Anesthesiology
62:732–737, 1985

The Cardiovascular and Metabolic Effects of Halothane in Normoxic and Hypoxic Newborn Lambs

C. B. Cameron, D.M.D., M.D., F.R.C.P.(C), G. A. Gregory, M.D.,† A. M. Rudolph, M.D.,‡ M. Heymann, M.B., B.Ch.§*

Oxygen consumption, cardiac output, and tissue oxygen delivery were measured in normoxic and hypoxic 1–3-day-old lambs during the following six conditions: 1) (control) paralysis with pancuronium and controlled ventilation with room air; 2) paralysis, controlled ventilation and hypoxia (Pa_{O_2} = 30 ± 3 mmHg, [SD]); 3) paralysis, controlled ventilation with room air and 0.5 MAC halothane; 4) paralysis, controlled ventilation, hypoxia, and 0.5 MAC halothane; 5) paralysis, controlled ventilation with room air, and 1 MAC halothane; and 6) paralysis, controlled ventilation, hypoxia, and 1 MAC halothane. During normoxia, 0.5 and 1 MAC halothane decreased total body oxygen consumption, cardiac output, and arterial blood pressure. One-half MAC halothane had no effect on blood flow to any organ except muscle, whose flow decreased 64%. One MAC halothane decreased blood flow to the brain, heart, kidney, muscle, and gut. Both concentrations of halothane decreased serum catecholamine levels below control values and prevented hypoxia from increasing catecholamine levels. Hypoxia decreased the oxygen consumption about 40% from the immediately previous normoxic value, whether the animals were anesthetized or not. Tissue oxygen delivery followed changes in blood flow. The cardiac output, arterial blood pressure, and heart rate of anesthetized, hypoxic animals were not different from those in the previous normoxic condition. Halothane did *not* prevent redistribution of blood flow to the heart and brain of hypoxic animals, nor did halothane prevent hypoxic pulmonary vasoconstriction. Halothane did prevent the increase in serum catecholamine levels that occurs in unanesthetized, hypoxic animals. If halothane has similar effects in humans, it may be useful in treating hypoxic infants in the operating room and intensive care unit. (Key words: Anesthesia: pediatric. Anesthetics, volatile: halothane. Heart: cardiac output. Hemodynamics: regional blood flow. Hypoxia. Metabolism: oxygen consumption.)

NONANESTHETIZED, PARALYZED, HYPOXIC LAMBS decrease total body oxygen consumption ($\dot{V}_{O_2}$)[1]; redistribute blood flow from muscle, gut, and kidneys to brain and heart (without changing their cardiac output)[2]; and constrict the pulmonary vasculature.[2] Whether halothane interferes with the neonate's ability to affect these responses to hypoxia in unknown. Therefore, we measured the $\dot{V}_{O_2}$, cardiac output, and regional blood flow of normoxic and hypoxic 1–3-day-old lambs.

These studies were approved by the Animal Care Committee of the University of California.

Methods

Surgical Preparation

Six term lambs, younger than 4 days old, were blindfolded and lightly restrained in the supine position. We anesthetized them with 70% nitrous oxide by face mask, and injected lidocaine (0.5%) into the neck and left groin. Then we inserted catheters into a femoral artery and vein and into a pulmonary artery (through a jugular vein) by cutdown. We inserted two catheters (0.3 mm id) into a carotid artery. One was advanced into the left ventricle and the other was positioned in the arch of the aorta. After performing a tracheostomy, we inserted a cuffed endotracheal tube, inflated the cuff, and ventilated the lungs to maintain normal blood gases. To obtain end-tidal halothane samples, we inserted a polyvinyl catheter (0.3 mm id) into the endotracheal tube and positioned the tip of the catheter at the tracheal end of the tube. We connected the proximal end of the catheter to a three-way stopcock and 10 ml glass syringe. Next, we paralyzed the lambs with pancuronium (0.1 $mg \cdot kg^{-1}$), discontinued the nitrous oxide, and controlled ventilation with a Harvard volume respirator. We set the tidal volume at 10 $ml \cdot kg^{-1}$ and adjusted the respiratory rate to maintain a Pa_{CO_2} of 35–40 mmHg and a Pa_{O_2} of 75–85 mmHg. A warming blanket and a servo controlled heating lamp were used to maintain a normal rectal temperature (39 ± 0.5° C). To maintain hydration, we infused 4 $ml \cdot kg^{-1} \cdot h^{-1}$ of normal saline. When the heart rate, the pulmonary and systemic arterial blood pressures, and the Pa_{O_2}, Pa_{CO_2}, and pH_a were stable for 30 min and not different from those of spontaneously breathing, quietly resting lambs, we began the studies.

Study Protocol

We made measurements during the following six conditions: 1) controlled ventilation with room air (control); 2) controlled ventilation with room air plus enough

* Research Fellow in Anesthesia and the Cardiovascular Research Institute. Dr. Cameron was supported by the Medical Research Council of Canada.

† Professor of Anesthesia and Pediatrics.

‡ Professor of Pediatrics, Physiology, and Obstetrics, Gynecology and Reproductive Sciences.

§ Professor of Pediatrics, Physiology, and Obstetrics, Gynecology, and Reproductive Sciences.

Received from the Departments of Anesthesia, Pediatrics, Physiology, and Obstetrics, Gynecology and Reproductive Sciences and the Cardiovascular Research Institute, University of California, San Francisco. Accepted for publication January 4, 1985. Supported in part by a grant from the National Institutes of Health (HL-23681). Presented in part at the Annual Meeting of the American Society of Anesthesiology, Las Vegas, October, 1982.

Address reprint requests to Dr. Gregory. University of California, Room S436, 3rd and Parnassus, San Francisco, California 94143.

nitrogen to reduce the Pa_{O_2} to 30 ± 3 mmHg (SD) (hypoxia); 3) controlled ventilation with room air plus 0.5 MAC halothane; 4) controlled ventilation with hypoxia plus 0.5 MAC halothane; 5) controlled ventilation with room air plus 1 MAC halothane; and 6) controlled ventilation with hypoxia plus 1 MAC halothane. The studies were done in sequence 1 through 6 with one exception; we altered the order in which we administered 0.5 MAC and 1 MAC halothane in successive animals. The animals were always made hypoxic (condition 2) before they were anesthetized with halothane. Each condition was maintained for 30 min before making measurements.

We continuously measured systemic and pulmonary arterial blood pressures with a Statham P23DB® pressure transducer and recorded these pressures on a Beckman® polygraph. The amplitude-frequency response of the pressure measuring systems (strain gauges, catheters, and connecting tubings) was flat to 15 Hz. To determine Pa_{O_2}, Pa_{CO_2}, pH_a, oxygen saturation; hemoglobin and lactate concentrations; and norepinephrine, epinephrine, and dopamine levels we withdrew 10 ml systemic arterial blood. We also obtained 2 ml blood from the pulmonary artery to determine mixed venous P_{O_2}, P_{CO_2}, and pH. The flow-through technique of Lister *et al.*[3,4] was used to continuously measure $\dot{V}_{O_2}$. Inspired gas entered the ventilator from a reservoir bag. Gas leaving the system contained a mixture of inspired and expired gas and was collected in a bag. At the end of each 10-min gas collection, we determined the oxygen concentration and volume of the gas. To calculate $\dot{V}_{O_2}$ we used the formula: $\dot{V}_{O_2} = Vs\ (FI_{O_2} - F_{s_{O_2}})$ (STPD), where Vs is the flow rate throughout the system; FI is the concentration of the inspired gas; F_s is the gas concentration of mixed expired gas; STPD is standard temperature and pressure dry. Validation of this method has been reported elsewhere.[4] To determine cardiac output and organ blood flow, we injected 15 μm radionuclide labeled microspheres (^{57}CO, ^{124}I, ^{51}CR, ^{85}SR, ^{113}SN, and ^{65}ZN) into the left ventricle[5,6] and obtained reference samples of blood from the carotid and femoral arteries. The blood samples were collected into preweighed syringes. We immediately replaced blood losses with equal volumes of blood from other lambs of the same age. We allowed 30 min for recovery after each period of hypoxia.

At the conclusion of the study, we killed the animals with an overdose of phenobarbital and removed, weighed, and incinerated the organs to determine the levels of radioactivity in each organ.

Measurements and Calculations

We measured P_{O_2}, P_{CO_2}, and pH with a Corning 175® blood gas analyzer and corrected all of the values for changes in body temperature. Hemoglobin concentrations and oxygen saturations were determined with an OXM-2 Hemoximeter® (Radiometer, Copenhagen). To determine the amount of radioactivity in the organs, we used a 512 multichannel pulse height analyzer (Searle Analytic, Des Plaines, Illinois).

We calculated oxygen delivery to the various organs by multiplying the absolute blood flow to an organ ($ml \cdot 100\ g^{-1} \cdot min^{-1}$) by the femoral arterial oxygen content ([oxygen saturation × hemoglobin concentration × 1.35] + dissolved oxygen).

To determine anesthetic levels, we collected end-tidal gas samples from the tracheal catheter and injected the samples into a Beckman LB-2® gas analyzer (Beckman Corporation), which we calibrated every 30 min with known concentrations of halothane. To prevent CO_2 from interfering with the measurement of halothane, we filled the head of the gas analyzer with CO_2. We assumed that the MAC for halothane was 1.09% for lambs of this age.[7] We calculated systemic and pulmonary vascular resistances by dividing mean femoral or pulmonary arterial pressure (mmHg) by cardiac output ($ml \cdot kg^{-1} \cdot min^{-1}$).

A sensitive, radioenzymatic assay was used to determine serum levels of epinephrine, norepinephrine, and dopamine.[8] Because the range of values obtained during the control periods was large (but within normal limits for lambs¶)—we compared the catecholamine levels as percentage change from control. We analyzed the data by two-way analysis of variance and the Neuman-Keuls test for multiple comparisons.[9] A P value <0.05 was considered significant.

Results

Tables 1–3 summarize the results. The data are presented for two states, normoxia and hypoxia. Control values are those obtained during controlled ventilation with room air. Systemic and pulmonary arterial blood gases, pH, oxygen content, and the arterial–venous oxygen content differences are presented in table 1.

Normoxia

One-half MAC halothane decreased $\dot{V}_{O_2}$ of normoxic animals by 25% ($P < 0.001$); one MAC decreased $\dot{V}_{O_2}$ 43% ($P < 0.001$) (table 2). One MAC halothane decreased cardiac output 48% from control levels ($P < 0.001$); heart rate was unchanged. Systemic arterial pressure decreased 16% ($P < 0.05$) at 0.5 MAC and 31% ($P < 0.04$) at 1 MAC halothane; pulmonary arterial pressure remained at control levels.

¶ Roizen MF: Personal communication.

TABLE 1. The Effects of Halothane on Arterial Blood Gases, *p*H, and Oxygen Content in Normoxic and Hypoxic Lambs

	Prior to Anesthesia		During Anesthesia			
			0.5 MAC		1.0 MAC	
	Normoxia	Hypoxia	Normoxia	Hypoxia	Normoxia	Hypoxia
Pa_{O_2} (mmHg)	78 ± 5	29 ± 1*†	70 ± 3‡	29 ± 1*†	71 ± 3‡	30 ± 0*†
Pa_{CO_2} (mmHg)	37 ± 2	36 ± 1	38 ± 2	35 ± 1	35 ± 1	33 ± 2§
pH_a	7.36 ± 0.02	7.34 ± 0.01	7.34 ± 0.02	7.38 ± 0.03	7.36 ± 0.02	7.37 ± 0.03
Arterial oxygen content (ml/dl)	13.8 ± 0.6	5.7 ± 0.3*†	11.6 ± 0.4‡	6.0 ± 0.5*†	12.6 ± 1.0‡	6.1 ± 0.4*†
Pv_{O_2} (mmHg)	41 ± 2	16 ± 1*†	39 ± 2‡	19 ± 1*†	36 ± 2‡	18 ± 1*†
Pv_{CO_2} (mmHg)	40 ± 3	40 ± 2	45 ± 4	39 ± 3	39 ± 2	40 ± 3
pH_v	7.33 ± 0.02	7.27 ± 0.01*†	7.32 ± 0.02¶	7.34 ± 0.03¶	7.32 ± 0.02¶	7.32 ± 0.03¶
Venous oxygen content (ml/dl)	8.3 ± 1.0	1.7 ± 0.3*	7.5 ± 1.8‡	2.3 ± 0.4*†	6.3 ± 0.6‡	2.3 ± 0.3*†
Arterial–venous oxygen content difference (ml/dl)	5.5 ± 0.5	4.0 ± 0.2	4.1 ± 0.4	3.7 ± 0.2§	6.3 ± 0.5	3.8 ± 0.2§**

Values are means ± SEM.
* Different from mechanical ventilation with room air, $P < 0.001$.
† Different from previous period of normoxia, $P < 0.001$.
‡ Different from mechanical ventilation and hypoxia before anesthesia, $P < 0.001$.
§ Different from mechanical ventilation with room air, $P < 0.05$.
¶ Different from previous period of normoxia, $P < 0.05$.
** Different from mechanical ventilation and hypoxia before anesthesia, $P < 0.05$.

TABLE 2. The Effects of Anesthesia on Oxygen Consumption, Cardiac Output, Vital Signs, and Lactic Acid and Catecholamine Concentrations in Normoxic and Hypoxic Lambs

	Prior to Anesthesia		Anesthesia			
			0.5 MAC		1 MAC	
	Normoxia	Hypoxia	Normoxia	Hypoxia	Normoxia	Hypoxia
Oygen consumption ($ml \cdot min^{-1} \cdot kg^{-1}$)	14.3 ± 0.5	9.5 ± 0.6*†	10.8 ± 0.9*	6.6 ± 0.5‡§	8.2 ± 1.0*†	4.7 ± 0.2*†¶
Cardiac output ($ml \cdot min^{-1} \cdot kg^{-1}$)	373 ± 18	349 ± 42	301 ± 35	284 ± 43‡§	195 ± 24*†	195 ± 35*†
Heart rate ($beats \cdot min^{-1}$)	241 ± 10	251 ± 16	240 ± 5	241 ± 12	208 ± 21	193 ± 20
Mean systemic arterial pressure (mmHg)	92 ± 3	94 ± 4	77 ± 5**††	70 ± 3**††	64 ± 3**††	52 ± 5*†
Mean pulmonary artery pressure (mmHg)	21 ± 2	44 ± 4*†	31 ± 6	44 ± 4‡	21 ± 2	36 ± 5‡
Pulmonary vascular resistance ($mmHg \cdot ml^{-1} \cdot kg \cdot min$)	0.070 ± 0.008	0.15 ± 0.003**††	0.095 ± 0.02	0.17 ± 0.04	0.14 ± 0.02‡	0.26 ± 0.05‡‡‡
Lactic acid ($mg \cdot dl^{-1}$)	23 ± 2	41 ± 5*†	42 ± 7*	45 ± 11‡	44 ± 6‡	51 ± 10*
		Percent of Control				
Norepinephrine ($pg \cdot ml\ plasma^{-1}$)	679 ± 200	190 ± 50*†	83 ± 20	98 ± 30§	55 ± 12*§§	68 ± 13*§§
Epinephrine ($pg \cdot ml\ plasma^{-1}$)	628 ± 216	95 ± 40	31 ± 17*	28 ± 11*§§	13 ± 5*§§	27 ± 20*§§
Dopamine ($pg \cdot ml\ plasma^{-1}$)	327 ± 71	140 ± 60	120 ± 45	100 ± 50	116 ± 63	136 ± 60

Values are mean ± SEM.
* Different from mechanical ventilation with room air, $P < 0.001$.
† Different from previous period of normoxia, $P < 0.001$.
‡ Different from mechanical ventilation with room air, $P < 0.01$.
§ Different from mechanical ventilation and hypoxia before anesthesia, $P < 0.05$.
¶ Different from mechanical ventilation and hypoxia before anesthesia, $P < 0.01$.
** Different from mechanical ventilation with room air, $P < 0.05$.
†† Different from previous period of normoxia, $P < 0.05$.
‡‡ Different from previous period of normoxia, $P < 0.001$.
§§ Different from mechanical ventilation and hypoxia before anesthesia, $P < 0.001$.

TABLE 3. The Effects of Anesthesia on Organ Blood Flow and Oxygen Delivery in Normoxic and Hypoxic Lambs

	Prior to Anesthesia		Anesthetic Level			
			0.5 MAC		1.0 MAC	
	Normoxia	Hypoxia	Normoxia	Hypoxia	Normoxia	Hypoxia
Blood flow (ml · 100 $g^{-1} \cdot min^{-1}$)						
Brain	81 ± 6	138 ± 12*·†	68 ± 3	111 ± 15‡·§	63 ± 6*·†	86 ± 13
Heart	324 ± 75	735 ± 153*·†	258 ± 28§	505 ± 94‡·¶	146 ± 9*·†	283 ± 82§
Liver	20 ± 5	58 ± 18	57 ± 19	59 ± 8	47 ± 9	36 ± 7
Kidney	331 ± 42	315 ± 48	317 ± 28	255 ± 25	218 ± 10**·††	152 ± 30‡·§·¶
Gut	119 ± 13	111 ± 16	113 ± 17	85 ± 17	60 ± 8**·††	69 ± 14*·†
Carcass	26 ± 3	16 ± 3**·‡‡	15 ± 3	12 ± 3*	7.6 ± 2**·††	8 ± 1‡·§
Muscle	25 ± 10	16 ± 4‡·¶	9 ± 3‡·§	10 ± 2*	6 ± 2*·††	8 ± 1**·††
Oxygen delivery (ml · 100 $g^{-1} \cdot min^{-1}$)						
Brain	10.1 ± 1.3	6.7 ± 1.2**·‡‡	7.2 ± 1.1**	5.6 ± 2.7*	7.1 ± 1.3‡	4.1 ± 0.8*·¶
Heart	33.6 ± 6.3	32.1 ± 8.3	27.8 ± 5.5	25.6 ± 5.6	15.5 ± 2.6	11.9 ± 3.9‡
Liver	3.0 ± 0.5	3.2 ± 1.3	6.2 ± 2.2	3.1 ± 0.8	4.9 ± 1.4	1.7 ± 0.3‡
Kidney	44.9 ± 4.5	16.1 ± 1.0*·†	30.2 ± 4.2**	13.4 ± 2.3*·¶	24.2 ± 3.1*	12.1 ± 4.2*
Gut	16.4 ± 1.9	5.0 ± 0.9**·‡‡	12.2 ± 2.9	4.4 ± 1.1**·‡‡	6.8 ± 1.5**	3.3 ± 0.7**
Carcass	3.1 ± 0.5	0.7 ± 0.2*·†	1.7 ± 0.4*	0.7 ± 0.2*·¶	0.9 ± 0.3*	0.4 ± 0.6*

Values are means ± SEM.
* Different from mechanical ventilation with room air, $P < 0.001$.
† Different from previous period of normoxia, $P < 0.001$.
‡ Different from mechanical ventilation with room air, $P < 0.05$.
§ Different from mechanical ventilation and hypoxia before anesthesia, $P < 0.05$.
¶ Different from previous period of normoxia, $P < 0.05$.
** Different from mechanical ventilation with room air, $P < 0.01$.
†† Different from mechanical ventilation and hypoxia before anesthesia, $P < 0.01$.
‡‡ Different from previous period of normoxia, $P < 0.01$.

Organ blood flow (ml · 100 $g^{-1} \cdot min^{-1}$) was unchanged during 0.5 MAC halothane, except that flow to muscle decreased 64% ($P < 0.001$) (table 3). One MAC halothane decreased blood flow to most organs (brain 23% [$P < 0.001$], heart 55% [$P < 0.001$], kidney 35% [$P < 0.01$]). Since the arterial oxygen content was constant, oxygen delivery to the various organs depended on the level of regional blood flow.

During the awake, hypoxic period, serum lactic acid concentrations increased 78% from control levels; they remained at this level for the rest of the study (table 2). Plasma epinephrine and norepinephrine levels decreased 45% ($P < 0.001$) and 87% ($P < 0.001$), respectively, with normoxia plus 1 MAC halothane. Dopamine levels were unchanged from control values.

HYPOXIA

Hypoxia decreased the $\dot{V}_{O_2}$ of unanesthetized animals 34% ($P < 0.001$) from control levels (table 2). Hypoxia plus 0.5 MAC and 1 MAC halothane decreased oxygen consumption 39% ($P < 0.01$) and 43% ($P < 0.001$) below that of the immediately previous normoxic condition and 54% and 68% below control levels.

During 0.5 MAC halothane plus hypoxia and during 1 MAC halothane plus hypoxia, the values of cardiac output, heart rate, and systemic arterial pressure were similar to those present during the previous normoxic condition (table 2). Pulmonary arterial pressure increased 110% ($P < 0.001$) above control levels in unanesthetized, hypoxic animals. During anesthesia, the mean pulmonary arterial pressure increased 42% (0.5 MAC, $P < 0.01$) and 71% (1 MAC, $P < 0.01$) from the levels present during the immediately previous normoxic condition. In all cases, the pulmonary vascular resistance increased approximately 95% from the level found in the previous normoxic condition.

Hypoxia induced several changes in regional blood flow. In the awake state (table 3), brain blood flow increased 70% ($P < 0.001$) and heart blood flow increased 127% ($P < 0.001$). Similar changes in these variables occurred during hypoxia and 0.5 MAC and 1 MAC halothane. The increased blood flow to the heart and brain maintained oxygen delivery near control levels. Hypoxia, with or without anesthesia, decreased oxygen delivery to the kidney and gut. During hypoxia and spontaneous ventilation, the serum lactic acid concentration of unanesthetized animals was 78% greater than it was during the control period. The lactic acid level did not increase further when anesthetized animals were made hypoxic. Plasma norepinephrine levels increased 90% ($P < 0.001$) above control levels in awake, hypoxic animals. The levels of norepinephrine remained at control values (0.5 MAC) or decreased 32% below control (1.0 MAC) during hypoxia. The epinephrine levels were 72% below control levels at both 0.5 and

1.0 MAC halothane and hypoxia. The levels of dopamine did not change.

Discussion

Halothane has been used to anesthetize pediatric patients for more than two decades. Despite this, it is unknown whether halothane affects pulmonary vasoconstriction and the redistribution of blood flow or whether halothane affects the total body oxygen consumption of hypoxic neonates. One might expect that the responses of neonates would differ from those of adults because the cardiac output ($ml \cdot kg^{-1}$) and heart rate of neonates are greater and because mean arterial blood pressure and systemic vascular resistance are lower.[2]

Eight-tenths per cent to 2.5% end-tidal halothane decreases oxygen consumption 7–17% in adult humans[10,11] and dogs.[12,13] The oxygen consumption of our normoxic lambs decreased 43% at 1 MAC (1.09% end-tidal) halothane. Thus, the decrease in $\dot{V}_{O_2}$ is four to five times greater in neonates than it is in adults at similar MAC levels. Theye and Sessler[12] reported that nearly half of the decrease in oxygen consumption occurring in anesthetized, adult dogs (47%) is due to a decrease in myocardial oxygen consumption. While we did not measure myocardial oxygen consumption, we[7] and others have shown that cardiac output[2] and myocardial oxygen requirements are greater in unanesthetized lambs than they are in adults when size is taken into account. Since halothane reduces the cardiac output of neonates relatively more than it does that of adults,[7] it is reasonable to expect that halothane might reduce the myocardial and total body oxygen consumption of neonates more than it does in adults. Another possible reason for the large decrease in $\dot{V}_{O_2}$ in anesthetized lambs is that anesthesia might eliminate the variable portion of oxygen consumption that neonates use for growth.

Barash *et al.*[14] reported a 32% decrease in cardiac index (M-Mode echocardiography) in two to 12–year-old children anesthetized with 1.12% end-tidal halothane. Data from the present study and those from a previous study in lambs,[7] agree with the finding of Barash *et al.* *In vivo*[10,15,16] and *in vitro*[17,18] studies demonstrate that halothane decreases the contractility of adult hearts. The decrease may be even greater in neonates because their hearts have less sympathetic innervation and less contractile proteins per cell.[19] The cardiovascular effects of inhaled anesthetics are also affected by whether patients breathe spontaneously or whether they are mechanically ventilated.[15] To avoid these differences, we controlled ventilation throughout this study.

One-half MAC halothane had no effect on the cardiac output or regional blood flow (except to muscle) of normoxic animals. However, one MAC halothane significantly decreased cardiac output and regional blood flow. The decreases in cardiac output occurring in our study are similar to those seen in newborn lambs anesthetized with either halothane[7] or enflurane.[20] The changes in the present study probably occurred because tissue oxygen requirements decreased and because the demand for cardiac output was reduced. Jones *et al.*[21] showed that the oxygen requirements of at least one organ, the brain, govern the blood flow of that organ in neonatal sheep.

We previously reported the cardiovascular effects of hypoxia, controlled ventilation, and muscle relaxants[1] in unanesthetized, newborn lambs. Hypoxia did not change cardiac output, but it reduced $\dot{V}_{O_2}$ by the same amount seen in the unanesthetized, hypoxic, paralyzed, mechanically ventilated lambs in the present study. Although the percentage decreases in $\dot{V}_{O_2}$ were similar when awake and anesthetized, the absolute levels of $\dot{V}_{O_2}$ were much lower. Thus, it is probable that the lamb would tolerate hypoxia better when anesthetized than when awake. The lack of change in *p*H and lactic acid levels in our anesthetized, hypoxic lambs tends to support this conclusion.

Although halothane attenuates the baroreflex of young animals and infants,[22,23] it does not alter the reflexes involved in redistributing blood flow to the heart and brain of hypoxic lambs. Thus, anesthetized, hypoxic lambs can maintain relatively normal oxygen delivery to their hearts and brains.

Whether inhaled anesthetics block hypoxic pulmonary vasoconstriction in adults is controversial. Benumof and Wahrenbrock originally suggested that it did[24]; subsequent studies failed to confirm this finding.[25] We do not believe that halothane interferes with hypoxic pulmonary vasoconstriction in the newborn lamb, because the percentage increase in pulmonary vascular resistance is similar in nonanesthetized and anesthetized hypoxic animals.

Finally, serum lactic acid levels increased in unanesthetized, hypoxic, mechanically ventilated animals. Both levels of halothane anesthesia prevented further increases in serum lactic acid, probably because halothane reduced total body metabolism and oxygen consumption.

In summary, we determined the cardiovascular and metabolic effects of halothane in normoxic and hypoxic newborn lambs. One MAC halothane significantly decreased oxygen consumption and cardiac output of normoxic animals and decreased norepinephrine levels. Despite this decrease in $\dot{V}_{O_2}$, $\dot{V}_{O_2}$ decreased further during hypoxia. Furthermore, halothane did not prevent redistribution of blood flow from the kidneys and splenchnic circulation to the heart and brain of hypoxic animals, nor did halothane prevent hypoxic pulmonary

vasoconstriction. If halothane causes similar effects in neonates, it may be useful in the treatment of such patients in the operating room and in the intensive care unit.

References

1. Cameron CB, Gregory GA, Rudolph AM, Heymann MA: The effects of curare on oxygen consumption in hypoxic lambs (abstract). ANESTHESIOLOGY 55:A325, 1981
2. Rudolph AM: Congenital Disease of the Heart, 1st edition. Chicago, Year Book Medical Publishers, 1974, pp 1–41
3. Lister G, Hoffman JIE, Rudolph AM: Oxygen uptake in infants and children: A simple method for measurement. Pediatrics 53:656–662, 1974
4. Lister G, Hoffman JIE, Rudolph AM: Measurement of oxygen consumption: Assessing the accuracy of a method. J Appl Physiol 43:916–917, 1977
5. Rudolph AM, Heymann MA: The circulation of the fetus in utero. Methods for studying distribution of blood flow, cardiac output and organ blood flow. Circ Res 21:163–184, 1967
6. Heymann MA, Payne BD, Hoffmann JIE, Rudolph AM: Blood flow measurements with radionuclide-labelled particles. Prog Cardiovasc Dis 20:55–79, 1977
7. Robinson S, Gregory GA: Circulatory effects of anesthesia in the developing sheep. I. Halothane. ANESTHESIOLOGY 53: S330, 1980
8. Roizen MF, Moss J, Henry DP, Kapin IJ: Effects of halothane on plasma catecholamines. ANESTHESIOLOGY 41:432–439, 1974
9. Glantz SA: Primer of Biostatistics. New York, McGraw-Hill, 1981, pp 292–296
10. Eger EI II, Smith NT, Stoelting RK, Cullen DJ, Kadis LB, Witcher CE: Cardiovascular effects of halothane in man. ANESTHESIOLOGY 32:396–409, 1970
11. Deutsch S, Linde HW, Dripps RD: Circulatory and respiratory actions of halothane in normal man. ANESTHESIOLOGY 23: 631–638, 1967
12. Theye RA, Sessler A: Effect of halothane anesthesia on rate of canine oxygen consumption. ANESTHESIOLOGY 28:661–669, 1967
13. Theye RA: Myocardial and total oxygen consumption with halothane. ANESTHESIOLOGY 28:1042–1047, 1967
14. Barash P, Katz JD, Firestone S, Hui S, Taunt K, Jaffe C, Talner NS, Kleinman CS: Cardiovascular performance in children during induction: An echocardiographic comparison of enflurane and halothane. ANESTHESIOLOGY 51:S315, 1979
15. Bahlman SH, Eger EI II, Halsey MJ, Stevens WC, Shakespeare TF, Smith NT, Cromwell TH, Fourcade H: The cardiovascular effects of halothane in man during spontaneous respiration. ANESTHESIOLOGY 36:494–502, 1972
16. Duke C, Fownes D, Wade JC: Halothane depresses baroreflex control of heart rate in man. ANESTHESIOLOGY 46:184–187, 1977
17. Kemmotsu O, Hashimoto Y: Inotropic effects of halothane on mechanics of contraction in isolated cat papillary muscle from normal and failing hearts. ANESTHESIOLOGY 39:470–477, 1973
18. Brown BR, Crout JR: A comparative study of the effect of five general anesthetics on myocardial contractility. ANESTHESIOLOGY 34:236–245, 1971
19. Friedman WF: The intrinsic physiologic properties of the developing hearts. Prog Cardiovasc Dis 15:87–111, 1972
20. Robinson S, Gregory GA: Circulatory effects of anesthesia in the developing sheep. II. Enflurane. ANESTHESIOLOGY 53: S331, 1980
21. Jones MD Jr, Traystman RJ, Simmons MA, Moletini RA: Effect of changes in arterial O_2 content on cerebral blood flow in the lamb. Am J Physiol H209–H215, 1981
22. Gregory GA: The baroresponses of preterm infants during halothane anesthesia. Can Anaesth Soc J 29:105–108, 1982
23. Wear R, Robinson S, Gregory GA: Effect of halothane on the baroresponse of adult and baby rabbits. ANESTHESIOLOGY 56:188–191, 1982
24. Benumof JC, Wahrenbrock EA: Local effects of anesthetics on regional hypoxic vasoconstriction. ANESTHESIOLOGY 43:525–532, 1975
25. Mathers J, Benumof, JL, Wahrenbrock EA: General anesthetics and regional hypoxic vasoconstriction. ANESTHESIOLOGY 46: 111–114, 1977