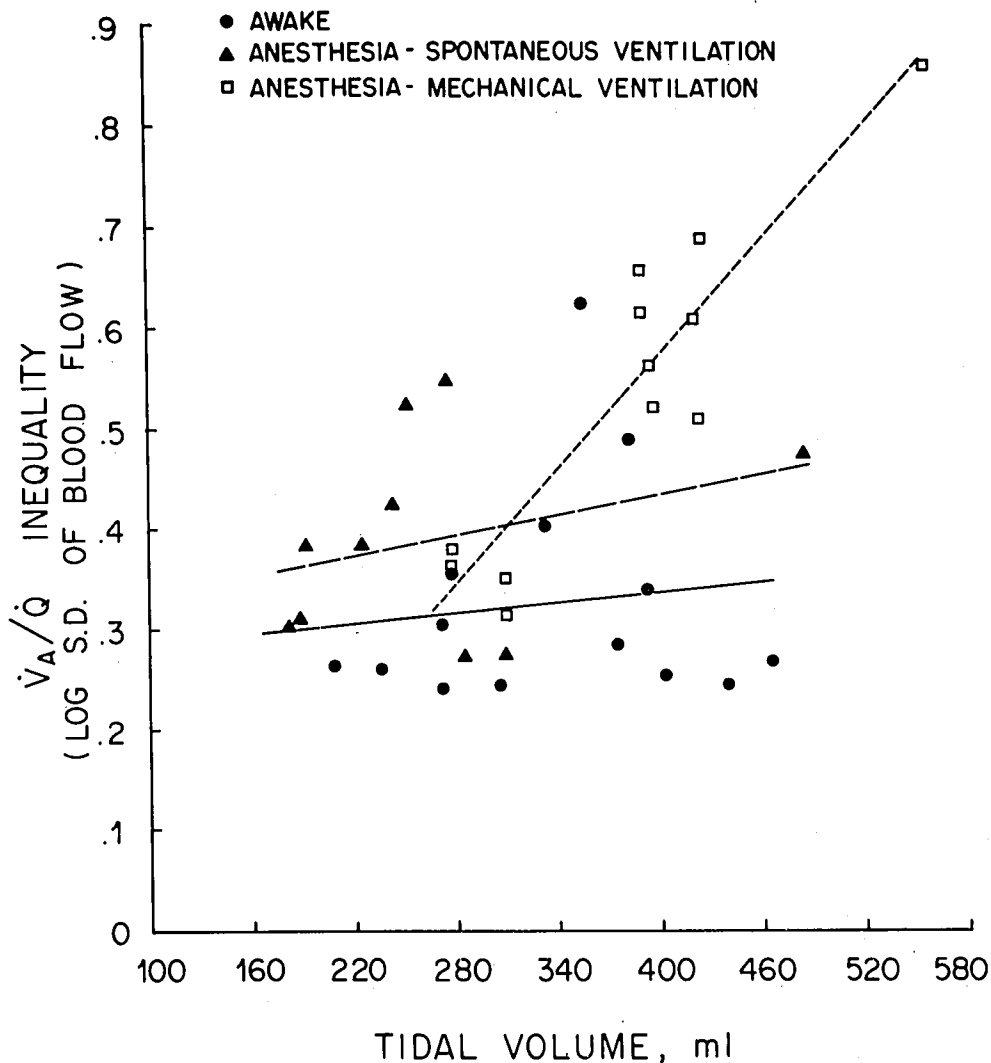


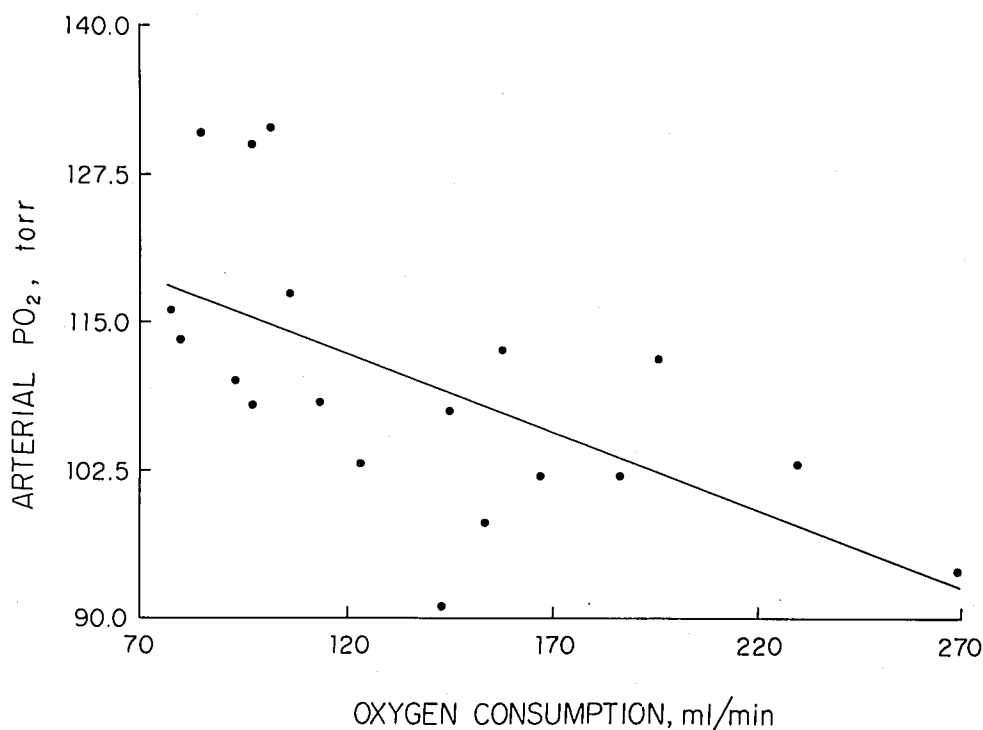
FIG. 4. Inequality of ventilation and blood flow distribution is plotted as log standard deviation of blood flow with respect to  $\dot{V}_A/\dot{Q}$  ratios in the intermediate range ( $0.1 < \dot{V}_A/\dot{Q} < 10.0$ ) vs. the tidal volume, ml BTFS. Note that only anesthesia with muscle paralysis and mechanical ventilation showed a significant positive correlation of  $\dot{V}_A/\dot{Q}$  inequality and breath size,  $r = 0.919$ , which was significantly different from either awake or anesthesia with spontaneous ventilation at  $P < 0.005$ .

$\dot{V}_A/\dot{Q}$  ( $10.0 < \dot{V}_A/\dot{Q} < 100.0$ ) regions could not be reliably differentiated from dead-space ventilation with the present method of analysis.<sup>2</sup> Since such high  $\dot{V}_A/\dot{Q}$  regions were at the extreme upper range of  $\dot{V}_A/\dot{Q}$  ratios, it was unlikely that their gas exchange consequences for  $\text{CO}_2$  elimination were significantly different from dead-space ventilation. This interpretation was supported by the marked increase in minute ventilation required to prevent  $\text{CO}_2$  accumulation during anesthesia studies. The apparent lack of a respiratory depressant effect of halothane during spontaneous ventilation studies may have been due to metabolism of Acepromazine® in the interval from awake control measurement to anesthesia measurement. Such an explanation also implies variability in the degree of metabolism of Acepromazine®, since there was a wide range of tidal volumes and frequencies, especially during spontaneous ventilation anesthesia studies. This accounted for the generally

greater amount of dead-space ventilation during spontaneous breathing studies. That is, tidal volumes were generally lower during spontaneous breathing studies (although the range of tidal volumes was comparable) than during mechanical ventilation, hence the higher  $V_D/V_T$  ratios. It is important to notice that both the increased dead-space ventilation and the inverse relationship of tidal volume and deadspace ventilation were significantly different from awake control findings over a comparable tidal volume range. It is likewise noteworthy that human studies in the normal tidal volume range have also failed to demonstrate a tidal volume effect on  $V_D/V_T$  ratio in awake subjects.<sup>18</sup> Anesthesia studies by Cooper *et al.*<sup>19</sup> and Kain *et al.*<sup>20</sup> have shown a similar though less dramatic effect of tidal volume on  $V_D/V_T$  ratio in adult patients. Studies by Rose and Froese<sup>21</sup> in pediatric patients demonstrated a positive correlation of dead-space and tidal volume during mechanical ventilation



FIG. 5. Measured arterial oxygen tension values (torr) obtained for all three study conditions (awake, anesthesia spontaneous and mechanical ventilation) are plotted with respect to estimated oxygen consumption rate (ml/min). In the absence of significant venous admixture (shunt or low  $\dot{V}_A/\dot{Q}$  regions) and with no significant change in cardiac output, the predominant effect of anesthesia (same  $F_{I_{O_2}}$ ) was to raise arterial  $P_{O_2}$  by reducing oxygen consumption,  $r = -0.568$ ,  $P < 0.01$ .



but not during spontaneous breathing. Such a positive correlation could have been spuriously shown since "dead space" was determined by the Bohr method and therefore contains tidal volume in both regression variables, *i.e.*, dead space =  $V_D/V_T$  ratio  $\times$  tidal volume. In addition, it should be noted that the pediatric spontaneous ventilation studies did not comprise a tidal volume range comparable to that studied during mechanical ventilation. Their range of tidal volumes during spontaneous breathing studies was in fact produced by varying anesthetic dose and agents (enflurane, halothane, and morphine).

Increased dead-space ventilation due to anesthesia has been shown to be dependent on both anesthetic agent and dose. Loh *et al.*,<sup>22</sup> using the Bohr method of analysis, found an average  $V_D/V_T$  ratio of 56.0 per cent during halothane 2 per cent inspired concentration studies in greyhounds. This was significantly different from the control mean value of 49.6 per cent during chloralose anesthesia. In contrast, 80 per cent nitrous oxide and 1.5 per cent trichlorethylene inspired concentration had no apparent effect on dead-space ventilation in Loh's study. Volunteer studies by Rehder *et al.*<sup>9</sup> using the multiple inert gas analysis method during methoxyflurane anesthesia demonstrated either no change or a decrease in dead-space ventilation. Dueck *et al.*<sup>23</sup> demonstrated no significant change from awake control in older patient studies during nitrous oxide and halothane 0.4 to 0.6 per cent end-tidal concentration. This

difference from the present study in dogs may in part be due to the reduction in anatomic dead space produced by orotracheal intubation in humans. In addition, the concentration of halothane in the patient study was relatively low. Kain *et al.* found an average  $V_D/V_T$  ratio of  $0.37 \pm 0.11$  ( $\pm$ SD) for inspired halothane concentrations less than 1 per cent *vs.*  $0.49 \pm 0.13$  at 1.5 to 2.5 per cent halothane in intubated patients. Such a dose-response relationship between halothane and dead space may have been present in our study although it could not be supported by our findings. We therefore suggest that further elucidation of this response and its mechanism be studied with careful control of both ventilatory pattern (tidal volume and frequency) and anesthetic dose.

In contrast to the inverse relationship of dead space and tidal volume,  $\dot{V}_A/\dot{Q}$  inequality in the intermediate range ( $0.1 < \dot{V}_A/\dot{Q} < 10.0$ ) showed a positive correlation with tidal volume during anesthesia, muscle paralysis and mechanical ventilation in the present study. The absence of a tidal volume effect on intermediate range  $\dot{V}_A/\dot{Q}$  inequality during spontaneous breathing anesthesia studies suggests that the tidal volume relationship during mechanical ventilation was produced by altered motion of the diaphragm. Froese and Bryan<sup>24</sup> used cineradiography to show that the nondependent portion of the diaphragm has greater relative motion than the dependent portion during anesthesia, muscle paralysis and mechanical ventilation. Landmark *et al.*<sup>25</sup> and Rehder *et al.*<sup>26</sup>

TABLE 3. Correlates of Oxygenation

	Arterial P <sub>O<sub>2</sub></sub>	Venous P <sub>O<sub>2</sub></sub>	Cardiac Output	Oxygen Consumption
Arterial P <sub>O<sub>2</sub></sub>	1.000	0.883 <i>P</i> < 0.001	0.472 <i>P</i> < 0.050	-0.568 <i>P</i> < 0.010
Venous P <sub>O<sub>2</sub></sub>	—	1.000	0.727 <i>P</i> < 0.001	-0.376 NS
Cardiac output	—	—	1.000	0.216 NS
Oxygen consumption	—	—	—	1.000

Product-moment correlations, *r* (simple linear regression) of arterial P<sub>O<sub>2</sub></sub>, venous P<sub>O<sub>2</sub></sub>, cardiac output and estimated oxygen consumption rate are presented to test the null hypothesis (H<sub>0</sub>), that the increase in arterial P<sub>O<sub>2</sub></sub> during anesthesia could have occurred by chance variability, and therefore not due to reduced oxygen consumption rate. Note that the highest correlations were for venous P<sub>O<sub>2</sub></sub>/arterial P<sub>O<sub>2</sub></sub>, and venous P<sub>O<sub>2</sub></sub>/cardiac output. Since oxygen consumption rate was calculated from these three values, we conclude that the null hypothesis should be rejected (at 18 degrees of freedom, *r* = 0.444 is significant at *P* < 0.05).

have shown that this change in motion of the diaphragm resulted in increased relative ventilation of nondependent lung regions, without a concomitant redistribution of blood flow. Similar findings were obtained by Chevrolet *et al.*<sup>27</sup> in awake subjects who voluntarily inhibited the diaphragm during intermittent positive pressure ventilation by mask. We therefore propose that altered motion of the diaphragm due to anesthesia, muscle paralysis and mechanical ventilation produced only modest  $\dot{V}_A/\dot{Q}$  inequality in the intermediate  $\dot{V}_A/\dot{Q}$  range in normal dog lungs. This implies further that altered diaphragm motion did not produce sufficient  $\dot{V}_A/\dot{Q}$  inequality to cause impaired arterial oxygenation during anesthesia in the present healthy dog study.

The primary determinant for arterial P<sub>O<sub>2</sub></sub> change due to anesthesia in this study was the reduced rate of oxygen consumption without a concomitant decrease in cardiac output. This conclusion was supported by the inverse correlation of oxygen consumption and arterial P<sub>O<sub>2</sub></sub> shown in figure 5. The internal consistency of this argument was further supported by the high level of correlation of arterial P<sub>O<sub>2</sub></sub> and mixed venous P<sub>O<sub>2</sub></sub>, as well as cardiac output and mixed venous P<sub>O<sub>2</sub></sub>, independently measured variables used for estimation of oxygen consumption by the Fick method (see table 3). The estimated reduction in oxygen consumption rate in the present study was somewhat greater than that seen by Loh *et al.* in comparably sized dogs during halothane 2 per cent inspired concentration studies. This apparent difference may be due in part to differences in control study conditions. Loh *et al.* obtained control oxygen

consumption rate values during maintenance chloralose anesthesia. This maintenance anesthesia, however, was initiated subsequent to an inhalation anesthesia induction with nitrous oxide and halothane to sufficient depth for orotracheal intubation. The combined sedative effects of this sequence of drugs produced a significantly lower metabolic rate than seen in awake nonpremedicated studies by Nahas *et al.*, especially considering the much larger size of the greyhound dogs in Loh's study. Anesthesia studies by Theye and Sessler<sup>28</sup> demonstrated a mean ± SD oxygen consumption rate of 119 ± 7 ml·min<sup>-1</sup>·m<sup>-2</sup> at halothane 2.5 per cent mixed expired concentration in dogs with 0.6 to 0.9 m<sup>2</sup> body surface area. Dogs used in the present study had an average 1.0 m<sup>2</sup> body surface area, and therefore our estimated oxygen consumption rate was comparable to that seen by Theye at the higher halothane dose. From this we conclude that nitrous oxide used in the present study had an additional effect on lowering oxygen consumption rate. The lack of a fall in cardiac output during anesthesia may have been in part due to circulatory depressant effects of Acepromazine® in the awake control study.<sup>16</sup> Mean ± SD values for cardiac output in awake nonpremedicated dogs studied by Nahas *et al.*, were 3.5 ± 0.9 l/min, *i.e.*, approximately 4.7 l·min<sup>-1</sup>·m<sup>-2</sup>. Alternatively, the sympathomimetic effect of nitrous oxide, in the presence of some residual alpha-adrenergic blockade due to Acepromazine®, may have in part counteracted the cardiac depressant effects of halothane. Such an effect has been shown by Smith *et al.*<sup>29</sup>

From these considerations we conclude that the primary effect of inhalation anesthesia with nitrous oxide and halothane on the distribution of pulmonary ventilation and blood flow in the dog was to produce increased dead-space ventilation. The pharmacologic nature of this dead-space effect is suggested by the earlier observation by Wagner *et al.*<sup>5</sup> that dogs studied during pentobarbital anesthesia, muscle paralysis and mechanical ventilation via an orotracheal tube (similar tidal volumes) had mean dead-space values 21.7 per cent of tidal volume and a mean log standard deviation of blood flow of 0.55 (essentially that seen in the present study when calculating this index of  $\dot{V}_A/\dot{Q}$  inequality without the high  $\dot{V}_A/\dot{Q}$  area—not present in the pentobarbital study). Since no upper airway changes were responsible for the dead-space effect (the chronic tracheostomy was present in the awake study), the changes were either due to lower airway dilatation or development of unperfused but ventilated lung regions. Bronchodilation due to halothane might have accounted for the former, but was unlikely as an important factor in the absence of any evidence

for bronchoconstriction in the awake control study. This leaves us with the hypothesis that redistribution of pulmonary blood flow occurred as a result of a pharmacologic effect of nitrous oxide and halothane anesthesia. Topographical studies in human subjects have not supported this hypothesis.<sup>25</sup> However, a similar discrepancy was observed for increased dead-space ventilation in the presence of severe hemorrhage in dog studies by Malik and Newell.<sup>30</sup> This implies either that topographical studies using radioactive tracer substances may have had insufficient resolution of  $\dot{V}_A/\dot{Q}$  differences for such extremely high  $\dot{V}_A/\dot{Q}$  ratios, or that there are pharmacologic differences for human and canine pulmonary circulation responses to halothane. Finally, we conclude that a small increase in  $\dot{V}_A/\dot{Q}$  inequality in the intermediate range of  $\dot{V}_A/\dot{Q}$  ratios during anesthesia was primarily due to altered motion of the diaphragm. This was caused by reduced tonic and active contraction of the diaphragm during spontaneous ventilation,<sup>31</sup> and accentuated by muscle paralysis during passive mechanical ventilation.

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