Anesthesiology
67:174–179, 1987

Effect of Halothane on Critical Levels of Oxygen Transport in the Anesthetized Newborn Lamb

Marc B. Hershenson, M.D., P. Pearl O'Rourke, M.D.,† James A. Schena, R.R.T.,‡ Robert K. Crone, M.D.§*

A critical level of oxygen transport has been defined as the level which is required to maintain tissue oxygen uptake ($\dot{V}O_2$). If halothane reduces the susceptibility to hypoxia, it should lower the critical levels of both O_2 delivery ($\dot{D}O_2$) and arterial oxygen tension (p_{O_2}). To test this hypothesis, 12 newborn lambs were anesthetized with either fentanyl and pancuronium (control group) or fentanyl, pancuronium, and 1.1% (1 MAC) halothane (halothane group). Baseline measurements of hemoglobin, cardiac output (CO), arterial and mixed-venous p_{O_2}, and saturation were obtained on $F_{I_{O_2}}$ 1.0, and repeated with $F_{I_{O_2}}$ .21, .15, and .10. O_2 delivery (CO $\times$ CaO_2) and O_2 consumption were calculated from measured parameters. Critical levels were selected using a system of repetitive linear regression. Halothane decreased baseline O_2 consumption (12.1 ± 0.7 to 8.4 ± 0.4 cc·kg^{-1}·min^{-1}, x ± SEM, $P < .001$, unpaired t test), but caused similar reductions in cardiac output (235 ± 15 to 132 ± 15 cc·kg^{-1}·min^{-1}, $P < .001$) and O_2 delivery (29.2 ± 2.9 to 20.2 ± 1.6 cc·kg^{-1}·min^{-1}, $P < .05$). Addition of halothane decreased the critical level of O_2 delivery from 17.9 to 14.3 cc·kg^{-1}·min^{-1}, but had no effect on the critical level of arterial p_{O_2} (control group, 47 mmHg halothane, 46 mmHg). Peripheral oxygen utilization was mildly reduced during halothane anesthesia, as evidenced by a decrease in oxygen extraction (control group O_2 extraction rate = 0.63; halothane group O_2 extraction = 0.51, $P < .05$, unpaired t test). The reduction in critical $\dot{D}O_2$ suggests that halothane, by reducing tissue oxygen requirements, may be protective in hypoxemic patients. (Key words: Anesthesia: pediatric. Anesthetics: halothane; volatile. Hemodynamics: cardiac output. Metabolism: oxygen consumption.)

HALOTHANE ANESTHESIA has been shown to reduce total-body oxygen consumption in animals[1,2] and humans.[3] This effect of halothane has led to speculation that anesthetics might be useful in situations where hypoxemia is present.[4,5] The hypothesis that halothane lowers the susceptibility to hypoxemia by reducing O_2 demand, however, has not been systematically studied.

A critical level of oxygen transport has been defined as the level which is required to meet tissue O_2 demand.[6,7] Above the critical level of O_2 transport, tissue oxygenation is adequate, and tissue O_2 consumption is independent of O_2 supply; below the critical level, tissue oxygenation is inadequate, and O_2 consumption falls proportionally with O_2 supply (fig. 1). Oxygen consumption may therefore be used as a marker of oxygen lack. By exposing an animal to hypoxia, one may determine critical levels of oxygen delivery (as calculated by the product of cardiac output and arterial oxygen content) and arterial oxygen tension.

If halothane lowers the susceptibility to hypoxia, the administration of halothane should reduce these critical levels of oxygen transport. To determine the effect of halothane on critical levels of O_2 transport, we exposed newborn lambs to hypoxic hypoxia while they were anesthetized with either fentanyl-oxygen or fentanyl and halothane.

Methods and Materials

Animal Preparation

Twelve newborn lambs (mean wt. 4.1 kg, range 2.7–5.9 kg, mean age 3.8 days, range 1–6 days), housed and bottle-fed in air-conditioned rooms at the Children's Hospital Animal Facility, were studied. Feedings were withheld the day of the experiment. Anesthesia was induced with thiopental, 10 mg·kg^{-1} iv, and fentanyl, 30 mcg·kg^{-1} iv. Preliminary observations confirmed that newborn lambs anesthetized with this dose of fentanyl show little hemodynamic or muscular response to thoracotomy. In addition, this dose of fentanyl has been used for infants undergoing thoracotomy for ligation of patent ductus arteriosus.[8] Following tracheal intubation, the lambs were ventilated with an Emerson Pediatric Volume Ventilator. Ventilation was adjusted to keep Pa_{CO_2} between 30–40 mmHg throughout the study. A catheter was placed in the femoral artery for monitoring of blood pressure and withdrawal of arterial blood samples. A 5 Fr thermodilution pulmonary artery catheter (Edwards Laboratories) was inserted for measurement of cardiac output and core temperature, and withdrawal of mixed-venous blood samples. Normothermia was maintained using a water-blanket and Hamilton K-thermia temperature control unit.

Each lamb then underwent a left anterolateral thoracotomy in the third intercostal space, and the ductus arteriosus was ligated. Ductal ligation was done to prevent left-to-right shunting of blood through the

* Fellow in Anaesthesia (Pediatrics).
† Assistant Professor of Anaesthesia (Pediatrics).
‡ Clinical Associate in Anaesthesia.
§ Associate Professor of Anaesthesia (Pediatrics).

Received from the Department of Anaesthesia, Harvard Medical School, The Children's Hospital, Boston, Massachusetts. Accepted for publication March 2, 1987. Presented in part at the American Society of Anesthesiologists Annual Meeting, Las Vegas, Nevada, October 1986.

Address reprint requests to Dr. Hershenson: Department of Anaesthesia, MICU Office/Farley 2505, The Children's Hospital, 300 Longwood Avenue, Boston, Massachusetts 02115.

ductus,which is likely to occur with exposure to hypoxia.[9] Ligation usually took approximately 15 min to complete.

Experimental Protocol

Animals were divided into two groups. In the six lambs of the control group, anesthesia was maintained with a continuous infusion of fentanyl, 30 mcg·kg^{-1}·hr^{-1}, and pancuronium, 0.1 mg·kg^{-1}·hr^{-1}. Fentanyl was chosen as the anesthetic for the control group because of its minimal effects on cardiac output[10] and oxygen consumption.[11] Preliminary observations confirmed that fentanyl had similarly mild cardiovascular effects in the newborn lamb (see Results). In the six lambs of the halothane group, anesthesia was maintained with fentanyl, 30 mcg·kg^{-1}·hr^{-1}, pancuronium, 0.1 mg·kg^{-1}·hr^{-1}, and halothane. Inspired halothane was titrated to give an end-tidal halothane concentration of 1.1% (1 MAC). End-tidal halothane was measured using an Engstrom Emma anesthetic gas analyzer. There were no significant differences in age, weight, or initial hemoglobin concentration between the two groups.

After a 1-h stabilization period, baseline measurements of hemoglobin, cardiac output, arterial and mixed-venous oxygen tension, and saturation were obtained while the lambs were being ventilated with 100% O_2. Cardiac output measurements were determined by thermodilution using an Instrumentation Laboratories 701 cardiac output computer; the recorded cardiac output was actually the mean of three separate measurements. Blood gases were measured using a Corning 168 *p*H/Blood Gas Analyzer. Hemoglobin concentration and percent saturation were determined using an Instrumentation Laboratories 282 Co-Oximeter and the appropriate animal coefficient.

All 12 animals were then exposed to progressively lower levels of inspired oxygen using 21, 15, and 10% O_2 in N_2. Measurements as described above were repeated 20 min after the initiation of each gas mixture. Animals were ventilated with room air for 30 min between exposures to hypoxic gas mixtures to allow for recovery from hypoxia.

Calculations and Statistical Analysis

Oxygen content was calculated using the standard formula [content = 1.34(Hb) × percent saturation + .003(p_{O_2})]. Oxygen consumption ($\dot{V}O_2$) was calculated using the Fick equation [$\dot{V}O_2$ = cardiac output × arteriovenous oxygen content difference (CO × C(a-v)O_2)]. Oxygen delivery ($\dot{D}O_2$) was calculated by multiplying cardiac output and arterial oxygen content (CaO_2).

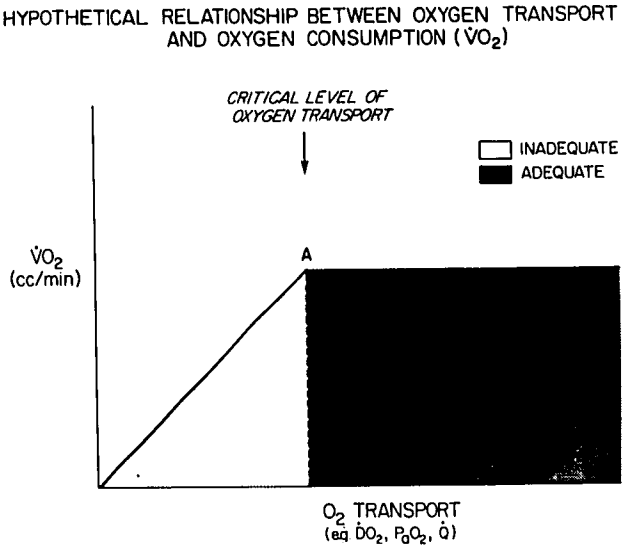

FIG. 1. Theoretical relationship between oxygen transport and oxygen consumption ($\dot{V}O_2$). Below the critical level of oxygen transport, $\dot{V}O_2$ decreases proportionally with O_2 supply. Oxygen transport may be represented by such variables as Pa_{O_2}, cardiac output, and O_2 delivery.

All group data were described as the mean ± standard error of the mean. A two-tailed, independent *t* test was used to compare group mean data from control and halothane groups; a two-tailed paired *t* test was used to compare group mean data within groups. The Bonferroni correction for multiple comparisons was used.[12]

Critical levels of O_2 transport (either critical $\dot{D}O_2$ or Pa_{O_2}) were identified by pairing all individual values of $\dot{D}O_2$ and Pa_{O_2} against corresponding values of $\dot{V}O_2$, and employing a system of repetitive linear regression in which the slope of the regression line determined by data points below each prospective critical value was maximized (see Appendix). Linear regression lines were drawn according to the method of least squares. Correlation coefficients were calculated by the square root of the ratio of the regression sum of squares and the total sum of squares. The statistical significance of such correlations was determined by analysis of variance.[12]

The oxygen extraction ratio for individual data points was calculated by dividing $\dot{V}O_2$ by $\dot{D}O_2$. Group oxygen extraction ratios were calculated as the slope of the best-fit regression line determined by data points below the critical level of oxygen delivery.[13] A *t* statistic was used to compare regression slopes.[12]

Results

Group mean hemodynamic and oxygen transport data during different levels of inspired oxygen are shown in Table 1. Table 1 includes data from both

TABLE 1. Group Mean Data (X ± SEM)

FI_{O_2}	1.0	0.21	0.15	0.10
Control group (n = 6)				
MAP (mmHg)	79 ± 2	78 ± 2	78 ± 2	79 ± 3
HR (beats · min^{-1})	205 ± 4	203 ± 3	211 ± 5	201 ± 6
CO (cc · kg^{-1} · min^{-1})	235 ± 15	269 ± 37	206 ± 20	174 ± 31
$\dot{D}O_2$ (cc · kg^{-1} · min^{-1})	29.2 ± 2.9	30.6 ± 3.9	18.1 ± 2.2¶	9.4 ± 1.5¶
$\dot{V}O2$ (cc · kg^{-1} · min^{-1})	12.1 ± 0.7	13.5 ± 0.6	10.7 ± 1.0	5.6 ± 0.7¶
Pa_{O_2} (mmHg)	259 ± 38	61 ± 5¶	38 ± 3¶	28 ± 2¶
Pv_{O_2} (mmHg)	36 ± 3	28 ± 3	20 ± 2§	16 ± 2¶
*p*H	7.48 ± .07	7.36 ± .07	7.27 ± .04§	7.19 ± .04§
OER	.38 ± .07	.46 ± .05	.60 ± .04	.61 ± .06
Hb (gm · dl^{-1})	9.4 ± 0.4			
Halothane group (n = 6)				
MAP (mmHg)	52 ± 4‡	50 ± 4‡	56 ± 4‡	45 ± 3‡
HR (beats · min^{-1})	166 ± 5‡	167 ± 6‡	161 ± 4‡	154 ± 5‡
CO (cc · kg^{-1} · min^{-1})	132 ± 13‡	141 ± 11†	98 ± 14†§	78 ± 11*¶
$\dot{D}O_2$ (cc · kg^{-1} · min^{-1})	20.2 ± 1.6*	19.9 ± 1.0*	10.9 ± 1.8	6.7 ± 1.0¶
$\dot{V}O_2$ (cc · kg^{-1} · min^{-1})	8.4 ± 0.4‡	8.0 ± 0.2‡	6.1 ± 1.0†	3.7 ± 0.4¶
Pa_{O_2} (mmHg)	324 ± 46	68 ± 7¶	40 ± 3¶	29 ± 1¶
Pv_{O_2} (mmHg)	28 ± 3	30 ± 4	17 ± 3§	13 ± 1§
*p*H	7.43 ± .09	7.38 ± .07	7.31 ± .05§	7.26 ± .05§
OER	.41 ± .02	.46 ± .02	.53 ± .02	.57 ± .03
Hb (gm · dl^{-1})	10.4 ± 0.4			

Significant difference from CONTROL group: *$P < .05$, †$P < .01$, ‡$P < .001$.

Significant difference from same group controls (FI_{O_2} = 1.0): §$P < .05$, ¶$P < .01$.

MAP = mean arterial pressure; HR = heart rate; CO = cardiac output; $\dot{D}O_2$ = oxygen delivery; $\dot{V}O_2$ = oxygen consumption; OER = oxygen extraction ratio; Hb = hemoglobin concentration.

control and halothane groups, and will be referred to in the following paragraphs.

Comparison of Control and Halothane Groups: Baseline (Normoxic) O_2 Transport Data

Average $\dot{V}O_2$ during fentanyl and pancuronium anesthesia for both normoxic groups combined (FI_{O_2} = 1.0 and 0.21) was 12.8 cc · kg^{-1} · min^{-1}. Based on previous data from lambs given only pancuronium,[2] we estimate that fentanyl decreases $\dot{V}O_2$ in the newborn lamb by approximately 10%. These calculations agree with observations made in adult animals given fentanyl.[11] As expected, baseline $\dot{V}O_2$ was significantly lowered by halothane; the average reduction in $\dot{V}O_2$ was 35%. This reduction is comparable to previously published data for newborn lambs.[2]

However, the addition of halothane also caused significant decrements in heart rate, mean arterial pressure, and CO. This reduction in cardiac output resulted in a decrease in $\dot{D}O_2$ averaging 33%. Because the halothane-induced reductions in O_2 delivery and consumption were roughly equal, there was no significant difference in oxygen extraction ratio between two groups. In other words, halothane did not alter the relationship between O_2 supply and demand in the normoxic state.

Comparison of Control and Halothane Groups: Response to Hypoxia

In both control and halothane groups, ventilation with hypoxic gas mixtures resulted in significant reductions in Pa_{O_2}, $\dot{D}O_2$, and $\dot{V}O_2$. In the halothane group, reductions in $\dot{D}O_2$ were due not only to reduced arterial oxygen content, but hypoxia-induced reductions in cardiac output.

Critical Levels of Oxygen Delivery

Figure 2 illustrates the relationship between O_2 delivery and consumption in animals of the control and halothane groups. The calculated critical level of $\dot{D}O_2$ during fentanyl and pancuronium anesthesia was 17.9 cc · kg^{-1} · min^{-1}. Below this critical level of $\dot{D}O_2$, $\dot{V}O_2$ fell proportionally to $\dot{D}O_2$ [$\dot{V}O_2 = 0.63\ \dot{D}O_2 + 0.20$, r = .89, $P < .01$, ANOVA]. Addition of halothane decreased the critical level of $\dot{D}O_2$ from 17.9 to 14.3 cc · kg^{-1} · min^{-1} (a 20% reduction). Below this critical level of $\dot{D}O_2$, $\dot{V}O_2$ fell proportionally to $\dot{D}O_2$ [$\dot{V}O_2 = 0.51\ \dot{D}O_2 + 0.35$, r = .96, $P < .01$, ANOVA]. Halothane reduced the O_2 extraction ratio during supply dependency from 0.63 to 0.51 ($P < .05$, unpaired *t* test, fig. 2).

Critical Levels of Arterial Oxygen Tension

Figure 3 shows the relationship between arterial oxygen tension and $\dot{V}O_2$ in animals of the control and halothane groups. Halothane had no significant effect on the critical value of Pa_{O_2}; the critical Pa_{O_2} of the control group was 47 mmHg, while the critical Pa_{O_2} of the halothane group was 46 mmHg.

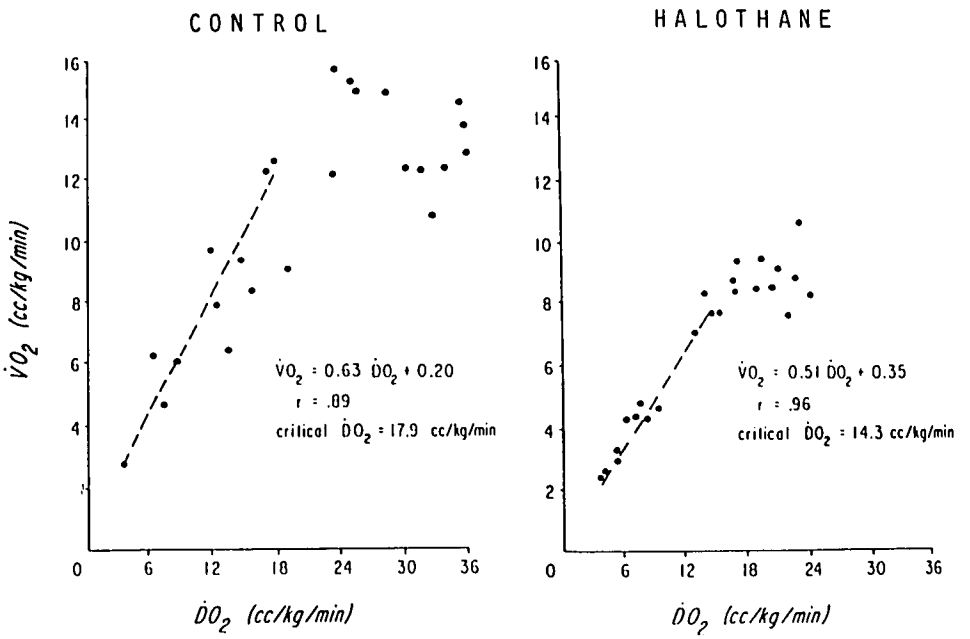

FIG. 2. Pooled oxygen delivery ($\dot{D}O_2$) and oxygen consumption ($\dot{V}O_2$) data from lambs of the control group (left) and the halothane group (right). Above the critical level of $\dot{D}O_2$, $\dot{V}O_2$ "plateaus" at a level independent of $\dot{D}O_2$. Below the critical $\dot{D}O_2$, $\dot{V}O_2$ falls proportionally to $\dot{D}O_2$. Addition of halothane decreased the critical level of oxygen delivery from 17.9 to 14.3 $cc \cdot kg^{-1} \cdot min^{-1}$ (20%). The high correlation between $\dot{D}O_2$ and $\dot{V}O_2$ below the critical level suggests that O_2 delivery is an excellent indicator of tissue O_2 supply in the newborn lamb (in both control and halothane groups, $P < .01$, ANOVA).

Discussion

We have shown that, when halothane is administered to lambs anesthetized with fentanyl-oxygen, the critical level of O_2 delivery is decreased. Halothane did not, however, reduce the critical level of arterial oxygen tension required to maintain O_2 uptake.

Reduction of the critical level of $\dot{D}O_2$ requires not only a fall in total-body $\dot{V}O_2$, but regulation of organ blood flow such that "$\dot{V}O_2/\dot{D}O_2$ mismatch" does not occur.[13] This presumably requires a system of vasomotor control at the tissue level, mediated either directly or indirectly by cellular O_2 tension.[14] Such control must, therefore, remain at least partially intact in animals anesthetized with halothane.

In our study, halothane reduced mean total body O_2 demand by 4.6 $cc \cdot kg^{-1} \cdot min^{-1}$ (35% of control). By comparison, halothane lowered the critical level of O_2 delivery by 3.6 $cc \cdot kg^{-1} \cdot min^{-1}$ (20% of control). If the reflexes involved in the regulation of organ blood flow were not altered under halothane anesthesia, one might expect equal decrements in $\dot{V}O_2$ and critical $\dot{D}O_2$.

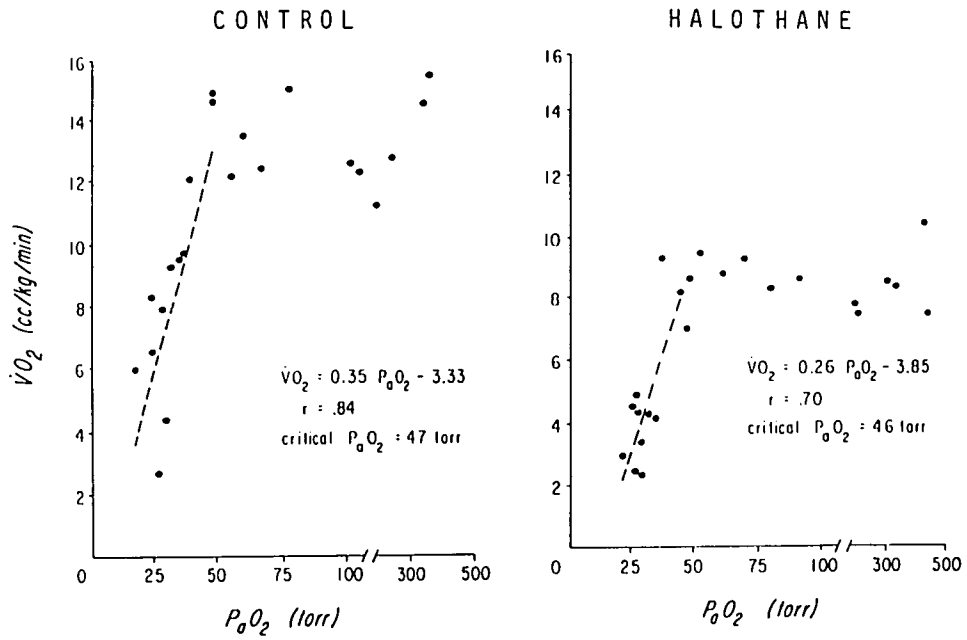

FIG. 3. Pooled Pa_{O_2} and $\dot{V}O_2$ data from lambs of the control group (left) and the halothane group (right). Addition of halothane had no significant effect on the critical level of Pa_{O_2}. Like $\dot{D}O_2$, Pa_{O_2} was a good indicator of tissue oxygen tension ($P < .01$ for both groups).

These data, combined with the reduction in oxygen extraction rate in the halothane group, suggest that halothane may reduce peripheral O_2 utilization during hypoxic hypoxia in the newborn lamb by interfering with the relationship of organ blood flow to organ O_2 demand. In a previous study investigating the effect of halothane on peripheral oxygen utilization, Cameron *et al.* concluded that halothane does not interfere with hypoxia-induced changes in cerebral and myocardial blood flow.[2] However, we calculate from their data that halothane decreased the oxygen extraction ratio during hypoxia from 0.66 to 0.57. Furthermore, halothane anesthesia appeared to exaggerate hypoxia-induced reductions in myocardial, cerebral, and hepatic oxygen delivery.[2]

Halothane-induced reductions in total-body O_2 demand did not result in reductions in the critical level of arterial oxygen tension. Reduction of the critical Pa_{O_2} not only requires a fall in oxygen demand, but, in addition, requires that the fall in O_2 demand be greater than that of O_2 delivery. Because halothane-induced reductions in cardiac output and O_2 delivery were roughly equal to reductions in O_2 consumption, halothane had little effect on the critical level of Pa_{O_2} obtained. Why should O_2 delivery and consumption be coupled in this way? One possible explanation is that halothane, by reducing O_2 consumption, increases tissue oxygenation. Such an improvement in tissue oxygenation would be expected to inhibit the formation of certain metabolites (*e.g.*, adenosine) which normally increase capillary blood flow by relaxing arteriolar and pre-capillary smooth muscle.[14] This relative increase in regional vascular resistance would reduce regional blood flow.[2,15] Changes in regional vascular resistance might then result in a reduction of cardiac output and oxygen delivery.[16] Alternatively, halothane's primary effect may be the reduction of myocardial contractility and cardiac output,[3,17] leading to simultaneous reductions in oxygen delivery and myocardial oxygen consumption.[18]

The clinical relevance of the above observations depends on the correlation between reductions in O_2 uptake and significant morbidity or mortality. Reductions in cerebral $\dot{V}O_2$ have been correlated with deterioration of the electroencephalogram in dogs exposed to hypoxia.[19] Reduced total-body oxygen consumption has been associated with increased mortality in patients with circulatory shock.[20] The susceptibility of $\dot{V}O_2$ to reductions in O_2 transport may, therefore, be a reasonable estimate of the susceptibility of the whole animal to hypoxemia. The data suggest that halothane, by reducing total-body oxygen demand, may "protect" patients from reductions in O_2 delivery, *i.e.*, prevent the depletion of high-energy phosphate compounds, cell death, and organ dysfunction which result when oxygen demand exceeds O_2 supply. However, the lack of change in critical Pa_{O_2} with halothane points out an important caveat with respect to halothane's "protective" effect: in order for halothane to lower the susceptibility to hypoxemia, cardiac output must be maintained at pre-anesthetic levels. Using adjuncts such as fluid administration or catecholamine infusion, one might actually reduce the susceptibility to hypoxemia using halothane.

We speculate that any anesthetic which lowers $\dot{V}O_2$ might reduce the critical level of O_2 delivery. Whether the critical Pa_{O_2} could also be reduced would depend on that anesthetic's cardiac effects. If, for example, isoflurane lowered $\dot{V}O_2$ to a similar degree as halothane, but had less cardiac effects, the critical Pa_{O_2} might be reduced.

Lister *et al.*[21,22] have determined critical levels of O_2 delivery in newborn lambs exposed to both hypoxic and stagnant hypoxia. In both classes of hypoxia studied, a critical value of 15 $cc \cdot kg^{-1} \cdot min^{-1}$ was obtained; this value is midway between values we obtained with and without halothane anesthesia. It is interesting to note that both our data and those of Lister *et al.* suggest that, when compared to anesthetized adult dogs,[6] the newborn lamb requires higher levels of oxygen delivery and arterial O_2 tension to maintain O_2 consumption. Factors which may contribute to the lamb's increased O_2 requirements include the greater affinity for oxygen of fetal hemoglobin, and the newborn's higher resting rate of oxygen consumption.[23]

Lactate accumulation has also been used as a marker for oxygen lack, and has been correlated with morbidity in critically ill patients.[24] Although higher lactate levels generally indicate tissue hypoxia, lactate accumulation may be an inaccurate measure of critical levels of oxygen transport. Non-hypoxic lactate production may occur under a variety of conditions, including alkalosis, glucose administration, and sympathomimetic activity;[25] non-hypoxic reductions in $\dot{V}O_2$, on the other hand, do not generally occur. In addition, because lactate accumulation results not only from increased production but decreased metabolism, lactate concentrations are inordinately affected by changes in hepatic blood flow and oxygen delivery.[26]

To summarize, halothane reduces the critical level of O_2 delivery in the newborn anesthetized lamb. Further studies are needed to determine whether halothane, by reducing O_2 demand, might protect the newborn from hypoxemia.

References

1. Theye RA: The contribution of individual organ systems to the decrease in whole-body $\dot{V}O_2$ with halothane. ANESTHESIOLOGY 37:367–372, 1972
2. Cameron CB, Gregory GA, Rudolph AM, Heymann MA: The cardiovascular and metabolic effects of halothane in normoxic

and hypoxic newborn lambs. ANESTHESIOLOGY 62:732–737, 1985
3. Eger EJ, Smith NT, Cullen DJ, Cullen BF, Gregory GA: A comparison of the cardiovascular effects of halothane, fluroxene, ether and cyclopropane in man; a resume. ANESTHESIOLOGY 34:25–41, 1971
4. Vacanti JP, Crone RK, Murphy JD, Smith SD, Black PR, Reid L, Hendren WH: The pulmonary hemodynamic response to perioperative anesthesia in the treatment of high risk infants with congenital diaphragmatic hernia. J Pediatr Surg 19:672–682, 1984
5. Hensley FA, Larach DR, Stauffer RA, Waldhausen JA: The effect of halothane/nitrous oxide/oxygen mask induction on arterial hemoglobin saturation in cyanotic heart disease (abstract). ANESTHESIOLOGY 63:A3, 1985
6. Cain SM: Oxygen delivery and uptake in dogs during anemic and hypoxic hypoxia. J Appl Physiol 42:228–234, 1977
7. Cain SM: Review: Supply dependence of oxygen uptake: Myth or reality? Am J Med Sci 288:119–124, 1984
8. Robinson S, Gregory GA: Fentanyl-air-oxygen anesthesia for ligation of patent ductus arteriosus in preterm infants. Anesth Analg 60:331–334, 1981
9. McMurphy DM, Heymann MA, Rudolph AM, Melmon KL: Developmental change in constriction of the ductus arteriosus: Response to oxygen and vasoactive substances in the isolated ductus arteriosus of the fetal lamb. Pediatr Res 6:231–238, 1972
10. Lunn JK, Stanley TH, Eisele J, Webster L, Woodward A: High-dose fentanyl anesthesia for coronary artery surgery: Plasma fentanyl concentrations and influence of nitrous oxide in cardiovascular responses. Anesth Analg 58:390–395, 1979
11. Westenskow DR, Jordan WS, Hodges MR, Stanley TH: Correlation of oxygen uptake and cardiovascular dynamics during N_2O-fentanyl and N_2O-thiopental anesthesia in the dog. Anesth Analg 57:37–41, 1978
12. Glantz SA: Primer of Biostatistics. New York, McGraw-Hill, 1981, pp 87–200
13. Cain SM: Peripheral oxygen uptake and delivery in health and disease. Clin Chest Med 4:139–148, 1983
14. Granger HJ, Goodman AH, Cook BH: Metabolic models of microcirculatory regulation. Fed Proc 34:2025–2030, 1975
15. Jones MD, Traystman RJ, Simmons MA, Moletini RA: Effect of changes in arterial O_2 content on cerebral blood flow in the lamb. Am J Physiol 240:H209–H215, 1981
16. Shepherd AP, Granger HJ, Smith EE, Guyton AC: Local control of tissue oxygen delivery and its contribution to the regulation of cardiac output. Am J Physiol 225:747–755, 1973
17. Price ML, Price HL: Effects of general anesthetics on contractile responses of rabbit aortic strips. ANESTHESIOLOGY 23:16–20, 1962
18. Sonntag H, Merin RG, Donath U, Radke J, Schenk HD: Myocardial metabolism and oxygenation in man awake and during halothane anesthesia. ANESTHESIOLOGY 51:204–210, 1979
19. Woodson RD, Fitzpatrick JH, Costello DJ, Gilboe DD: Increased blood oxygen affinity decreases canine brain oxygen consumption. J Lab Clin Med 100:411–424, 1982
20. Shoemaker WC, Montgomery ES, Kaplan E, Elwyn DH: Physiologic patterns in surviving and non-surviving shock patients. Arch Surg 106:630–636, 1973
21. Fahey JT, Lister G: A simple method for reducing cardiac output in the conscious lamb. Am J Physiol 249:H188–H192, 1985
22. Moss M, Moreau G, Lister G: Oxygen consumption and tissue metabolism in the hypoxic lamb (abstract). Pediatr Res 19:144A, 1985
23. Lister G, Moreau G, Moss M, Talner NS: Effects of alterations of oxygen transport in the neonate. Semin Perinatol 8:192–204, 1984
24. Frewen TC, Hassan SU, Gordon BA, Sommerauer JF, Kronick JB, Kisson N: Serial lactate measurements and outcome in pediatric brain injury (abstract). Pediatr Res 20:179A, 1986
25. Huckabee WE: Relationships of pyruvate and lactate during anaerobic metabolism. I. Effects of infusion of pyruvate or glucose and of hyperventilation. J Clin Invest 37:244–263, 1958
26. Gladden LB: Current "anaerobic threshold" controversies. Physiologist 27:312–318, 1984

Appendix

Determination of Critical Levels of Oxygen Transport

A critical level of oxygen transport is that level above which oxygen uptake is independent of supply, and below which oxygen uptake decreases proportionally to supply (fig. 1). As O_2 transport falls toward the critical level required to maintain O_2 uptake, oxygen extraction increases. When oxygen extraction is maximal, further reductions in O_2 transport must result in reductions in O_2 uptake. Below the critical level of O_2 transport, oxygen extraction remains maximal. Thus, below the critical level of O_2 transport, the slope of the line relating O_2 transport and O_2 uptake should be maximal.

Critical levels of O_2 transport (either critical DO_2 or Pa_{O_2}) were therefore identified by pairing all individual values of O_2 transport against corresponding values of $\dot{V}O_2$, and employing a system of repetitive linear regression in which the slope of the regression line determined by the data points below each prospective critical value was maximized.

This method is illustrated in table 2, which demonstrates how the critical Pa_{O_2} of the halothane group was determined. First, all data points were sorted into ascending numerical order. Next, linear regression equations for all data points below each prospective critical value were calculated. The point at which the slope of the regression line was highest was selected as the critical value. In this case, the critical value was 46 mmHg.

TABLE 2. Determination of Critical Pa_{O_2} in the Halothane Group

Pa_{O_2} (mmHg)	$\dot{V}O_2$ (cc · kg^{-1} · min^{-1})	n	Regression Equation
24	3.1	1	
.	.	.	
.	.	.	
.	.	.	
35	3.5	8	$\dot{V}O_2 = .043\ Pa_{O_2} + 2.41$
37	4.1	9	$\dot{V}O_2 = .049\ Pa_{O_2} + 2.23$
38	9.4	10	$\dot{V}O_2 = .248\ Pa_{O_2} - 3.54$
46	8.2	11	$\dot{V}O_2 = .258\ Pa_{O_2} - 3.84$
49	8.5	12	$\dot{V}O_2 = .251\ Pa_{O_2} - 3.63$
49	7.1	13	$\dot{V}O_2 = .223\ Pa_{O_2} - 2.77$
.	.	.	
.	.	.	
.	.	.	
453	7.7	24	$\dot{V}O_2 = .009\ Pa_{O_2} + 5.73$

Critical Pa_{O_2} = 46 mmHg.