Pulmonary Diffusing Capacity and Gas Exchange during Halothane Anesthesia

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Diffusing capacity of the lung for carbon monoxide ($D_{L_{CO}}$) and pulmonary gas exchange were measured in twelve subjects in the conscious state and again after approximately an hour of halothane anesthesia with artificial ventilation. Respiratory frequency, tidal volume and $P_{a_{CO_2}}$ were not significantly different in conscious and anesthetized states. Significant changes associated with the anesthetized state were increases in alveolar–arterial oxygen tension difference (AaP_{O_2}) and ratio of deadspace to tidal volume (V_D/V_T) and decreases in oxygen consumption and carbon dioxide production. There was an increase in $D_{L_{CO}}$ during anesthesia, but it was not statistically significant. Diffusing characteristics of the lung during anesthesia under conditions of this study were not remarkably different from those in the conscious state. Diffusion abnormalities did not contribute to the increase in AaP_{O_2} during anesthesia. (Key words: Pulmonary diffusing capacity; Respiratory function during anesthesia; Alveolar–arterial oxygen tension difference; Oxygen consumption; Artificial ventilation.)

ABNORMALLY LARGE alveolar–arterial oxygen tension differences (AaP_{O_2}) during general anesthesia have been demonstrated by numerous investigators in the majority of subjects studied. The mechanism of the increase in AaP_{O_2} during anesthesia remains obscure. Previous studies showed that during halothane anesthesia with artificial ventilation significant increases in shunting of blood through or across the lung occurred. Under these conditions ventilation–perfusion abnormalities were no greater than in healthy, conscious spontaneously-breathing individuals.[1, 2] In addition to true shunt and ventilation–perfusion abnormalities, diffusion characteristics of the lung can influence the magnitude of AaP_{O_2}.[3] The present study was undertaken to determine the extent to which alterations in diffusing properties of the lungs might contribute to the abnormally large AaP_{O_2} which occurs during anesthesia.

Methods

Diffusing capacity of the lung for carbon monoxide ($D_{L_{CO}}$) and pulmonary gas exchange were studied in twelve subjects in the conscious state and again after approximately an hour of halothane anesthesia. $D_{L_{CO}}$ was measured using the steady-state method as proposed by Filley, MacIntosh and Wright.[4] Physical characteristics of the subjects, who were male hospital patients scheduled for elective surgery under general anesthesia, are presented in table 1. All were free of systemic disease except two subjects who had mild chronic bronchitis attributed to smoking.

Subjects were oriented to the laboratory and the apparatus and then assumed the supine position for a 30-minute rest period before commencement of the study. None had received medication except Patient 5, who received atropine and hydroxyzine 30 minutes before reporting for the study. The region surrounding the brachial or radial artery was infiltrated with procaine solution for subsequent arterial blood sampling. The apparatus used for conscious subjects is illustrated in figure 1. Following application of a nose clip, subjects initially breathed room air through a mouthpiece. When they had become accustomed to the apparatus and a regular respiratory pattern was established, rotation of the three-way tap in the inspiratory line permitted inspiration of 0.1 per cent CO in air from the 120-liter recording spirometer. Breathing of this mixture continued for six minutes. During the first two minutes subjects exhaled to atmosphere. During the third minute exhaled

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gas was diverted into the bag of the box–bag system by rotation of the three-way tap in the expiratory line. During the fourth minute subjects again exhaled to atmosphere while the bag in the box was emptied. Then, during the fifth and sixth minutes, exhalation was directed into the bag to provide a sample of mixed expired gas for subsequent analysis, exhaled tidal volume was recorded by displacement of air from the box surrounding the bag into a 13-liter spirometer, an arterial blood sample was obtained, and temperatures of both inspired and expired gas were recorded.

The study was repeated after approximately an hour of halothane anesthesia. In the interval, patients had been premedicated with various combinations of atropine, pentobarbital and hydroxyzine in the usual clinical dosage range. Anesthesia was induced with thiopental and a cuffed endotracheal tube was inserted during succinylcholine paralysis. Initially, anesthesia was maintained with 1 per cent halothane in oxygen and sufficient *d*-tubocurarine was administered to prevent motion and spontaneous respiratory efforts. All subjects were supine and horizontal except Patient 5 who was in the prone position. Measurements were made during the course of surgery. The apparatus used for anesthetized patients is illustrated in figure 2. To begin the study the subject was ventilated with 1 per cent halothane in air using a piston pump (Harvard Apparatus Co., Dover, Mass.) at a frequency and tidal volume close to those measured for the individual in the conscious state. Competence of the valves on the pump was verified before and after each study. After 15 to 20 minutes of ventilation with 1 per cent halothane in air, rotation of the three-way tap in the inspiratory line permitted ventilation with 0.1 per cent CO, 1 per cent halothane, and the balance air which had been prepared previously by passing the 0.1 per cent CO in air through a Fluotec Vaporizer and into a 120-liter Douglas Bag. Ventilation with the anesthetizing mixture containing CO continued for six minutes following the same time sequence as in the conscious state. Thus in the fifth and sixth minutes exhaled gas was collected, expired tidal volume was recorded, an arterial blood sample was obtained, and temperature of exhaled gas and patient were recorded.

Inspired tidal volume in the conscious state was determined from the 120-liter spirometer tracing and in the anesthetized state, by measuring stroke volume of the pump. In both portions of the study exhaled tidal volume and respiratory frequency were determined from the 13-liter spirometer tracing. Oxygen concentrations of both inspired and mixed expired gas were measured with a paramagnetic oxygen analyzer (Servomex DCL 101, Servomex Controls Ltd., England). This instrument has an accuracy and reproducibility comparable to that of Haldane analysis.[5] CO concentrations in both inspired and exhaled gas were measured with an infrared CO analyzer (Beckman IR-215, Beckman Instruments, Inc., Fullerton, Calif.). This analyzer was calibrated for use both with and without halothane in the gas mixtures. Carbon dioxide ten-

TABLE 1. Characteristics of the Experimental Subjects

	Age (years)	Weight (kg)	Height (cm)	Hematocrit (per cent)	Smoking History	Operation	Physical Status
Patient 1	52	70	173	47	+	Hernia repair	Chronic bronchitis
Patient 2	52	80	180	52	+	Hernia repair	Healthy
Patient 3	18	56	165	45	−	Orchiopexy	Healthy
Patient 4	46	89	183	51	+	Hernia repair	Healrhy
Patient 5	22	66	173	38	±	Bone graft, tibia	Healthy
Patient 6	39	73	173	49	−	Cholecystectomy	Healthy
Patient 7	41	91	188	55	+	Hernia repair	Healthy
Patient 8	55	70	178	48	+	Hernia repair	Healthy
Patient 9	28	80	170	48	−	Hernia repair	Healthy
Patient 10	58	70	175	52	−	Hernia repair	Healthy
Patient 11	44	68	173	47	+	Menisectomy	Chronic bronchitis
Patient 12	18	60	165	52	+	Arthrotomy, elbow	Healthy

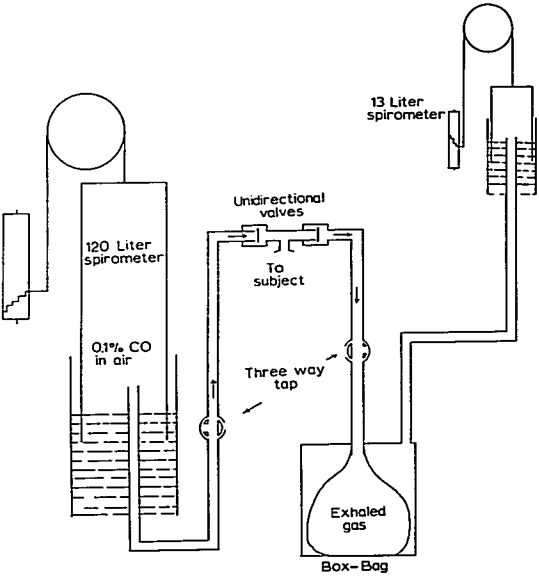

FIG. 1. Schema of experimental apparatus employed for conscious subjects.

sion in mixed expired gas and oxygen and carbon dioxide tensions in arterial blood were measured with appropriate electrodes in an Instrumentation Laboratory System (Instrumentation Laboratory Inc., Lexington, Mass.).

Uptake of oxygen and uptake of carbon monoxide, as well as production of carbon dioxide, were calculated from volumes of and respective concentrations of these gases in both inspired and exhaled gas. Respiratory exchange ratio was calculated as the ratio of carbon dioxide production to oxygen consumption. Ideal alveolar oxygen tension was determined using measured respiratory parameters in an alveolar air equation.[6] Physiologic deadspace was calculated using Bohr's equation and was corrected for apparatus deadspace.

Diffusing capacity of the lung for carbon monoxide ($D_{L_{CO}}$) is the number of milliliters of CO transferred from alveolar gas to pulmonary capillary blood per minute per millimeter tension difference for CO existing between alveolar gas and pulmonary capillary blood. In the present study tension of CO in mixed venous blood was assumed to be zero, so that $D_{L_{CO}}$ could be calculated from the formula:

$$D_{L_{CO}} = \frac{\dot{V}_{CO}}{P_{A_{CO}}}$$

$\dot{V}_{CO}$ (carbon monoxide uptake) was calculated, as mentioned previously, from volumes and CO concentrations of both inspired and exhaled gas. $P_{A_{CO}}$ (mean alveolar CO tension) was calculated by the method of Filley *et al.*[4] It was assumed that deadspace for CO and CO_2 were identical. Therefore, Bohr's equation applicable to each gas could be equated:

$$\frac{F_{A_{CO_2}} - F_{E_{CO_2}}}{F_{A_{CO_2}}} = \frac{F_{A_{CO}} - F_{E_{CO}}}{F_{A_{CO}} - F_{I_{CO}}}$$

This expression could then be solved for $F_{A_{CO}}$:

$$F_{A_{CO}} = F_{I_{CO}} - \frac{F_{A_{CO_2}}}{F_{E_{CO_2}}} (F_{I_{CO}} - F_{E_{CO}})$$

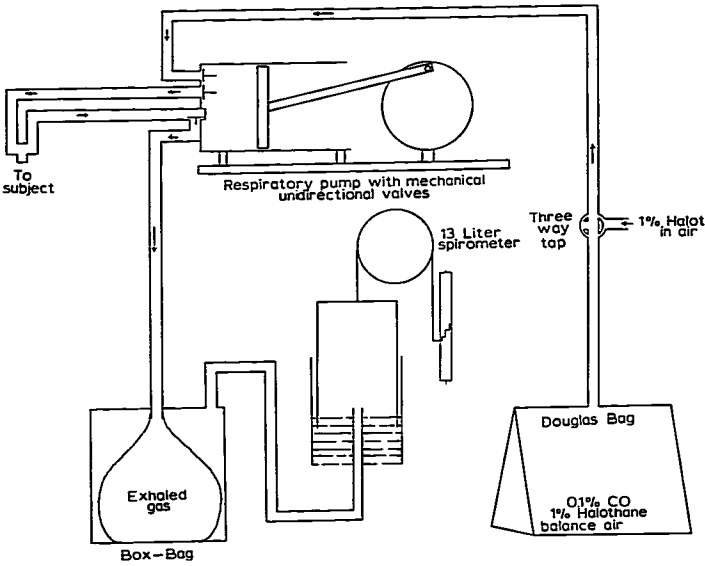

FIG. 2. Schema of experimental apparatus employed for anesthetized subjects.

Since all quantities on the right side of the equation had been measured $F_{A_{CO}}$ could be calculated. (Alveolar and arterial tensions of CO_2 were assumed to be equal.) $P_{A_{CO}}$ was then calculated by multiplying dry barometric pressure by $F_{A_{CO}}$.

Fractional CO uptake is the ratio of CO absorbed per minute to the total quantity of CO inspired per minute. It was calculated from volumes and CO concentrations of both inspired and exhaled gas:

$$\text{Fractional CO uptake} = \frac{F_{I_{CO}} \cdot \dot{V}_I - F_{E_C} \cdot \dot{V}_E}{F_{I_{CO}} \cdot \dot{V}_I}$$

Differences between mean values for individual respiratory parameters in conscious and anesthetized states were tested for statistical significance using Student's t test. The 5 per cent level was designated as the level of significance.

Results

The present study was conducted at an elevation of 4,780 feet above sea level. Total barometric pressure was 640 mm Hg and all subjects were resident and acclimatized to this altitude. Results for the conscious state are presented in table 2 and for the anesthetized state in table 3.

Respiratory frequency, tidal volume, minute volume and respiratory exchange ratio were virtually identical in the conscious and anesthetized states and indicate a mild level of hyperventilation during both portions of the study. O_2 uptake and CO_2 production were significantly decreased during anesthesia. CO uptake was not significantly different in conscious and anesthetized states.

Mean arterial carbon dioxide tension was 32.5 mm Hg in the conscious state, and the small decrease to 30.6 mm Hg in the anesthe-

TABLE 2. Experimental Results Obtained during the Conscious State

	Frequency (min⁻¹)	Tidal Volume (ml BTPS)	Minute Volume (ml BTPS)	O_2 Uptake (ml STPD)	CO_2 Production (ml STPD)	Respiratory Exchange Ratio	CO Uptake (ml STPD)	P_{ACO_2} (mm Hg)	P_{AO_2} (mm Hg)	P_{aO_2} (mm Hg)	$A-aDO_2$ (mm Hg)	V_D/V_T	D_{LCO}	Fractional CO Uptake
Patient 1	17.7	395	6,984	220	152	0.691	1.84	32.2	79.6	64.2	15.4	0.397	12.0	0.415
Patient 2	15.8	763	12,053	209	216	1.03	2.83	—	87.0	60.0	26.1	—	—	0.373
Patient 3	20.2	326	6,748	214	177	0.827	2.30	35.2	85.6	83.6	2.0	0.331	19.2	0.516
Patient 4	13.9	764	10,575	313	278	0.888	3.71	31.0	89.1	69.4	19.7	0.264	28.5	0.550
Patient 5	12.1	464	5,616	202	131	0.649	1.98	34.9	84.0	76.1	7.9	0.405	26.1	0.524
Patient 6	14.3	702	10,036	228	231	1.01	3.08	31.4	90.3	78.4	11.9	0.359	28.0	0.494
Patient 7	7.7	915	7,047	158	169	1.07	2.22	24.2	93.4	77.5	15.9	0.138	11.7	0.525
Patient 8	20.8	589	12,254	206	215	1.04	2.58	27.8	90.5	66.5	24.0	0.443	15.2	0.344
Patient 9	10.0	750	7,500	291	244	0.838	3.06	35.9	76.2	70.8	5.4	0.209	32.2	0.643
Patient 10	17.6	600	10,566	286	275	0.962	3.13	35.1	84.9	83.2	1.7	0.348	22.4	0.468
Patient 11	12.0	546	6,551	193	165	0.855	1.74	36.1	81.6	60.5	21.1	0.383	10.9	0.416
Patient 12	17.4	381	6,621	220	182	0.795	2.27	34.0	82.4	—	—	0.268	20.6	0.555
Mean	14.9	599	8,446	229	203	0.888	2.56	32.5	85.4	71.9	13.7	0.322	20.7	0.485
SE	1.8	53	677	13	14	0.040	0.18	1.1	1.5	2.5	2.6	0.028	2.2	0.025

TABLE 3. Experimental Results Obtained during the Anesthetized State

	Frequency (min⁻¹)	Tidal Volume (ml BTPS)	Minute Volume (ml BTPS)	O_2 Uptake (ml STPD)	CO_2 Production (ml STPD)	Respiratory Exchange Ratio	CO Uptake (ml STPD)	P_{ACO_2} (mm Hg)	P_{AO_2} (mm Hg)	P_{aO_2} (mm Hg)	$A-aDO_2$ (mm Hg)	V_D/V_T	D_{LCO}	Fractional CO Iptake
Patient 1	11.9	625	7,434	194	161	0.830	2.00	32.6	81.0	50.3	30.7	0.413	16.7	0.440
Patient 2	15.5	791	12,266	166	186	1.12	2.10	23.4	109.8	56.2	44.6	0.431	7.5	0.265
Patient 3	13.5	508	6,838	173	161	0.931	2.05	33.1	87.5	82.4	5.1	0.370	27.0	0.513
Patient 4	14.5	677	9,812	220	185	0.841	2.81	26.7	94.2	70.0	24.2	0.383	23.4	0.468
Patient 5	12.7	493	6,264	185	136	0.735	2.22	31.8	82.1	64.3	17.8	0.391	40.3	0.544
Patient 6	13.9	623	8,660	172	165	0.959	2.77	28.8	90.5	45.8	44.7	0.417	42.6	0.498
Patient 7	8.3	821	6,811	239	175	0.732	2.36	34.6	77.8	62.3	15.5	0.352	26.2	0.535
Patient 8	20.5	526	10,702	160	161	1.01	2.30	26.4	94.1	64.8	29.3	0.496	13.5	0.335
Patient 9	10.6	706	7,484	226	186	0.823	2.04	35.2	79.9	72.9	7.0	0.381	46.3	0.545
Patient 10	18.7	563	10,535	164	199	1.21	3.27	26.1	100.9	79.4	21.5	0.361	27.3	0.480
Patient 11	12.3	536	6,591	150	151	1.01	1.66	36.8	90.8	50.6	40.2	0.446	11.9	0.392
Patient 12	18.0	374	6,730	178	152	0.854	2.26	32.2	85.0	87.8	−2.8	0.374	31.8	0.523
Mean	14.2	604	8,351	186	168	0.921	2.37	30.6	88.7	65.6	23.2	0.401	27.0	0.462
SE	1.0	37	570	8.3	5.3	0.043	0.13	1.3	2.3	3.9	3.2	0.012	3.9	0.030

tized state was not statistically significant. The levels of Pa_{CO_2} verify the existence of a state of mild hyperventilation. Alveolar oxygen tensions in conscious and anesthetized states were quite comparable. Arterial oxygen tension decreased from 71.9 mm Hg in conscious subjects to 65.6 mm Hg during anesthesia, but this decrease was not significant. There was, however, a significant increase in mean alveolar–arterial oxygen tension difference from 13.7 mm Hg in the conscious state to 23.2 mm Hg in the anesthetized state. Physiologic deadspace also increased significantly, from 32.2 per cent of tidal volume in conscious subjects to 40.1 per cent of tidal volume in anesthetized subjects. Diffusing capacity of the lung for carbon monoxide increased from 20.7 ml/mm Hg/min in the conscious state to 27.0 ml/mm Hg/min during anesthesia, but the increase was not significant. Fractional carbon monoxide uptake was 48.5 per cent of total inspired CO in conscious subjects and 46.2 per cent of total inspired CO during anesthesia. This difference was not significant.

Discussion

Measurement of diffusing capacity of the lung for CO is a commonly-used test of pulmonary function and has been extensively studied under a variety of circumstances in conscious individuals. Values for $D_{L_{CO}}$ obtained for conscious subjects in the present study agree with those presented by other workers who have measured steady-state $D_{L_{CO}}$ in comparable resting subjects.[7] Determination of $D_{L_{CO}}$ during anesthesia presented some special problems in choice of technique and interpretation of results. Three general methods have been proposed for $D_{L_{CO}}$ measurement: the single-breath method, the equilibration method, and the steady-state method. In the single-breath technique the subject inspires the test gas mixture containing CO and helium and holds his breath for approximately ten seconds. $D_{L_{CO}}$ is calculated from change in CO concentration during breath-holding and independently-determined lung volume.[8] This method was deemed unsuitable in the anesthetized patient because the sustained positive intrathoracic pressure required to produce the period of breath-holding would reduce pulmonary capillary blood volume. A Valsalva maneuver is known to reduce $D_{L_{CO}}$ in conscious subjects.[9]

In the equilibration (or rebreathing) method the subject breathes the gas mixture containing CO in a closed circuit at fast respiratory frequencies (25/min) in order to attain rapid equilibration between gas in the external circuit and the lung. $D_{L_{CO}}$ is calculated from change in CO concentration in the system during the period of rebreathing and from simultaneously-determined lung volume.[10] Application of this method in the anesthetized patient would necessitate a period of vigorous passive hyperventilation in order to produce rapid gaseous equilibration. The high mean intrathoracic pressure associated with this maneuver would, of itself, be expected to diminish venous return, reduce pulmonary capillary blood volume, and produce a decrease in $D_{L_{CO}}$. Kallos and Smith, using the equilibration method in subjects anesthetized with halothane, have reported reductions in $D_{L_{CO}}$ and pulmonary capillary blood volume.[11]

The steady-state method, used in the present study, is known to become inaccurate in the presence of non-uniform distribution of inspired gas and a large deadspace. Anesthesia with artificial ventilation does not change distribution of inspired gas from that measured in the conscious, spontaneously-breathing individual.[12] An abnormally large physiologic deadspace, however, seems to be an unavoidable consequence of the anesthetized state. In addition, application of the steady-state method to the apneic, anesthetized subject requires positive-pressure breathing, but at a much lower mean intrathoracic pressure than with other methods for measurement of $D_{L_{CO}}$. Attempts to measure steady-state $D_{L_{CO}}$ in spontaneously-breathing anesthetized patients would probably be invalid (and possibly dangerous). In such individuals respiratory depression due to the anesthetic agent would require an excessively long period of CO breathing in order to establish a steady-state for CO during which large quantities of carboxyhemoglobin might accumulate.

Thus, each technique for $D_{L_{CO}}$ measurement had inherent disadvantages for use in

anesthetized subjects. Of the methods available, the steady-state method during artificial ventilation seemed most applicable to a study of pulmonary gas exchange in the anesthetized subject. Fractional CO uptake is regarded as an index rather than a true measurement of pulmonary diffusion since it is influenced by both minute volume and deadspace as well as by $D_{L_{CO}}$.[13]

In the present study $D_{L_{CO}}$ increased during anesthesia, but the increase was not statistically significant. Both absolute and fractional CO uptakes were quite comparable in conscious and anesthetized states. The nonsignificant increase in $D_{L_{CO}}$ is attributed to the increase in deadspace occurring during anesthesia. Filley *et al.* showed that during use of the steady-state method in resting subjects with large deadspace, small erreros in deadspace determination caused large errors in calculated $D_{L_{CO}}$.[4]

Eight of the twelve subjects were smokers. Absolute values for $D_{L_{CO}}$ may have been in error because of appreciable amounts of carboxyhemoglobin in the blood of these subjects, but there was no apparent relationship between change in $D_{L_{CO}}$ with anesthesia and smoking history. Thus, there was no demonstrable impairment of diffusion of gas from alveolus to pulmonary capillary blood associated with the anesthetized state in subjects of this study. Diffusion abnormalities did not contribute to the simultaneously-measured significant increase in AaP_{O_2}. A number of factors influence diffusing properties of the lungs. Failure to demonstrate a significant change in $D_{L_{CO}}$ in the present study suggests that there was probably no remarkable alteration in such factors as properties of alveolar capillary membrane and pulmonary capillary blood volume associated with halothane anesthesia. Interpretation of diffusion measurements is complex, and for further details the reader is referred to the comprehensive reviews of Forster.[14-16]

Atropine in the conscious subject decreases $D_{L_{CO}}$.[17] Subjects of the present study received atropine as preanesthetic medication. This was done so that results of this study could be compared with our previous studies of pulmonary gas exchange using premedicated patients. It is possible that atropine may have minimized increases of $D_{L_{CO}}$ during anesthesia. Continuous positive-pressure breathing in the conscious individual also decreases $D_{L_{CO}}$.[17] It is possible that intermittent positive-pressure artificial ventilation as employed in the present study has the same effect. One can speculate, therefore, that perhaps halothane anesthesia actually causes a significant increase in $D_{L_{CO}}$ which was underestimated in the present study because of the modifying influences of atropine premedication and intermittent positive-pressure ventilation. The most likely cause for such an increase would be an increase in pulmonary capillary blood volume.

No problem in the analysis of CO in the presence of halothane was encountered. The infrared CO analyzer had a 10-inch sample cell. When zero was set with compressed air the instrument did not respond to 100 per cent oxygen or nitrogen, water vapor, or 5 per cent CO_2. One per cent halothane increased apparent CO readings by about 5 per cent of the true value, and this was corrected for in the present study. Nitrous oxide in concentrations lower than 10 per cent drove the analyzer meter off scale, precluding analysis of CO in the presence of N_2O.

The significant changes in blood oxygenation and pulmonary gas exchange associated with the anesthetized state in the present study have been demonstrated repeatedly by previous investigators. Increases in AaP_{O_2} and physiologic deadspace seem to be almost-inescapable consequences of the anesthetized state in most patients.[18] The modest reductions in oxygen consumption and carbon dioxide production during anesthesia have also been reported previously.[10] Results of the present study demonstrate that reductions in oxygen consumption during anesthesia are not attributable to impairment of diffusion. In a previous study it was suggested that the primary cause of the increase in AaP_{O_2} during halothane anesthesia with artificial ventilation was an increase in true shunt of blood without much change in ventilation–perfusion abnormalities from those present in the conscious state.[1] Price and associates reported, under comparable circumstances, a significant increase in true shunt during anesthesia with

little change in magnitude of virtual shunt from that measured in the conscious state.[2] The present study demonstrates that diffusing capacity of the lungs is not decreased during halothane anesthesia. Shunting of blood through or across the lungs, therefore, remains as the predominant cause of the increased AaP_{O_2} during halothane anesthesia with artificial ventilation. The mechanism and pathways of the shunt associated with anesthesia remain to be determined.

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