The Effects of Halothane on Respiratory and Cardiovascular Responses to Hypoxia in Dogs:

A Dose–Response Study

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The effects of 0.75 to 2 per cent end-tidal halothane on cardiovascular and respiratory responses to hypoxia were quantitated. Moderate hypoxia (Pa_{O_2} 45 torr) caused stimulation of ventilation and cardiac output at all levels of halothane anesthesia. Although severe hypoxia (Pa_{O_2} 30 torr) further stimulated ventilation and cardiac output at 0.75 to 1.25 per cent halothane, increasing the halothane concentration to 1.0–1.5 per cent rapidly converted hyperventilation and elevated cardiac output to respiratory or cardiac arrest. Oxygen transport did not meet oxygen consumption requirements; hence, severe metabolic acidosis developed during severe hypoxia. Within narrow limits, the dose of halothane is most important in determining the physiologic response to severe hypoxia. (Key words: Halothane; Hypoxia; Ventilation; Pa_{CO_2}; Cardiac output; Oxygen consumption; Oxygen transport; Respiratory arrest; Cardiac arrest.)

CLINICAL ANESTHESIA may modify the hyperventilation, hypertension, and tachycardia induced by hypoxia. The extent to which depth of anesthesia attenuates these and other cardiorespiratory responses has not been studied, despite the importance of such signs in the clinical recognition of hypoxia.

This report describes the effects of hypoxia at several concentrations of halothane anesthesia.

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Methods

Two groups of dogs were studied. In Group 1, we measured respiratory responses to hypoxia during spontaneous ventilation. In Group 2, cardiovascular function was measured while respiration was controlled or assisted to avoid hypoventilation at higher halothane concentrations.

GROUP 1

Six dogs weighing 12.4 ± 0.6 kg (SE) were anesthetized with halothane and oxygen. After intubation of the trachea without neuromuscular blockade, an esophageal thermistor probe was inserted and the temperature maintained between 36 and 38 C. $P_{ET_{CO_2}}$ was monitored continuously with a Beckman LB-1 infrared CO_2 analyzer. End-tidal halothane was measured with a Beckman LB-1 infrared halothane analyzer. Inspired oxygen concentration was monitored with a Pauling oxygen meter. A catheter was inserted into the femoral artery for blood pressure and pulse rate measurements. Arterial blood samples were analyzed for P_{O_2}, P_{CO_2}, *p*H, and hematocrit. Tidal volume was measured with a recording ventimeter.[1] Blood pressure (transduced with a Statham P23 strain gauge), pulse rate, $P_{ET_{CO_2}}$, tidal volume and respiratory rate were recorded on a Grass Model 7 polygraph. Control determinations were made at 1 per cent end-tidal halothane in oxygen. All measurements were repeated at 1.25, 1.5, 1.75 and 2 per cent halothane. No measurements were made until at least 15 minutes of equilibration had elapsed at a given halothane concentration. Following these measurements of the

TABLE 1. Halothane–Hypoxia Dose–Response Study: Respiratory Data, Group 1*

Alveolar halothane (per cent)	Breathing 100 Per Cent Oxygen					During Moderate Hypoxia					During Severe Hypoxia		
	1.0	1.25	1.5	1.75	2.0	1.0	1.25	1.5	1.75	2.0	0.75	1.0	1.25
Number of dogs	6	6	6	6	5	6	6	6	5	3	6	5	2
P_{AO_2} (torr)	488 ±7.7	471 ±24.5	468 ±34	486 ±30	472 ±14	42.8 ±0.8	43.8 ±1.3	43.2 ±2.1	43.2 ±1.1	40	31.3 ±0.6	32 ±1.3	30
P_{ACO_2} (torr)	42.3 ±3.1	40.2[a] ±4.1	55.5[a] ±6.1	65[a] ±11.2	65.4[a] ±3.7	35.1[b] ±3.3	41[a,b] ±3.6	44.2[a,b] ±4.7	45.6[a,b] ±1.5	57	25.7 ±2	28.4 ±3.1	33.4
V_T (ml)	176 ±0.4	89 ±5.3	81[a] ±8	75[a] ±11	49[a] ±21	92 ±5.2	86 ±7.6	79 ±9	79	71	110 ±12	94 ±6.5	HA
f (/min)	23.4 ±3	99 ±6.1	113 ±16	122 ±26	60 ±30	107[b] ±17.4	171[b] ±31	200[b] ±48	152	149	201 ±27	240[c] ±35	HA
V_E (ml)	4180 ±600	87 ±3.6	88 ±16	81 ±10	45 ±21	152[b] ±9.8	149[b] ±19.5	154[b] ±29	122	102	215 ±23	226[c] ±30	HA
Systolic BP (torr)	113 ±5.3	91 ±2	79 ±3.9	68 ±4	51 ±2.2	108 ±4.8	95 ±4.1	85 ±3.1	80 ±5.5	87	112 ±10	113 ±5	—
HR (beats/min)	89 ±6.1	104 ±4.2	108 ±8.7	110 ±6.2	108 ±10	127 ±8	123 ±10.5	126 ±12.5	118 ±7.4	120	151 ±16.7	138 ±6.5	—

* The upper number in each row is the mean value. The lower number is one standard error. For tidal volume (V_T), f (respiratory frequency), V_E (expired minute volume), systolic blood pressure and heart rate, all values are percentages of control. Control values were obtained at 1 per cent halothane with 100 per cent O_2. Grouped data were not obtained at 1.25 per cent halothane during severe hypoxia because of respiratory arrest (HA) in three dogs. Statistical comparisons were made for respiratory data only.

[a] $P < .05$ compared with 1 per cent value during hyperoxia or moderate hypoxia.

[b] $P < 0.05$ moderate hypoxia *vs.* hyperoxia at identical halothane concentrations.

[c] $P < 0.05$ severe hypoxia *vs.* moderate hypoxia at identical halothane concentrations.

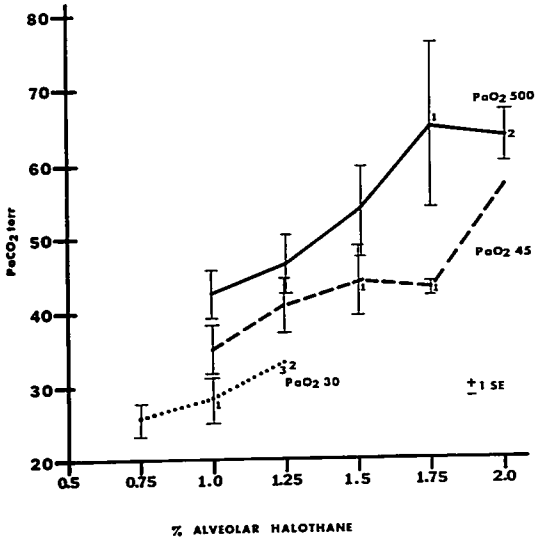

FIG. 1. Resting Pa_{CO_2} rose as halothane concentration increased to 2 per cent. The entire curve shifted downward (respiratory stimulation) during hypoxia. Small arabic numerals refer to the number of dogs in which respiratory arrest occurred at each halothane concentration.

effects of halothane and oxygen, Pa_{O_2} was reduced to approximately 45 torr by vaporizing halothane with appropriate mixtures of nitrogen and air. At the same time, the end-tidal halothane concentration was reduced to 1 per cent. A second dose–response curve began at 1 per cent, with 0.25 per cent increments up to 2 per cent or until respiratory arrest occurred. After respiration was restored, Pa_{O_2} was reduced to 30 torr and halothane concomitantly reduced to 0.75 per cent (since we have shown that at Pa_{O_2} 30 torr, MAC for halothane is reduced by about 30 per cent.[2] A dose–response curve was again started, with 0.25 per cent increments until respiratory arrest occurred. Thus, for each level of oxygenation, dose–response curves for halothane versus Pa_{CO_2} and minute ventilation were constructed.

GROUP 2

Six dogs weighing 11.3 ± 2.7 kg were prepared and made hypoxic as in Group 1. However, respiration was controlled or assisted; CO_2 was added to inspired gas when necessary and mean Pa_{CO_2} maintained between 25 and 34 torr. In addition, right atrial and ventricular catheters were inserted for recording pressure transduced with a Statham P23 strain gauge. Mixed venous blood from the right ventricle was sampled for P_{O_2} and *p*H. Cardiac output was measured with a Beckman Cardiodensitometer. Cardiogreen dye was injected into the right atrium and sampled from the femoral artery by continuous withdrawal with a Harvard pump. Stroke volume, total peripheral resistance, oxygen transport, base excess and oxygen consumption were calculated. The method for calculating arterial and mixed venous oxygen content was described previously.[2] To eliminate the possible effect of duration of anesthesia on recovery of cardiovascular function during administration of halothane,[3-5] dose–response curves during hyperoxia and during moderate hypoxia were obtained in three dogs from 1 to 2 per cent halothane, and in the other three dogs from 2 to 1 per cent halothane. In all six dogs

TABLE 2. Halothane–Hypoxia Dose–Reponse Study; Cardiovascular Data, Group 2*

Alveolar halothane (per cent)	Breathing 100 Per Cent Oxygen					During Moderate Hypoxia					During Severe Hypoxia		
	1.0	1.25	1.5	1.75	2.0	1.0	1.25	1.5	1.75	2.0	0.75	1.0	1.25
Number of dogs	6	6	6	6	6	6	6	6	6	6	6	4	4
$P_{a_{O_2}}$ (torr)	518 ±8	531 ±17	537 ±17.6	521 ±19	532 ±17	43.8 ±0.7	44.7 ±0.8	46.3 ±1.8	46 ±0.9	46 ±0.8	28.3 ±0.8	31.8 ±0.6	32.5 ±1.0
$P_{a_{CO_2}}$ (torr)	33.7 ±2.8	34.3 ±3	33.6 ±2.6	33.3 ±2.3	33.6 ±3.7	29[b] ±1.8	28[b] ±1.2	29.2[b] ±1.7	30.7[b] ±2.7	31 ±2.6	26 ±1.1	25.4 ±0.9	26.5 ±1.8
Base excess (mEq/l)	−1.7 ±0.8	−3.2 ±0.9	−1.4 ±1.0	−2.7 ±1.1	−2.3 ±1.4	−4.2 ±1.3	−4.3 ±1.2	−5.8[b] ±0.9	−5.7[b] ±1.5	−4.6 ±2.0	−0.2 ±2.6	−7.3[c] ±1.9	−7.5 ±2.8
$\dot{Q}$ (l/min)	1.91 ±0.4	84[a] ±0.7	72.5[a] ±7.3	61[a] ±7.5	46[a] ±7.4	136[b] ±14.1	122[a,b] ±11.1	118[a,b] ±8.9	115[a,b] ±13.4	107[a,b] ±12.9	200 ±46	221[c] ±29	192[c] ±21
HR*(beats/min)	101 ±12.3	106 ±2.3	118 ±11.3	118 ±7.2	121 ±17.8	134[b] ±10	133[b] ±11.2	136 ±13	139[b] ±17	145 ±16	159 ±20	180[c] ±23	177 ±22
SV (ml)	18.8 ±2	70[a] ±5.6	69[a] ±4.0	52[a] ±4.4	39.3[a] ±3.6	102.3 ±9.3	92.8 ±8.1	89 ±7	85[b] ±8.9	76[b] ±10.8	124 ±26	123 ±19	110 ±4.7
$\overline{AP}$ (torr)	71.5 ±6.6	93 ±6.3	84[a] ±5.3	71[a] ±5.8	58[a] ±6.5	122 ±16.9	105[a] ±16.7	95[a] ±14.1	87[a] ±7.1	77[a] ±7.7	141 ±23.6	148[c] ±27.8	121 ±16.9

TABLE 2.—*Continued*

Alveolar halothane (per cent)	Breathing 100 Per Cent Oxygen					During Moderate Hypoxia					During Severe Hypoxia		
	1.0	1.25	1.5	1.75	2.0	1.0	1.25	1.5	1.75	2.0	0.75	1.0	1.25
MRAP (torr)	−2.2 ±0.7	−1.8 ±0.7	−1.75 ±0.9	−1.5 ±0.6	−0.8 ±0.7	−2.8 ±0.5	−2.8 ±0.7	−2.5 ±0.6	−1.7 ±0.5	−2 ±0.6	0.4 ±1.9	−2 ±1.5	−0.9 ±1.3
MRVP (torr)	3.1 ±1.4	2.3 ±0.8	2.4 ±1.0	2.7 ±0.9	3.3 ±1.0	7[b] ±2.3	5[b] ±1.7	5.6[b] ±1.4	6.2[b] ±1.8	5.7[b] ±1.6	11.7 ±2.1	5.3 ±1.5	7.8 ±1.74
TPR (dyne-sec/cm^{-5})	3510 ±488	114 ±10.9	119 ±13	125 ±10.7	131 ±12.4	92 ±10.1	88[b] ±7.3	81[b] ±8.4	77[b] ±4.4	76[b] ±7.3	74 ±11	66[c] ±6.5	64[c] ±10.9
T_{O_2} (ml/min)	318 ±42	84 ±6.6	73[a] ±7.3	61[a] ±7.4	46[a] ±7.2	93 ±10	85 ±8.2	99 ±16.8	80 ±9.1	75 ±7.3	88 ±11	113 ±6.5	99 ±10.9
$\dot{V}_{O_2}$ (ml/min)	59.4 ±7.9	84 ±5.8	73[a] ±6.8	64[a] ±8.6	54.4[a] ±7.3	95 ±13	94 ±18.5	89 ±17.5	79 ±18	81 ±14	108 ±33.4	127 ±29.2	179 ±13.4

[a] The upper number in each row is the mean value; the lower number is one standard error. For cardiac output ($\dot{Q}$), heart rate, stroke volume (SV), mean arterial pressure ($\bar{AP}$), total peripheral resistance (TPR), oxygen transport (T_{O_2}), and oxygen consumption ($\dot{V}_{O_2}$), all values are percentages of control. Control values were obtained at 1 per cent halothane with 100 per cent O_2. MRAP is mean right atrial pressure; MRVP, mean right ventricular pressure.

[a] $P < 0.05$ compared with 1 per cent value during hyperoxia or moderate hypoxia.

[b] $P < 0.05$ moderate hypoxia *vs.* hyperoxia at identical halothane concentrations.

[c] $P > 0.05$ severe hypoxia *vs.* moderate hypoxia at identical halothane concentrations.

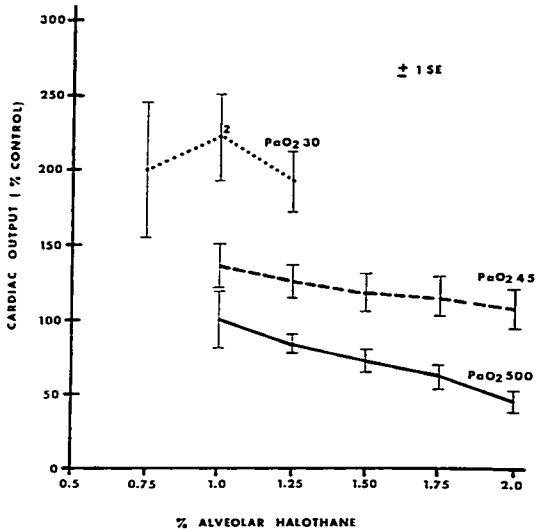

FIG. 2. Cardiac output decreased as halothane concentration rose to 2 per cent. During moderate hypoxia, the curve shifted upward (cardiovascular stimulation) and no significant depression of cardiac output occurred as halothane increased. During severe hypoxia at 0.75 per cent halothane, cardiac output was further stimulated to 200 per cent of control. Arabic numerals indicate the number of dogs in which cardiac arrest occurred at each halothane concentration. At 1.25 per cent halothane during severe hypoxia, four dogs survived with elevated cardiac outputs. Upon raising halothane to 1.5 per cent cardiac arrests occurred in three of these four dogs.

severe hypoxia started at 0.75 per cent halothane. The experiment terminated with cardiac arrest during severe hypoxia.

Results

GROUP 1: SPONTANEOUS VENTILATION—TABLE 1 AND FIGURE 1

Moderate hypoxia (Pa_{O_2} 45 torr). Although Pa_{CO_2} rose as halothane concentration increased, it was significantly lower than the 100 per cent oxygen value for each identical level of halothane. The significant increase in minute ventilation during moderate hypoxia resulted from tachypnea alone, since tidal volume was similar to the control value.

GROUP 2: CONTROLLED VENTILATION—TABLE 2 AND FIGURES 2–4

Cardiac output was significantly higher than the control value during moderate hypoxia at every level of halothane anesthesia, due to both tachycardia and increased stroke volume. Like the ventilatory response, the response of cardiac output to hypoxia was well preserved to 2 per cent halothane (table 3). In fact, cardiac output at 2 per cent halothane during moderate hypoxia was higher than that during 1 per cent halothane in oxygen.

SEVERE HYPOXIA—GROUPS 1 AND 2

During severe hypoxia (Pa_{O_2} 30 torr) cardiorespiratory function in both groups was stimulated at lower levels of halothane. At 0.75 to 1.25 per cent halothane, one further 0.25 per cent increment in halothane concentration rapidly converted hyperventilation and cardiovascular stimulation to respiratory arrest (Group 1) or cardiac arrest (Group 2) (fig. 5) (table 4). Oxygen transport ($Q \times Ca_{O_2}$) did not meet the needs of oxygen consumption during moderate or severe hypoxia. Slight metabolic acidosis developed during moderate hypoxia, progressing to severe metabolic acidosis at 0.75 per cent halothane during severe hypoxia.

Discussion

The results demonstrate that the cardiorespiratory stimulus of moderate hypoxia per-

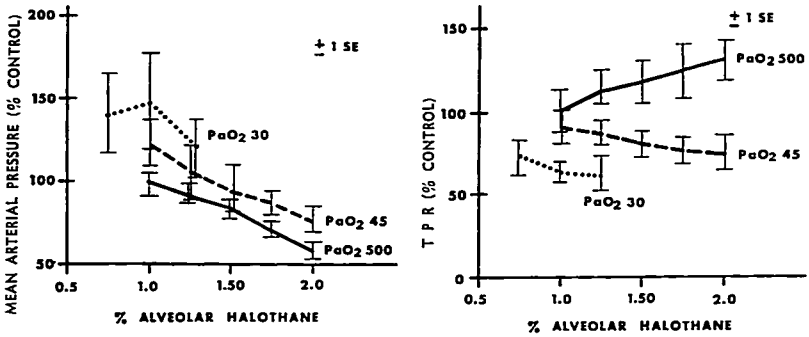

FIG. 3 (above). Mean arterial pressure decreased as halothane concentration rose. With hypoxia, the curve shifted toward elevated blood pressure at light levels of anesthesia. Total peripheral resistance (TPR) rose with increased halothane concentration. During moderate hypoxia, TPR fell as halothane concentration increased. TPR was much lower during severe hypoxia accompanying the very high cardiac output at this time.

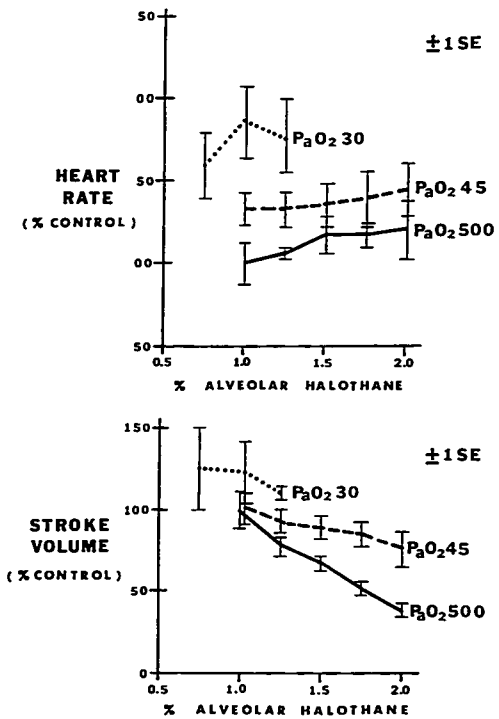

FIG. 4. Heart rate was not affected by halothane concentration at any level of oxygenation. The curves shifted upward (tachycardia) in response to hypoxia. Stroke volume decreased as halothane concentration rose. However, stroke volume shifted upward with hypoxia, similar to changes seen with cardiac output.

TABLE 3.*

	2 Per Cent Halothane-Oxygen	2 Per Cent Halothane during Moderate Hypoxia	P
Pa_{O_2}	532 ± 17	46 ± 0.8	<0.001
Pa_{CO_2}	33.6 ± 3.7	31 ± 2.6	NS
Cardiac output (l/min)	0.88 ± 0.065	2.04 ± 0.26	<0.005
Heart rate (beats/min)	122 ± 21.7	146 ± 23.3	NS
Stroke volume (ml)	7.3 ± 0.3	14.3 ± 1.5	<0.001
Mean arterial pressure (torr)	45 ± 5.4	56 ± 6	NS
Total peripheral resistance (dyne-sec/cm^{-5})	4,600 ± 580	2,670 ± 195	<0.005
Mean right atrial pressure (torr)	−0.8 ± 0.7	−2 ± 0.6	NS

* At the same halothane concentration and Pa_{CO_2} (Group 2), moderate hypoxia raised cardiac output and stroke volume while reducing total peripheral resistance (mean ± one standard error).

sisted to deep levels of halothane anesthesia (table 3). This agrees with the findings of Skovsted *et al.*, who showed a depressed but still-responsive sympathetic nervous system during deep halothane anesthesia.[6] The stimulus of severe hypoxia further increased cardiorespiratory activity at light planes of halothane anesthesia, but depression supervened at 1 to 1.5 per cent end-tidal halothane (clinically useful levels of halothane anesthesia).

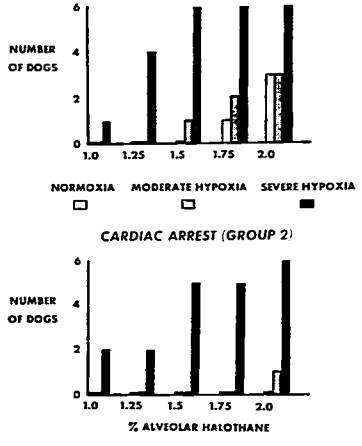

FIG. 5. The numbers of dogs that developed respiratory arrest (Group 1) and cardiac arrest (Group 2) are shown cumulatively at each halothane concentration. In Group 1, respiratory arrest had occurred in all six dogs at 1.5 per cent halothane during severe hypoxia. In Group 2 (controlled respiration), one near-cardiovascular collapse occurred at 2 per cent halothane during moderate hypoxia. During severe hypoxia, cardiac arrest had occurred in five of six dogs at 1.5 per cent halothane.

In the absence of anesthesia, the circulatory response to hypoxia results from the interaction of 1) the direct vasodilatory effect on peripheral vasculature,[7, 8] 2) the direct depressant effect on myocardial function,[9-12] 3) reflex pressor responses from aortic and carotid-body chemoreceptor stimulation,[13-17] 4) central sympathetic excitation,[18, 19] and 5) the effects of circulating catecholamines released from the adrenal medulla.[20, 21]

Halothane probably interferes with each of the five functions listed above.[5, 22-26] Combining severe hypoxia with the usual clinical concentration of halothane (1–1.5 per cent) proved fatal to 11 of 12 dogs studied (table 4). Why did an increase of 0.25 per cent halothane abruptly convert cardiorespiratory stimulation to cardiac or respiratory arrest? One possible explanation involves interference by halothane with chemoreceptor function. In cats halothane reduced chemoreceptor activity during normoxia.[24] If the stimulatory effects of severe hypoxia on respiration and circulation via the chemoreceptor reflex were blocked by halothane, the direct central and peripheral depressant effects of hypoxia and acidosis would prevail.[27-29] Recently it has been shown that the carotid baroreceptor reflex is almost completely abolished at 1–1.5 per cent halothane

TABLE 4. Severe Hypoxia*

	Steady-state Values Prior to the Final 0.25 Per Cent Increase in Halothane Concentration							Values at Time of Arrest	
	Per Cent End-tidal Halothane	V_E (Per Cent Control)	Systolic BP (Per Cent Control)	HR (Per Cent Control)	Base Excess (mEq/l)	Pao_2 (torr)	$Paco_2$ (torr)	Per Cent End-tidal Halothane at Time of Respiratory Arrest	Minutes from Final Increase of Halothane to Respiratory Arrest
Group 1									
Dog 1	1.02	—	111	118	−2	37	22	1.13	3
Dog 2	0.98	300	119	145	−7	33	27	1.25	2
Dog 3	0.76	129	80	89	−13	34	33	0.98	2
Dog 4	1.25	137	105	133	−5	30	47	1.52	5
Dog 5	1.25	129	92	132	−2	30	24	1.49	1
Dog 6	1.02	216	128	147	−1	30	28	1.25	1
	Per Cent End-tidal Halothane	$\dot{Q}$ (Per Cent Control)	$\overline{AP}$ (Per Cent Control)	HR (Per Cent Control)	Base Excess (mEq/l)	Pao_2 (torr)	$Paco_2$ (torr)	Per Cent End-tidal Halothane at Time of Cardiac Arrest	Minutes from Final Increase of Halothane to Cardiac Arrest
Group 2									
Dog 7	0.75	100	118	142	−19	28	31	1.02	21
Dog 8	0.75	68	84	109	−14	31	24	0.96	2
Dog 9	1.25	172	91	135	−5	30	23	1.50	12
Dog 10	1.28	177	114	116	−4	34	24	1.52	18
Dog 11	1.25	168	167	145	−16	34	31	1.49	2
Dog 12	1.75	223	100	220	−6	31	27	2.00	14

* The final steady-state values of respiratory and cardiac function for each of the 12 dogs studied are shown. In Group 1, minute ventilation (V_E), systolic blood pressure, and heart rate are percentages of control (1 per cent halothane–oxygen). 2.3 ± 0.6 minutes after the final 0.25 per cent increase in halothane concentration, respiratory arrest occurred. In Group 2, cardiac output ($\dot{Q}$), mean arterial pressure ($\overline{AP}$), and heart rate are percentages of control (1 per cent halothane–oxygen). 11.5 ± 3.7 minutes after the final increase in halothane concentration, cardiac arrest occurred.

anesthesia.[30] Perhaps denervation of the carotid chemoreceptor reflex also could occur at the same concentration. If true, this might explain the rapid onset of respiratory arrest shortly after the concentration of halothane is increased to this level.

Our findings apply directly to clinical anesthesia. Since hypoxia stimulates respiration and circulation, these changes could be used in the diagnosis of hypoxia. However, such cardiorespiratory stimulation is not unique to hypoxia, but may also result from too light a plane of anesthesia. Failure to distinguish between these two causes of cardiorespiratory stimulation might be hazardous since a level of halothane which is safe under normal circumstances can be fatal during severe hypoxia.

Halothane (Fluothane) for this study was supplied by Ayerst Laboratories.

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ASPIRATION PNEUMONIA A pregnant woman aspirated highly acid gastric contents during anesthesia for a cervical circlage procedure after she had received alcohol intravenously to stop premature labor. Pulmonary lavage extended and intensified the pneumonitis. She required several days of intensive pulmonary therapy with intermittent positive-pressure ventilation monitored by frequent blood-gas determinations, in addition to treatment with steroids and antibiotics. Alcohol is a potent gastric acid secretagogue. Patients in premature labor treated with alcohol intravenously must be considered to have stomach contents. (*Greenhouse, B. S., and others: Aspiration Pneumonia following Intravenous Administration of Alcohol during Labor, J.A.M.A. 210: 2393 (Dec.) 1969.*)