

Halothane Alters the Oxygen Consumption-Oxygen Delivery Relationship Compared with Conscious State

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ABBREVIATIONS

\dot{D}_{O_2}	= oxygen delivery ($\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)
\dot{V}_{O_2}	= oxygen consumption ($\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)
CI	= cardiac index ($\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)
COD	= critical oxygen delivery ($\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), the value of \dot{D}_{O_2} below which \dot{V}_{O_2} is not maintained
B1	= asymptotic or delivery-independent estimate of \dot{V}_{O_2} ($\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)
B2	= "delivery constant," i.e., \dot{D}_{O_2} at $\dot{V}_{O_2} = 63\%$ B1 ($\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)
P_{aO_2} , $P\bar{v}_{O_2}$	= arterial and mixed venous oxygen tension (mmHg)
P_{aCO_2} , $P\bar{v}_{CO_2}$	= arterial and mixed venous carbon dioxide tension (mmHg)
pH_a , $pH\bar{v}$	= arterial and mixed venous pH
Ca_{O_2} , $C\bar{v}_{O_2}$	= arterial and mixed venous oxygen content (vol%)
Sa_{O_2} , $S\bar{v}_{O_2}$	= arterial and mixed venous oxygen saturation (%)
IVCC	= inferior vena caval constriction
SAP	= systemic arterial pressure (mmHg)
HR	= heart rate (beats per min)
$C(a-\bar{v})_{O_2}$	= arterial-venous blood oxygen content difference (vol%)

The authors' objectives were as follows: 1) to characterize for the first time the relationship between whole body O_2 delivery (\dot{D}_{O_2}) and O_2 consumption (\dot{V}_{O_2}) in adult conscious dogs; and 2) to assess the effects of the inhalational anesthetic, halothane, on that relationship. \dot{D}_{O_2} was varied over a wide range in chronically instrumented dogs by gradual inflation and deflation of a hydraulic occluder implanted around the thoracic inferior vena cava to alter venous return and cardiac output. \dot{V}_{O_2} was measured at different values of \dot{D}_{O_2} in dogs in the fully conscious state and again during halothane anesthesia. A "binning" technique indicated that halothane decreased \dot{V}_{O_2} ($P < 0.01$) at any given value of \dot{D}_{O_2} over a broad range of \dot{V}_{O_2} . A two-

line piecewise linear regression analysis technique indicated that halothane decreased ($P < 0.01$) the critical O_2 delivery (COD) from 20 ± 3 to $10 \pm 1 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and increased ($P < 0.01$) O_2 extraction at COD from 31 ± 3 to $40 \pm 2\%$. However, the \dot{D}_{O_2} - \dot{V}_{O_2} plots measured in both conscious and halothane-anesthetized dogs did not exhibit a discrete discontinuity but rather were closely fit (correlation coefficient = 0.98) by an exponential equation of the following form:

$$O_2 \text{ extraction} = B1 \cdot (1 - \exp(-\dot{D}_{O_2}/B2))/\dot{D}_{O_2},$$

where B1 is the delivery-independent estimate of \dot{V}_{O_2} and B2 is the "delivery constant," i.e., the \dot{D}_{O_2} associated with a \dot{V}_{O_2} equal to 63% of B1. Halothane decreased B1 ($P < 0.01$) from 5.3 ± 0.1 to $3.9 \pm 0.1 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and decreased B2 ($P < 0.01$) from 5.6 ± 0.3 to $3.6 \pm 0.3 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ compared with that measured in conscious dogs. Thus, compared with the conscious state, halothane anesthesia alters the fundamental relationship between \dot{D}_{O_2} and \dot{V}_{O_2} and may have a beneficial effect on tissue oxygenation at low values of \dot{D}_{O_2} . (Key words: Anesthesia. Blood pressure. Cardiac output. Chronic instrumentation. Critical oxygen delivery.)

INHALATIONAL ANESTHETICS (e.g., halothane) are the anesthetic agents of choice in a wide variety of clinical surgical procedures. Moreover, they are commonly used as background anesthetics in experimental studies of the cardiovascular system. It has clearly been established that halothane decreases both whole body O_2 delivery (\dot{D}_{O_2}) and O_2 consumption (\dot{V}_{O_2}).¹⁻³ However, there are no published clinical or experimental data that describe the simultaneous effects of halothane on both \dot{D}_{O_2} and \dot{V}_{O_2} . Thus, the net effect of halothane on tissue oxygenation is difficult to predict. Halothane could have a deleterious effect on tissue oxygenation if \dot{D}_{O_2} is decreased below the critical value at which \dot{V}_{O_2} becomes dependent on \dot{D}_{O_2} . Conversely, halothane could have a beneficial effect on tissue oxygenation if \dot{V}_{O_2} is decreased at a common value of \dot{D}_{O_2} (compared with the conscious state) while the critical value of \dot{D}_{O_2} necessary to maintain \dot{V}_{O_2} simultaneously decreases. This latter effect could be achieved by increasing O_2 extraction and would contrast with the effects of another metabolic depressant, hypothermia, which decreases \dot{V}_{O_2} but either impairs⁴⁻⁶ or has no effect⁷ on peripheral O_2 extraction.

To assess the effects of halothane anesthesia on the \dot{D}_{O_2} - \dot{V}_{O_2} relationship, it is essential to first characterize that relationship in the conscious state. It is surprising

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that neither the \dot{D}_{O_2} - \dot{V}_{O_2} relationship nor the critical O₂ delivery (COD) have ever been characterized in healthy adult conscious animals. COD is defined as the value of \dot{D}_{O_2} below which \dot{V}_{O_2} cannot be maintained.^{5,6} Our first objective was to delineate the \dot{D}_{O_2} - \dot{V}_{O_2} relationship in chronically instrumented, intact conscious dogs. Our second objective was to assess the extent to which halothane anesthesia modifies the \dot{D}_{O_2} - \dot{V}_{O_2} relationship without the confounding effects of acute surgical trauma. To achieve this goal, we used three separate analytic techniques: 1) a "binning" technique to assess changes in \dot{V}_{O_2} at any given value of \dot{D}_{O_2} over a broad range of \dot{D}_{O_2} ; 2) a two-line linear regression analysis technique⁸ to calculate changes in the value of critical O₂ delivery, *i.e.*, when \dot{V}_{O_2} becomes linearly dependent on \dot{D}_{O_2} ; and 3) a technique that mathematically transforms the \dot{D}_{O_2} - \dot{V}_{O_2} plots into \dot{D}_{O_2} -O₂ extraction plots and fits these data to an exponential equation to provide a continuous quantitative estimate of the effects of halothane on the \dot{D}_{O_2} - \dot{V}_{O_2} relationship. Results from all three techniques indicate that halothane has a profound effect on the \dot{D}_{O_2} - \dot{V}_{O_2} relationship compared with that measured in conscious dogs.

Materials and Methods

SURGICAL PREPARATION

Nine male mongrel dogs, weighing 26–33 kg and free of microfilaria, were sedated with morphine sulfate (10 mg, im) and anesthetized with pentobarbital sodium (30 mg/kg, iv). After tracheal intubation, their lungs were mechanically ventilated. A left thoracotomy was performed through the fifth intercostal space. The pericardium was incised, allowing exposure of the heart and great vessels. Heparin-filled Tygon[®] catheters (1.02 mm ID, Norton, Akron, OH) were placed in the descending thoracic aorta, left and right atria, and main pulmonary artery. A hydraulic occluder (20 mm ID, Jones, Silver Springs, MD) was positioned loosely around the thoracic inferior vena cava (IVC). The free ends of the implanted catheters and occluder were exteriorized through the lateral chest wall and were tunneled subcutaneously to a final position between the scapulae. Analgesics were administered for 24 h, and antibiotics were administered for 10 days after the surgery. A recovery period of at least 2 weeks was allowed before experimentation.

EXPERIMENTAL MEASUREMENTS AND CALCULATIONS

Experimental data were recorded on magnetic tape (model 3958 A[®], Hewlett-Packard, Palo Alto, CA) and were played back on an eight-channel stripchart recorder (model 2800[®], Gould-Brush, Eastlake, OH). Phasic and mean (passive electronic filter, 2-s time constant) vascular

pressures were measured at end-expiration by connecting the fluid-filled catheters to transducers (P23ID[®], Gould Statham, Oxnard, CA). Heart rate (HR) was measured from the phasic aortic pressure trace. On the day of each experiment and after topical anesthesia and sterile preparation of the skin, a 7-Fr Swan-Ganz catheter was inserted percutaneously into the external jugular vein, and the tip was advanced into the pulmonary artery with the aid of pressure monitoring. Correct position of the catheter was verified by comparing pressure measured at its distal port with pressure measured from the chronically implanted pulmonary arterial catheter. Pressures transduced through the proximal and distal ports of the Swan-Ganz catheter were monitored continuously during the experiment to prevent unintentional displacement of either port into the right ventricle. The catheter was removed at the end of each experiment. Cardiac output was measured by the thermal dilution technique (cardiac output computer model 9520 A[®], American Edwards Laboratories, Irvine, CA). The injectate consisted of 5 ml of iced 5% dextrose in water. Values of cardiac output represent the average of at least three measurements after discarding the initial measurement. Arterial and mixed venous blood samples were withdrawn simultaneously and slowly to avoid respiratory fluctuations in hemoglobin saturation. The blood samples were collected anaerobically and were analyzed for pH, P_{O₂}, P_{CO₂}, O₂ saturation (S_{O₂}), and hemoglobin concentration (Radiometer ABL 3[®] [Copenhagen, Denmark] and Instrumentation Laboratories CO-Oximeter 282[®] [Lexington, MA], respectively). Body temperature was recorded with each set of blood gases for temperature correction. Blood lactate concentrations were measured by precipitating whole blood with 7% perchloric acid. After centrifugation, the supernatant was decanted and stored at -20° C. Samples were analyzed in duplicate with the use of a lactate dehydrogenase spectrophotometric assay (Sigma, St. Louis, MO).

Cardiac index (CI) was calculated as the quotient of cardiac output and body weight. \dot{D}_{O_2} was calculated as the product of CI and arterial oxygen content (Ca_{O₂}) (dissolved O₂ + hemoglobin-bound O₂). \dot{V}_{O_2} was calculated as the product of CI and Ca_{O₂} - mixed venous oxygen content (C \bar{v}_{O_2}). O₂ extraction was calculated as (Ca \bar{v}_{O_2})/Ca_{O₂}.

EXPERIMENTAL PROTOCOLS

Conscious

Each experiment was performed in a quiet, dimly illuminated laboratory with the healthy, unsedated conscious dog lying on its right side. Seven animals were studied in the conscious state. After baseline hemodynamic and blood gas measurements were obtained, \dot{D}_{O_2} was decreased in a stepwise fashion by gradual inflation

of the hydraulic occluder implanted around the IVC. Cardiac output was decreased by ~ 0.5 l/min at each new level of IVC constriction until systemic arterial pressure was decreased to ~ 50 mmHg, at which time stepwise deflation of the occluder (in an analogous fashion to inflation) was begun. Further inflation of the occluder to reduce \dot{D}_{O_2} to very low values can result in death, which is unacceptable in this unanesthetized experimental preparation. Cardiac output and blood gas measurements were made at each level of IVC inflation and deflation after systemic and pulmonary hemodynamics had achieved new steady state values for at least 5 min. Pressure measurements were referenced to atmospheric pressure at each level of IVC constriction, with the transducers positioned at the level of the spine. Blood lactate concentrations were measured at baseline and during maximum IVC constriction. An average of 10 ± 1 points were obtained to generate each individual \dot{D}_{O_2} - \dot{V}_{O_2} plot over approximately a 1-h period.

Halothane Anesthesia

On a separate day, baseline hemodynamic and blood gas measurements were again made in the conscious state, followed by mask induction with halothane, using a small preanesthetic dose of thiopental sodium (4 mg/kg, iv) to minimize excitatory behavior. Tracheal intubation was performed without the need for muscle relaxants or other agents. The lungs were ventilated with a Harvard[®] (Millis, MA) animal ventilator at a tidal volume of 15 ml/kg, and the respiratory rate was adjusted to match P_{aCO_2} to values measured in the conscious state. End-tidal CO_2 was monitored continuously (Beckman LB-2[®], Fullerton, CA). Supplemental O_2 was administered as necessary to maintain P_{aO_2} more than 100 mmHg. The end-tidal concentration of halothane was monitored with an anesthesia gas analyzer (Siemens model 120[®], Schaumburg, IL), which was calibrated on the day of each experiment with a gas of known halothane concentration. One hour was allowed after induction of anesthesia to establish steady-state conditions. At this time the end-tidal halothane concentration averaged $1.1 \pm 0.1\%$ and the blood concentration of thiopental sodium measured by gas chromatography (National Medical Services) was 3.9 ± 0.6 $\mu\text{g/ml}$. Seven animals were studied during halothane anesthesia. A minimum of 5 days elapsed between experiments on the same animal, and the order of the conscious and halothane experiments was randomized. These protocols were approved by the Animal Care and Use Committee of the Johns Hopkins Medical Institutions.

DATA AND STATISTICAL ANALYSIS

"Binning" Technique

To characterize the \dot{D}_{O_2} - \dot{V}_{O_2} relationship without imposing any form of relationship on the empirical data,

values of \dot{D}_{O_2} and \dot{V}_{O_2} in conscious and halothane-anesthetized dogs were averaged at nonoverlapping \dot{D}_{O_2} intervals of $5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ over the empirically measured range of \dot{D}_{O_2} . Values of \dot{V}_{O_2} in each \dot{D}_{O_2} "bin" ($5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ intervals of \dot{D}_{O_2}) measured in conscious and halothane-anesthetized dogs were compared by Student's *t* test for group comparisons.⁹

Two-line Piecewise Linear Regression Analysis

Critical O_2 delivery (COD) was determined by two-line piecewise linear regression analysis.[§]

This technique generates two straight lines that intersect between the extremes of the \dot{D}_{O_2} and \dot{V}_{O_2} data and minimizes the total residual sum of squares between each data point and the regression line. The intersection of the two lines defines the COD as well as the associated extraction and \dot{V}_{O_2} . This was done for each experiment and each condition. Values of COD, \dot{V}_{O_2} at COD, and extraction at COD in conscious and halothane-anesthetized dogs were compared by Student's *t* test for group comparisons.

Exponential Fit of \dot{D}_{O_2} - \dot{V}_{O_2} Plots

We represented the relationship between \dot{D}_{O_2} (independent variable) and \dot{V}_{O_2} (dependent variable) by the exponential equation:

$$\dot{V}_{O_2} = B1 \cdot (1 - \exp(-\dot{D}_{O_2}/B2)) \quad (1)$$

B1 is the asymptotic or delivery-independent estimate of \dot{V}_{O_2} . B2 is the "delivery constant," *i.e.*, that \dot{D}_{O_2} at which \dot{V}_{O_2} equals 63% of B1 and defines the curvilinear shape of the \dot{D}_{O_2} - \dot{V}_{O_2} relationship. O_2 extraction is defined as follows:

$$\begin{aligned} O_2 \text{ extraction} &= C(a-\bar{v})_{O_2}/Ca_{O_2} \\ &= [CI \cdot C(a-\bar{v})_{O_2}]/(CI \cdot Ca_{O_2}) = \dot{V}_{O_2}/\dot{D}_{O_2} \end{aligned}$$

Thus, dividing equation 1 by \dot{D}_{O_2} yields the following:

$$O_2 \text{ extraction} = B1 \cdot (1 - \exp(-\dot{D}_{O_2}/B2))/\dot{D}_{O_2} \quad (2)$$

Empiric measurements of O_2 extraction and \dot{D}_{O_2} in conscious and halothane-anesthetized states were fit to equation 2 by a nonlinear regression least-squares method to calculate B1 and B2.[¶] Equation 2 eliminates CI as a parameter common to the dependent (\dot{V}_{O_2}) and independent (\dot{D}_{O_2}) variables. This is important because shared variables might result in the appearance of a causal relationship where none exists. Also, equation 2 can be used to fit empiric data of a variety of forms. Thus, it does not

[§] Wilkinson L: Systat: The System for Statistics. Evanston, Systat, Inc., 1987.

[¶] Crunch Interactive Statistical Package, Oakland, Crunch Software Corporation, 1986.

constrain empiric data to one particular relationship. The reasonableness of fit of the \dot{V}_{O_2} - \dot{D}_{O_2} data to equations 1 and 2 was examined by means of a Runs Test.⁹ This allows identification of systematic or continuous departures of the data from the fitted curve. Use of the Runs Test does not confer legitimacy on the particular function chosen, but it is a statistical method that permits a statement as to the ability of a given function to represent the data. Data from each individual experiment were fit to equation 2. The resulting parameters (B1 and B2) were then weighted by the reciprocal of the square of the standard error associated with each measure.¹⁰ This increases reliance on values that are more precise and minimizes the effect of "outliers." The weighted mean values of B1 and B2 in each group were then compared by Student's *t* test for group comparisons.

The relation between mixed venous oxygen tension ($P\bar{v}_{O_2}$) and \dot{D}_{O_2} was analyzed by fitting a least-squares linear regression line for each animal and each condition. This allowed computation of $P\bar{v}_{O_2}$ at 5 ml · kg⁻¹ · min⁻¹ intervals of \dot{D}_{O_2} over the empirically measured range of \dot{D}_{O_2} . Differences in $P\bar{v}_{O_2}$ between conscious and halothane-anesthetized dogs were assessed by two-way analysis of variance with repeated measures (split-plot design).¹¹ Changes in baseline hemodynamics and blood lactate and blood gas values during maximum IVC constriction within each group were assessed by Student's *t* test for paired comparisons. Differences in baseline values and values measured during maximum IVC constriction between groups were assessed by Student's *t* test for group comparisons. Values presented in the tables and text represent the mean ± SE.

Results

HEMODYNAMIC, BLOOD GAS, AND METABOLIC PARAMETERS

Conscious State

Table 1 summarizes the hemodynamic and metabolic parameters over the range of \dot{D}_{O_2} achieved during the

study. Systemic arterial pressure (SAP), CI, and \dot{D}_{O_2} were decreased, heart rate (HR) was unchanged, and O₂ extraction and lactate were increased at maximum IVC constriction (IVCC) compared with baseline values. Significantly, \dot{V}_{O_2} was decreased to 72% of the baseline value (*P* < 0.01) at maximum IVCC. Table 2 summarizes the blood gas values at baseline and during maximum IVCC. Arterial blood gas values were unchanged from baseline values during IVCC except for a decrease in PaCO₂. At maximum IVCC, mixed venous pH (*pH* \bar{v}), $P\bar{v}_{O_2}$, mixed venous oxygen saturation ($S\bar{v}_{O_2}$), and $C\bar{v}_{O_2}$ were all decreased, and mixed venous carbon dioxide tension ($P\bar{v}_{CO_2}$) was increased compared with baseline. Arterial-venous blood oxygen content difference ($C(a-\bar{v})_{O_2}$) was increased during maximum IVCC, and hemoglobin and body temperature were unchanged compared with baseline values.

Halothane Anesthesia

Halothane decreased baseline SAP, CI, and \dot{D}_{O_2} and increased HR, O₂ extraction, and lactate when compared with conscious values (table 1). Halothane decreased \dot{V}_{O_2} to 71% of its conscious baseline value (*P* < 0.02). During IVCC, SAP was lower during halothane than in the conscious state despite similar values of CI. During maximum IVCC, \dot{V}_{O_2} was decreased by an additional 12% compared with the halothane baseline value (*P* < 0.01), which was lower than the conscious value during IVCC despite similar values of \dot{D}_{O_2} . The increase in lactate from baseline values at minimum \dot{D}_{O_2} was less during halothane anesthesia than that observed in the conscious state (0.3 ± 0.1 vs. 1.1 ± 0.3 mM/l; *P* < 0.02). HR was unchanged during IVCC. Baseline CaO₂ was lower during halothane, reflecting the decrease in hemoglobin concentration, but it did not decrease further during IVCC (table 2). There was a mild baseline metabolic acidosis during halothane, which also was unchanged during IVCC. During halothane, body temperature was identical to that measured at baseline in conscious dogs, and it decreased very slightly during IVCC.

TABLE 1. Systemic Hemodynamics and Metabolic Parameters at Maximum and Minimum O₂ Delivery in Conscious and Halothane-anesthetized Dogs

	Conscious		Halothane	
	Baseline	Max IVCC	Baseline	Max IVCC
SAP (mmHg)	108 ± 3	52 ± 3*	73 ± 3†	43 ± 2*†
CI (ml · kg ⁻¹ · min ⁻¹)	164 ± 22	43 ± 3*	97 ± 7†	45 ± 2*
HR (bpm)	84 ± 5	97 ± 9	104 ± 4†	103 ± 8
\dot{D}_{O_2} (ml · kg ⁻¹ · min ⁻¹)	26.8 ± 3.9	6.9 ± 0.4*	14.5 ± 1.2†	6.4 ± 0.3*
\dot{V}_{O_2} (ml · kg ⁻¹ · min ⁻¹)	5.8 ± 0.5	4.2 ± 0.2*	4.1 ± 0.2†	3.6 ± 0.1*†
O ₂ extraction (%)	23 ± 2	61 ± 3*	29 ± 2†	58 ± 2*
Lactate (mM/l)	1.3 ± 0.2	2.3 ± 0.3*	1.8 ± 0.3†	2.1 ± 0.3*

* *P* < 0.01 compared to baseline. † *P* < 0.02 compared to values in conscious dogs.

TABLE 2. Systemic Arterial and Mixed Venous Blood Gases

	Conscious		Halothane	
	Baseline	Max IVCC	Baseline	Max IVCC
pHa	7.39 ± 0.01	7.39 ± 0.02	7.33 ± 0.02†	7.34 ± 0.02†
PaCO ₂ (mmHg)	35 ± 2	27 ± 1*	38 ± 1	33 ± 2*†
PaO ₂ (mmHg)	101 ± 5	101 ± 6	125 ± 7†	123 ± 7†
SaO ₂ (%)	94.5 ± 0.3	94.4 ± 0.7	95.6 ± 0.3†	95.6 ± 0.4
CaO ₂ (vol %)	16.2 ± 0.6	16.1 ± 0.6	14.1 ± 0.5†	14.1 ± 0.5†
pH \bar{v}	7.36 ± 0.01	7.30 ± 0.02*	7.30 ± 0.02†	7.26 ± 0.02*
P \bar{v} CO ₂ (mmHg)	39 ± 2	43 ± 1*	43 ± 1	45 ± 1
P \bar{v} O ₂ (mmHg)	48 ± 2	28 ± 1*	48 ± 3	32 ± 1*†
S \bar{v} O ₂ (%)	73.2 ± 1.9	37.2 ± 2.3*	69.2 ± 2.2	41.6 ± 1.8*
C \bar{v} O ₂ (vol %)	12.5 ± 0.7	6.3 ± 0.4*	10.1 ± 0.6†	6.0 ± 0.5*†
C(a-v)O ₂ (vol %)	3.7 ± 0.2	9.8 ± 0.6*	4.0 ± 0.3	8.1 ± 0.2*†
Hemoglobin (g/dl)	12.1 ± 0.5	12.1 ± 0.5	10.4 ± 0.4†	10.4 ± 0.4†
Body temp. (°C)	38.2 ± 0.1	38.2 ± 0.2	38.2 ± 0.2	38.0 ± 0.2*

* $P < 0.01$ compared to baseline. † $P < 0.05$ compared to values in conscious dogs.

EFFECTS OF HALOTHANE ON THE \dot{D}_{O_2} - \dot{V}_{O_2} RELATIONSHIP

"Binning" Technique

The pooled data in figure 1 (shown for descriptive purposes only) depict the \dot{D}_{O_2} - \dot{V}_{O_2} plots in conscious (top) and halothane-anesthetized (bottom) dogs. The individual \dot{D}_{O_2} - \dot{V}_{O_2} plots from seven conscious and halothane-anesthetized dogs are shown in figures 2 and 3, respectively. The results of the "binning" technique are shown in figure 4. \dot{V}_{O_2} was significantly decreased over the range of \dot{D}_{O_2} studied in both conscious and halothane-anesthetized dogs ($P < 0.001$). Halothane significantly decreased \dot{V}_{O_2} at any given value of \dot{D}_{O_2} . The P \bar{v} O₂ level was also higher during halothane compared with that measured in the conscious state at all but the lowest value of \dot{D}_{O_2} (fig. 5).

Two-line Linear Regression Analysis

Compared with the conscious state, halothane decreased both the COD and the \dot{V}_{O_2} at COD and increased O₂ extraction at COD (table 3).

Exponential Fit

The curves obtained by fitting the individual \dot{D}_{O_2} - \dot{V}_{O_2} plots from seven conscious dogs to equation 2 are shown in figure 6. The composite plot showing the pooled data from these experiments is shown in figure 7. The fitted curve in figure 7 was obtained by using the weighted values of B1 and B2 derived by fitting each individual experiment to equation 2. The correlation coefficient was 0.98. Results of the Runs Test were not significant, which indicates that there was no systematic deviation of the data from the fitted curve. The values of B1 (delivery-independent estimate of \dot{V}_{O_2}) and B2 (delivery constant) are summarized in table 3.

The curves obtained by fitting the individual \dot{D}_{O_2} - \dot{V}_{O_2} plots from seven halothane-anesthetized dogs to equation 2 are shown in figure 8, and the composite plot is shown in figure 9. The correlation coefficient was 0.98, and results of the Runs Test were again not significant. When compared with the conscious state, halothane decreased B1 and B2 (table 3).

Discussion

Except for a single study in conscious lambs,¹² this is the first characterization of the \dot{D}_{O_2} - \dot{V}_{O_2} and \dot{D}_{O_2} -O₂ extraction relationships over a broad range of \dot{D}_{O_2} without the use of background anesthesia. Having characterized these relationships in the conscious state, it was then possible to assess the specific effects of halothane anesthesia on these relationships. The three analytic techniques used to assess the effects of halothane all clearly indicate that this inhalational anesthetic caused significant changes in the \dot{D}_{O_2} - \dot{V}_{O_2} and \dot{D}_{O_2} -O₂ extraction relationships.

By averaging the empirically measured \dot{D}_{O_2} - \dot{V}_{O_2} points in 5 ml · kg⁻¹ · min⁻¹ "bins" of \dot{D}_{O_2} , we were able to compare values of \dot{V}_{O_2} in the conscious and halothane-anesthetized states at common values of \dot{D}_{O_2} without imposing any form of relationship on the empiric data. Compared with the conscious state, halothane had the effect of decreasing \dot{V}_{O_2} at any given value of \dot{D}_{O_2} over a broad range of \dot{D}_{O_2} . This effect was also observed as a higher P \bar{v} O₂ at all but the lowest value of \dot{D}_{O_2} in the halothane-anesthetized animals compared with those in the conscious state. The fact that halothane decreases both \dot{V}_{O_2} and \dot{D}_{O_2} has been clearly documented.¹⁻³ However, this is the first study to demonstrate that this effect does not result from a simple shift along a common \dot{D}_{O_2} - \dot{V}_{O_2} relationship but rather is the result of moving to an entirely new \dot{D}_{O_2} - \dot{V}_{O_2} relationship. These results suggest that either halothane acted as a generalized metabolic depressant or that

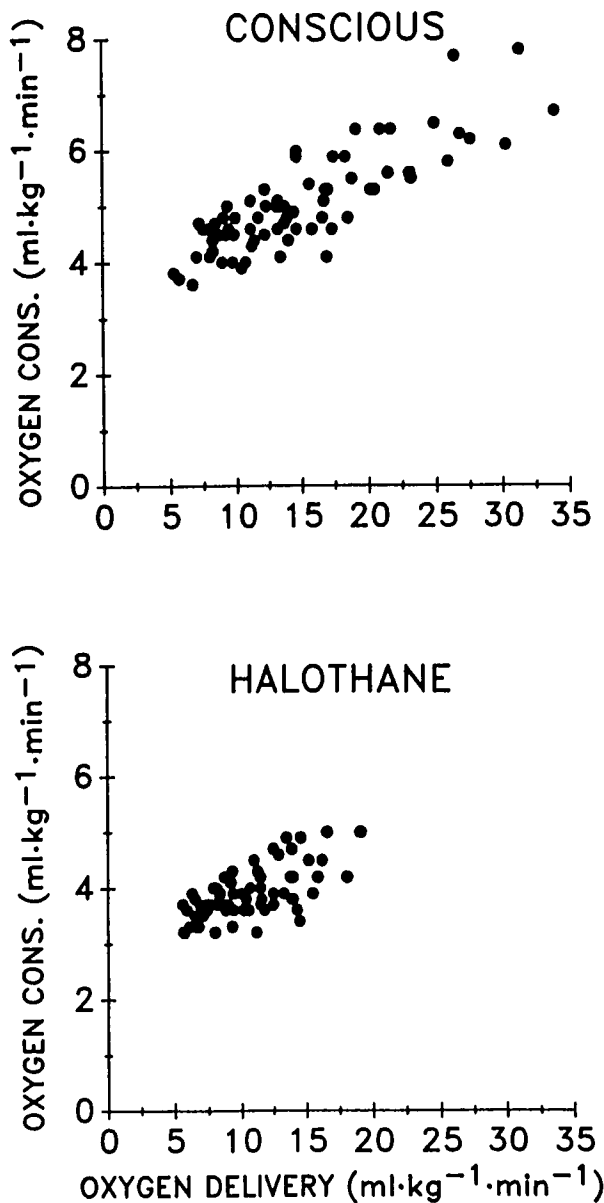


FIG. 1. Pooled data showing oxygen delivery-consumption relationship in seven conscious (*top*) and seven halothane-anesthetized (*bottom*) dogs. Oxygen delivery was varied by inflation and deflation of a hydraulic occluder chronically implanted around the thoracic inferior vena cava to change venous return and cardiac output.

halothane resulted in a redistribution of cardiac output to tissues with a low metabolic rate. This latter possibility appears unlikely, because baseline O₂ extraction was increased during halothane anesthesia compared with the conscious state (table 1). Although the binning technique (fig. 4) is useful in describing the general effects of halothane on the \dot{D}_{O_2} - \dot{V}_{O_2} relationship compared with that measured in animals in the conscious state, it does not permit calculation of COD or extraction at COD. More-

over, because the binning technique averages values over intervals of \dot{D}_{O_2} , it lacks the resolution necessary to reveal the actual underlying continuous form of the empiric data. To gain more insight into the mechanisms by which halothane could alter the \dot{D}_{O_2} - \dot{V}_{O_2} relationship, we used two additional analytic techniques to quantify the effects of halothane.

The COD has been defined by numerous investigators,^{5,6,8,12} as the value of \dot{D}_{O_2} below which \dot{V}_{O_2} can no longer be maintained, resulting in a decrease in \dot{V}_{O_2} when \dot{D}_{O_2} is decreased further. A variety of analytic techniques have been used to mathematically define the value of COD. Although there is no universal agreement about the best analytic approach to determine the value of COD, all techniques have in common the concept that COD is achieved when \dot{V}_{O_2} begins to decrease. We observed a significant decrease in \dot{V}_{O_2} from baseline values in both conscious and halothane-anesthetized dogs during maximum IVCC, so by definition COD was achieved in both groups.

A two-line piecewise linear regression analysis technique was used to calculate the effect of halothane on the COD. Recently, an examination of different methods of analysis of the \dot{D}_{O_2} - \dot{V}_{O_2} relationship determined that this technique was superior to single-line or polynomial methods.⁸ The \dot{D}_{O_2} - \dot{V}_{O_2} relationship has often been idealized into two components. At low values of \dot{D}_{O_2} , \dot{V}_{O_2} varies linearly with \dot{D}_{O_2} . At higher values of \dot{D}_{O_2} , \dot{V}_{O_2} is relatively independent of \dot{D}_{O_2} . The COD has been defined as the \dot{D}_{O_2} at the intersection of the linear and flat portions of the \dot{D}_{O_2} - \dot{V}_{O_2} plot. Halothane significantly decreased the COD compared with that measured in the conscious state (table 3). Moreover, halothane decreased the \dot{V}_{O_2} at COD and increased the O₂ extraction at COD. Thus, in addition to the metabolic depressant effect of halothane mentioned above, halothane also allowed \dot{V}_{O_2} to be maintained to a lower value of \dot{D}_{O_2} . The fact that O₂ extraction was increased at COD suggests that halothane may have had a beneficial effect on O₂ exchange at the microcirculatory level. A beneficial effect of halothane on critical values of O₂ transport has also been reported recently in anesthetized newborn lambs,¹³ although in that study halothane decreased O₂ extraction at COD. The increase in baseline lactate values during halothane may indicate a relative hypoperfusion in some tissues. However, the smaller increase in lactate values during halothane when \dot{D}_{O_2} was decreased to minimum values may also indirectly reflect a halothane-induced improvement in tissue oxygenation. These results can be contrasted with the effects of another well-known metabolic depressant, hypothermia, in which extraction at COD has been reported to be either unchanged⁷ or decreased.⁴⁻⁶

Use of the two-line technique also allowed us to compare our results with previous reports in the literature.

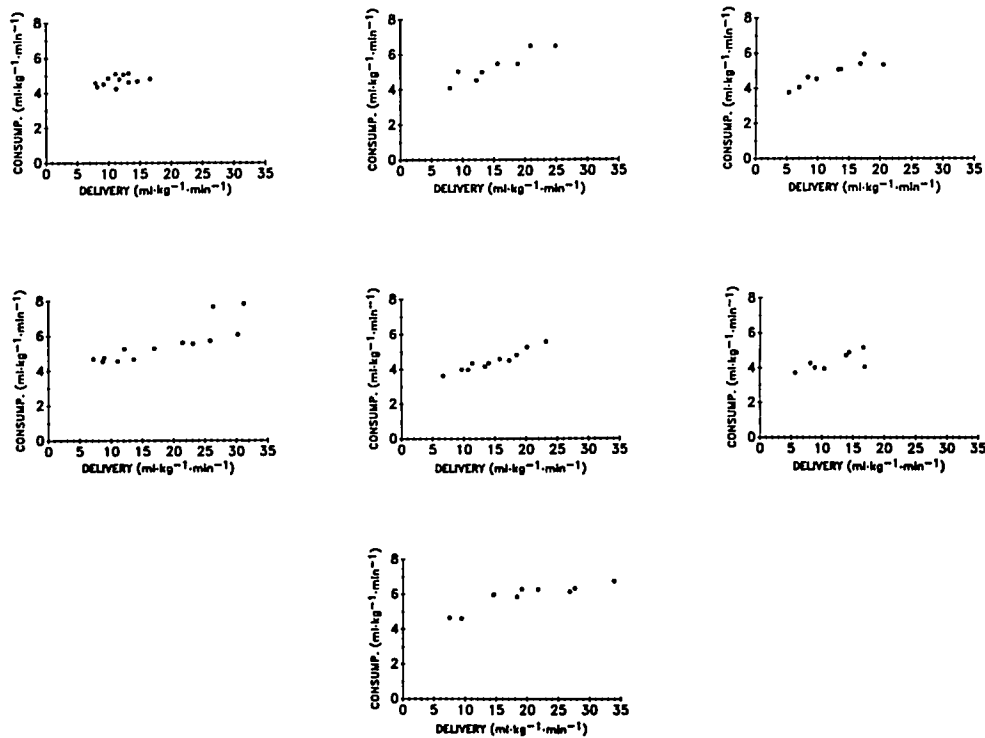


FIG. 2. Relationship between oxygen consumption and oxygen delivery in seven conscious dogs.

The COD during halothane was similar to values previously reported during anesthesia, although extraction at COD was either higher^{6,14-16} or similar^{7,17} to our values. There are no reports in the literature to compare with

our conscious data, although COD was higher and extraction at COD was lower than previous results in anesthetized animals. The value for the COD is dependent on the baseline value of \dot{V}_{O_2} .¹⁵ Because baseline \dot{V}_{O_2} was

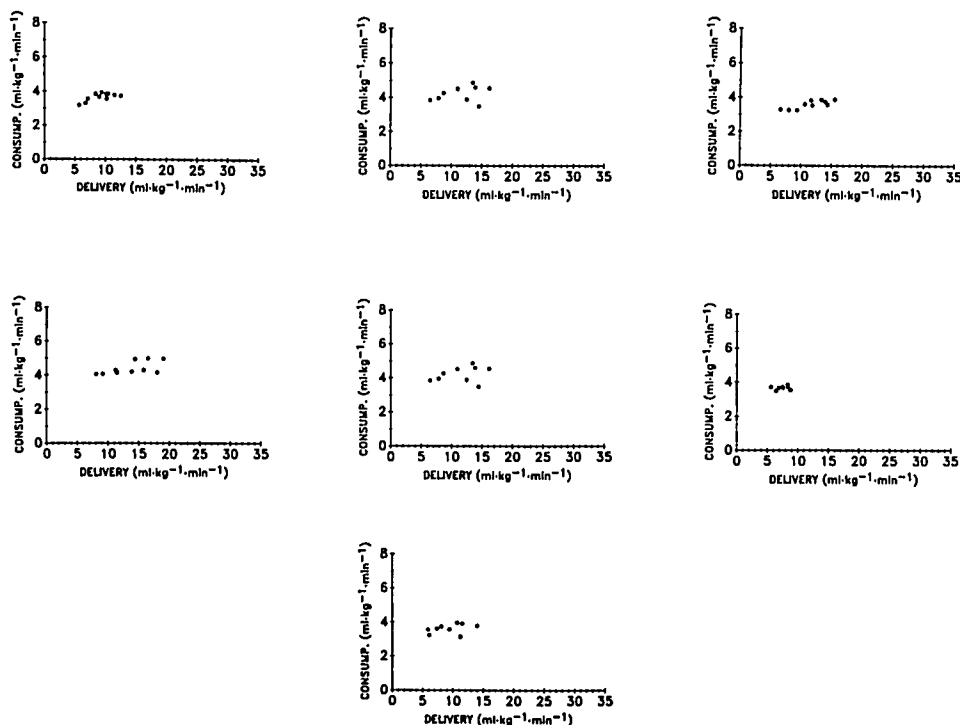


FIG. 3. Relationship between oxygen consumption and oxygen delivery in seven halothane-anesthetized dogs.

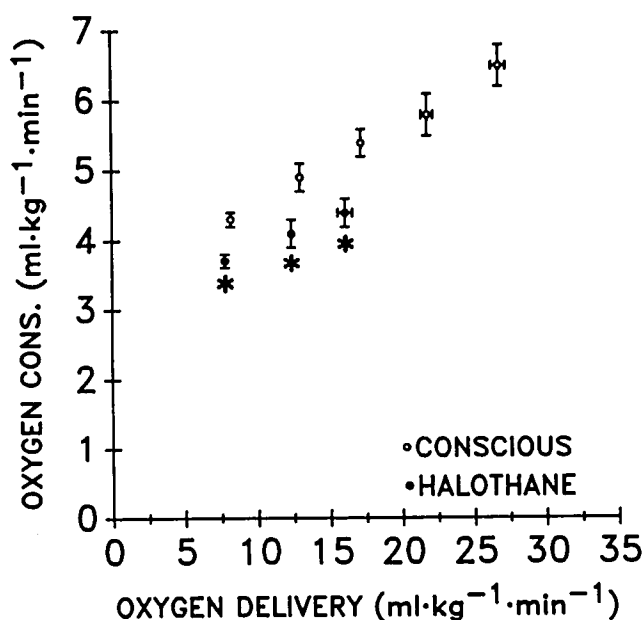


FIG. 4. Pooled data presented in figure 1 were "binned" at 5 ml·kg⁻¹·min⁻¹ intervals of oxygen delivery. Starting from 5-10 ml·kg⁻¹·min⁻¹, the bins contain seven, seven, seven, five, and two conscious dogs (open circles), and 7, 6, and 4 halothane-anesthetized dogs (filled circles). Halothane anesthesia decreased (**P* < 0.01) oxygen consumption at any given value of oxygen delivery. Some error bars fall within the symbols.

higher during the conscious state, it is not surprising that COD was also higher compared with during the anesthetized state. The higher values for O₂ extraction at COD previously reported may reflect the effects of anesthesia and surgical trauma in those acute preparations. We believe it is also possible that applying the two-line technique may yield spurious results because the empiric data are not necessarily well described by two intersecting straight lines (figs. 2 and 3). The two-line technique implies a sharp discontinuity in the \dot{D}_{O_2} - \dot{V}_{O_2} relationship. The calculation of COD with the use of the two-line technique yields only one point along the continuum of the \dot{D}_{O_2} - \dot{V}_{O_2} relationship. Some investigators have observed such a "breakpoint,"^{6,14-16} whereas others have not.^{7,18,**} There is evidence to suggest that COD and maximal O₂ extraction ability are different in different organs.¹⁵ If this is correct, one might expect a curvilinear \dot{D}_{O_2} -O₂ extraction plot. Thus, we used a third analytic technique to characterize the \dot{D}_{O_2} -O₂ extraction relationship in conscious and halothane-anesthetized dogs.

Using equation 2, we have mathematically transformed the \dot{D}_{O_2} - \dot{V}_{O_2} relationship into the \dot{D}_{O_2} -O₂ extraction re-

** Gutierrez G, Pohil RJ: Oxygen consumption is linearly related to O₂ supply in critically ill patients. *Journal of Critical Care* 1:45-53, 1986.

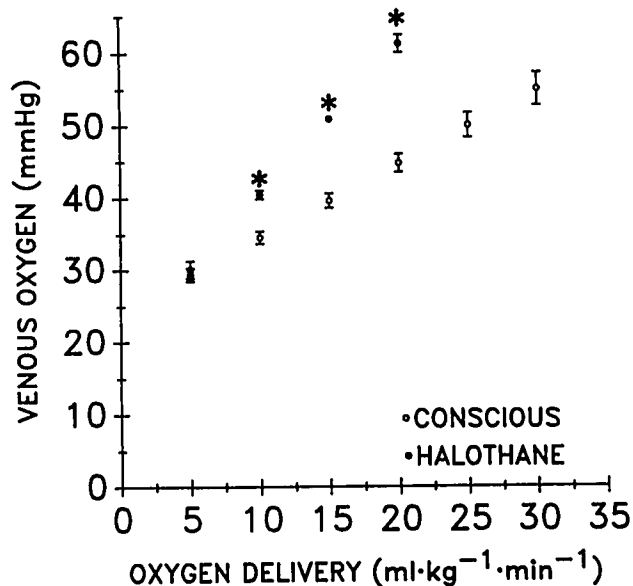


FIG. 5. Mixed venous oxygen was increased (**P* < 0.01) at all but the lowest value of oxygen delivery in halothane-anesthetized (filled circles) compared to conscious (open circles) dogs. Some error bars fall within the symbols.

lationship. The \dot{D}_{O_2} -O₂ extraction relationship represents the same empiric information as the \dot{D}_{O_2} - \dot{V}_{O_2} relationship but in a different form. In the \dot{D}_{O_2} - \dot{V}_{O_2} plot, O₂ extraction is the slope of the line from the origin to any single point in the plot. Conversely, in the \dot{D}_{O_2} -O₂ extraction plot, \dot{V}_{O_2} at any value of \dot{D}_{O_2} is simply the product of O₂ extraction and \dot{D}_{O_2} . This mathematical transformation has been commonly used in studies of the cerebral circulation,¹⁹ and it offers several important advantages. First, the use of equation 2 virtually eliminates the issue of shared variables because O₂ extraction is calculated from CaO₂ and C $\bar{V}O_2$, thereby removing cardiac output as a shared variable in the measurement of \dot{D}_{O_2} and \dot{V}_{O_2} . Second, the analytic model defined by equation 2 closely fits the empiric data (*r* = 0.98 in both groups), as illustrated in figures 6 and 8. The Runs Test further verifies that the exponential curve provides a reasonable fit of the data. This analytic model does not preclude the existence of a

TABLE 3. Parameters Describing the \dot{D}_{O_2} - \dot{V}_{O_2} Relationship in Conscious and Halothane-anesthetized Dogs

	Conscious	Halothane-anesthetized
COD (ml·kg ⁻¹ ·min ⁻¹)	19.76 ± 2.55	10.48 ± 0.90*
\dot{V}_{O_2} at COD (ml·kg ⁻¹ ·min ⁻¹)	5.72 ± 0.30	4.07 ± 0.16*
O ₂ ext. at COD (%)	31 ± 3	40 ± 2*
B1 (ml·kg ⁻¹ ·min ⁻¹)	5.32 ± 0.09	3.86 ± 0.05*
B2 (ml·kg ⁻¹ ·min ⁻¹)	5.56 ± 0.29	3.57 ± 0.26*
R	0.98	0.98

* *P* < 0.01 compared to values in conscious dogs.

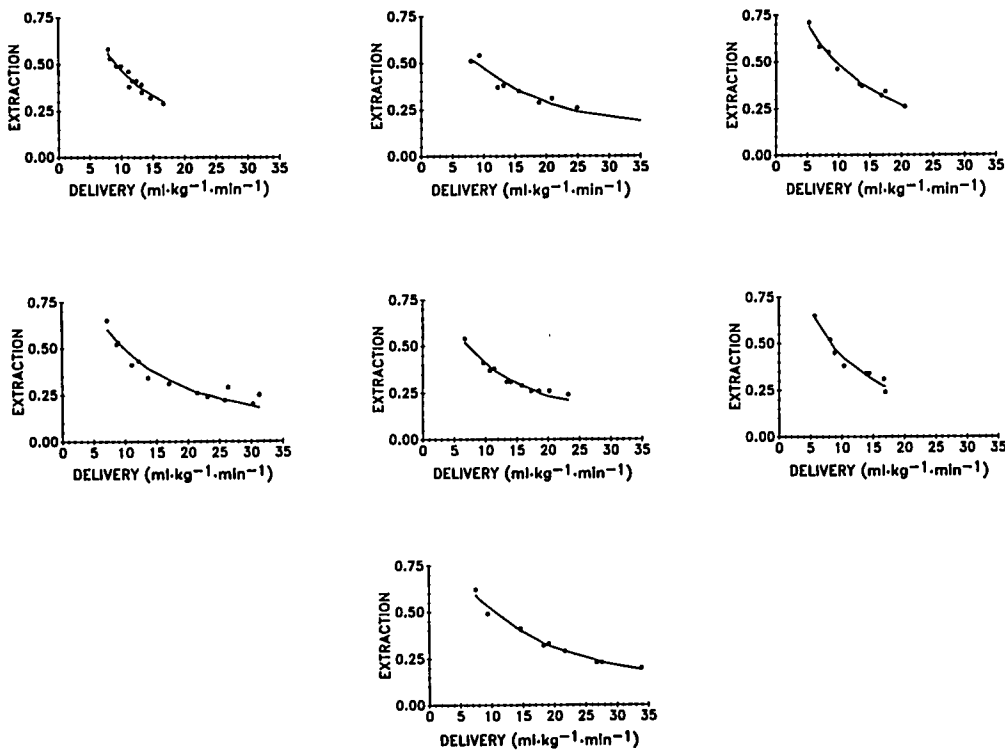


FIG. 6. Relationship between oxygen extraction and oxygen delivery in seven conscious dogs. The curves were obtained by fitting the individual data points from each experiment to equation 2.

sharp discontinuity in the empiric data, but it does not force the data to this form if the relationship is smooth and curving. This can be contrasted with the use of the

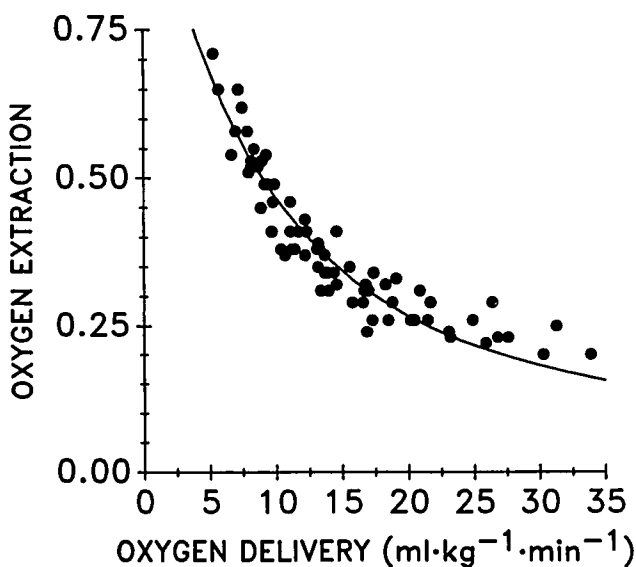


FIG. 7. Plot of pooled data from the seven conscious dogs shown in figure 6. Curve was obtained by using the weighted values of B1 and B2 derived by fitting each individual experiment to equation 2. One point above a \dot{D}_{O_2} of $35 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ is included in the curve-fitting analysis.

two-line technique to fit the individual \dot{D}_{O_2} - \dot{V}_{O_2} plots. A discrete discontinuity in the \dot{D}_{O_2} - \dot{V}_{O_2} relationship is not apparent when assessing the individual plots in figures 2 and 3. Using the model defined by equation 2, we observed a lower delivery-independent value for \dot{V}_{O_2} (B1) during halothane, as well as a lower delivery constant (B2). In essence, these results support the combined conclusions that were drawn from the binning technique and the calculation of COD. Specifically, changes in B1 and B2 indicate that halothane decreased \dot{V}_{O_2} at a given value of \dot{D}_{O_2} and that \dot{V}_{O_2} is better maintained as \dot{D}_{O_2} is reduced compared with during the conscious state. The two-line technique used to assess COD and the exponential method used to analyze the \dot{D}_{O_2} - \dot{V}_{O_2} extraction relationship are complimentary techniques. These techniques are not directly comparable. However, the combined use of these techniques was intended to enhance our understanding of what happens to \dot{V}_{O_2} as \dot{D}_{O_2} is decreased in conscious and halothane-anesthetized animals.

Oxygen extraction is represented continuously by equation 2. The highest extraction achieved in either the conscious or anesthetized animals was 0.70. The mean blood pressure in the two groups at maximum IVCC was $\sim 50 \text{ mmHg}$. Although higher extraction ratios have been reported in acute studies,^{6,15,16} the decreases in blood pressure during IVCC prevented us from decreasing \dot{D}_{O_2} further in this chronic preparation. Previous studies used anesthetized preparations in which \dot{D}_{O_2} was pro-

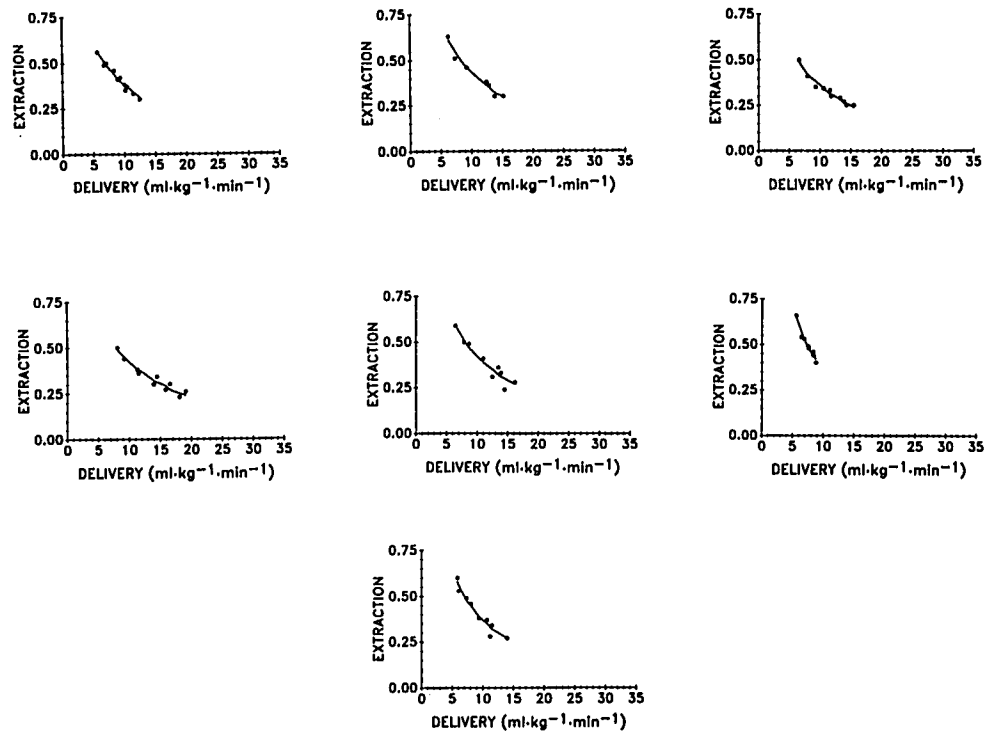


FIG. 8. Relationship between oxygen extraction and oxygen delivery in seven halothane-anesthetized dogs. The curves were obtained by fitting the individual data points from each experiment to equation 2.

gressively decreased until the animals died. We believe it would be unethical to subject an unanesthetized dog to progressive reduction in cardiac output leading to death. Our experience with this experimental preparation is that an additional reduction in blood pressure and cardiac output can result in the death of the animal. Thus, in this

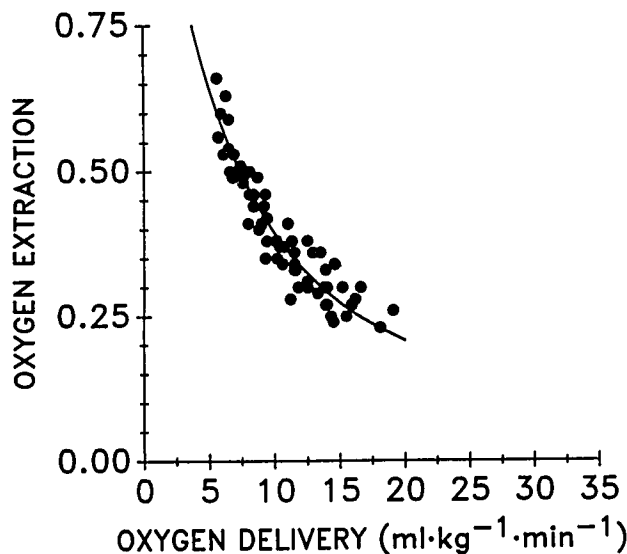


FIG. 9. Plot of pooled data from the seven halothane-anesthetized dogs shown in figure 8. Curve was obtained by using the weighted values of B1 and B2 derived by fitting each individual experiment to equation 2.

conscious model of O₂ supply-dependency, we did not achieve the maximum reduction in \dot{D}_{O_2} . Although it is possible to reduce \dot{D}_{O_2} further, little additional information would be gained to justify this, in light of the already low value of \dot{D}_{O_2} that was achieved. The minimum \dot{D}_{O_2} was approximately 6 ml · kg⁻¹ · min⁻¹ in both groups of animals, which is comparable to values reported by other investigators.^{4,13,17,18} Moreover, increases in lactate values and decreases in \dot{V}_{O_2} were observed in both groups of animals. Thus, although we were unable to decrease \dot{D}_{O_2} as severely as in some acute preparations, there is no doubt that supply limitation of O₂ was achieved in both groups.

Hemodynamic stability was achieved before measurement of \dot{V}_{O_2} and O₂ extraction at every value of \dot{D}_{O_2} . It is possible that equilibration of O₂ extraction at any decrement of \dot{D}_{O_2} may not have occurred. Cain and co-workers have suggested in hypoxic and embolization models that up to 20 min may be required for adjustments both within and between organ beds before maximum extraction is reached.^{††}²⁰ In contrast, Fahey and co-workers, in a model similar to ours, found that extraction was maximized at 5–10 min even at low \dot{D}_{O_2} levels.^{‡‡} The tech-

†† Cain SM, King CE, Chapler CK: Effects of time and microembolization on O₂ extraction by dog hindlimb in hypoxia. *Journal of Critical Care* 3:89–95, 1988.

‡‡ Fahey JT, Lister G: Oxygen transport in low cardiac output states. *Journal of Critical Care* 2:288–305, 1987.

niques used to decrease \dot{D}_{O_2} may account for the apparent differences. However, incomplete equilibration is unlikely to be responsible for the observed differences between the conscious and halothane-anesthetized states.

A small dose of thiopental sodium was used during induction of anesthesia to prevent excitatory behavior. Although it is possible that this could have affected our results, the blood levels 1 h after administration and before generation of the plots were far below concentrations required to produce or maintain anesthesia.²¹ The pharmacokinetics of thiopental are such that blood concentrations in response to this dose would have been similar at 1 h or 24 h after administration.²¹ It is likely that mechanical ventilation contributed somewhat to the decrease in metabolic rate during halothane. However, halothane decreased BI by $\sim 27\%$ and \dot{V}_{O_2} by $\sim 30\%$, whereas the O_2 consumption of respiratory muscles normally represents less than 5% of total \dot{V}_{O_2} .²² The small ($0.2^\circ C$) decrease in body temperature observed at the lowest value of \dot{D}_{O_2} during halothane could also have slightly decreased \dot{V}_{O_2} . On the other hand, the modest degree of metabolic acidosis during halothane could have caused a leftward shift in the oxyhemoglobin dissociation curve. This would have the effect of attenuating the halothane-induced decrease in \dot{V}_{O_2} by increasing the supply of O_2 to metabolizing tissues. This latter effect could also increase O_2 use by non-adenosine triphosphate (ATP)-requiring enzyme systems. Such systems are thought to account for up to 10% of total \dot{V}_{O_2} and are much more sensitive to hypoxemia than ATP-requiring systems.²³⁻²⁵

As reported previously,²⁶ halothane decreased the baseline hemoglobin concentration. The consequent decrease in Ca_{O_2} and the concomitant decrease in CI resulted in a decrease in baseline \dot{D}_{O_2} during halothane. These multifactorial changes in the determinants of \dot{D}_{O_2} and \dot{V}_{O_2} demonstrate the importance of assessing the effects of a given intervention (*e.g.*, halothane) on the \dot{D}_{O_2} - \dot{V}_{O_2} relationship over a broad range of \dot{D}_{O_2} .

The individual plots were generated by inflation and deflation of the IVC occluder. Although it is possible that an O_2 debt was "repaid"^{20,27} during the deflation phase, our conclusions were unaltered when inflation and deflation phases were analyzed separately. Numerous methods have been used to decrease \dot{D}_{O_2} (*e.g.*, changing hematocrit,²⁸ changing Pa_{O_2} ,^{7,13} application of positive end-expiratory pressure,¹⁷ hypovolemia by hemorrhage with a normal hematocrit,^{6,14-16} and IVC occlusion to decrease venous return^{12,17,††}). There is no evidence to indicate that the technique used to modulate \dot{D}_{O_2} will lead to differential changes in the \dot{D}_{O_2} - \dot{V}_{O_2} relationship. IVC constriction clearly produced a global reduction in \dot{D}_{O_2} , although the effects could have been accentuated in the lower extremities and gut if an increase in venous pressure distal to the site of constriction further decreased the per-

fusion pressure to those organs. However, it must be emphasized that there was no evidence of either acute or chronic ischemic injury resulting from these experiments.

Finally, despite the significant decrease in systemic arterial pressure at the lowest value of \dot{D}_{O_2} , there was no consistent increase in HR. We have observed this previously in conscious dogs,²⁹ and it may represent interactions between several reflexes (*e.g.*, arterial and cardiopulmonary baroreflexes) activated during IVCC.

In summary, we have assessed the \dot{D}_{O_2} - \dot{V}_{O_2} relationship in adult conscious animals for the first time. Three separate analytic techniques indicate that halothane anesthesia significantly alters the \dot{D}_{O_2} - \dot{V}_{O_2} relationship compared with that measured in the conscious state. Unlike some metabolic depressants, halothane appears to have a beneficial effect on tissue oxygenation by increasing O_2 extraction when O_2 availability is limited.

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