Anesthesiology
V 36, No 5, May 1972

The Cardiovascular Effects of Halothane in Man during Spontaneous Ventilation

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The effects of duration of anesthesia on the cardiovascular responses to halothane in eight healthy male volunteers were studied during spontaneous ventilation and CO_2 challenge. We compared these results with those obtained in a previous study of another group of volunteers during controlled respiration. Spontaneous ventilation lessened the depression of the cardiovascular system associated with halothane anesthesia. Cardiac output, heart rate, mean arterial pressure, left ventricular work, IJ-wave amplitude, and muscle blood flow were all greater during spontaneous than during controlled ventilation. Cardiovascular stimulation also occurred with duration of anesthesia in the presence of spontaneous ventilation. Cardiac output, heart rate, left ventricular minute work, and myocardial function increased 20 to 40 per cent in the course of five hours of halothane anesthesia, while total peripheral resistance and mean right atrial pressure decreased. Finally, halothane (like Forane, fluroxene, ether, and cyclopropane) depressed the cardiovascular responsiveness to carbon dioxide challenge. However, at twice MAC, the depression of the cardiac output and arterial pressure responses was more with halothane than with fluroxene or ether. (Key words: Halothane; Circulation; Circulatory effects of anesthesia; CO_2 response.)

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Received from the Departments of Anesthesia, University of California, San Francisco, California 94122, and Stanford University, Stanford, California 94305. Accepted for publication December 8, 1971. Supported by USPHS Grants 1P01 GM 15571-02 and 03, NIH Training Grant 5 T1 GM 00063-12 and 13 and NIH Training Grant GM 00862-10. Presented at the annual meeting of the American Society of Anesthesiologists, Atlanta, Georgia, October 1971.

In normocapnic man halothane causes cardiovascular depression proportional to the depth of anesthesia.[1] Cardiac output, arterial pressure, and myocardial function decrease and right atrial pressure increases as end-tidal halothane concentration is increased. However, if spontaneous ventilation is allowed during halothane anesthesia, hypercapnia occurs[2] and may antagonize the cardiovascular depression. The work of Hornbein and colleagues[3] suggested such an antagonism; they made measurements during halothane anesthesia approximately two hours after induction with and without nitrous oxide. They found far less depression than did Eger and his colleagues. However, as has been shown recently, increasing duration of halothane anesthesia is associated with spontaneous recovery of normal cardiovascular function.[1] The depression seen during the first hour of anesthesia may be completely reversed by the fifth hour. Furthermore, nitrous oxide itself may have cardiovascular stimulating properties[3-5] which may alter the observed response to halothane. Because of these unresolved questions, we studied the effects of duration of anesthesia on the circulatory effects of halothane without nitrous oxide in the presence of spontaneous respiration. We also examined the effects of duration and depth of halothane anesthesia on the cardiovascular responses to imposed increases in arterial carbon dioxide (CO_2 response curves).

TABLE 1. Control (Awake) Values (Mean ± SE)

	Spontaneous Respiration	Controlled Respiration
Number of subjects	8	15
Age (years)	23 ± 1	23 ± 1
Height (cm)	178 ± 3	183 ± 2
Weight (kg)	72 ± 3	78 ± 2
Hemoglobin (g/100 ml)	14.4 ± 0.3*	16 ± 0.2
Core temperature (C)	36.8 ± 0.1	36.8 ± 0.1
Cardiac output (l/min)	5.0 ± 0.3*	6.3 ± 0.2
Mean right atrial pressure (torr)	4.7 ± 0.9*	1.8 ± 0.4
Mean arterial pressure (torr)	90 ± 3	95 ± 2
Total peripheral resistance (ohms)	1,416 ± 114	1,221 ± 67
Heart rate (beats/min)	59 ± 2*	77 ± 3
Stroke volume (ml)	85 ± 6	83 ± 4
Pa_{O_2} (torr)	456 ± 15*	503 ± 8
Pa_{CO_2} (torr)	36.6 ± 1.2	35.2 ± 0.9
Base excess (mEq/l)	−4.1 ± 0.65*	−2.2 ± 0.06
*p*H	7.37 ± 0.01	7.40 ± 0.01
Forearm (muscle) blood flow (ml/100 ml/min)	3.3 ± 0.4	3.5 ± 0.7 (n = 10)
Forearm venous compliance (ml/100 ml/torr)	0.11 ± 0.03	0.09 ± 0.01 (n = 11)
Left ventricular minute work (kg-meters/min)	6.04 ± 0.40*	8.13 ± 0.32
Left ventricular stroke work (kg-meters)	0.103 ± 0.007	0.103 ± 0.007
Oxygen consumption (ml/min)	173 ± 23*	236 ± 19 (n = 11)
Ratio of cardiac output to oxygen consumption (l/ml)	31.7 ± 3.2	27.2 ± 2.0 (n = 11)

* Significant difference at the 5 per cent level.

Material and Methods

We studied eight unpremedicated, fasting healthy 23-year-old male volunteers after having obtained informed consent. The study protocol, procedures, and consent form had been approved by the University of California and Stanford University committees on human experimentation. We recorded arterial and right atrial pressures, cardiac output, venous and arterial blood gases, end-tidal carbon dioxide tension, electrocardiogram, skin and esophageal temperatures, heart sounds, blood volume, IJ-wave amplitude of the ballistocardiogram (which is thought to vary directly with myocardial function [6]) and forearm (muscle) blood flow. We previously described the methods and calculations for these determinations.[4, 7]

Control (awake) measurements were made with the volunteers spontaneously breathing oxygen and included responses to stepwise increases in arterial CO_2 (Pa_{CO_2}) (CO_2 response curve). Resistance to breathing was minimized by the use of an in-circuit circulator. Halothane–oxygen anesthesia was administered by mask, and orotracheal intubation was accomplished without the use of muscle relaxants. Cardiovascular measurements were made at 1.0 and 1.6 per cent end-tidal halothane (ultraviolet analysis) during the first hour and during the fifth hour from the start of anesthesia. All measurements were made after end-tidal halothane had been held constant for a minimum of 15 minutes.

Between the first and fifth hours, alveolar halothane was held constant at 1.0 per cent; during this time, we obtained two consecutive CO_2 response curves for the cardiovascular variables mentioned above. After the fifth hour of anesthesia, in four of the volunteers, end-tidal halothane was held constant at 1.6 per cent and another CO_2 response curve was obtained. Finally, CO_2 responses were measured again at 1.0 per cent end-tidal halothane.

The results during anesthesia were compared with control (awake) values and with results from a similar study of volunteers anesthetized with halothane at equivalent concen-

TABLE 2. Durations and Depths of Anesthesia during Spontaneous and Controlled Respiration (Values are Mean Per Cent of Control ±SE Unless Otherwise Indicated)

	Early		Late	
	1 Per Cent	1.6 Per Cent	1 Per Cent	1.6 Per Cent
Number of subjects				
Spontaneous respiration	8	8	8	8
Controlled respiration	15	6	12	14
Duration of anesthesia (min)				
Spontaneous respiration	26 ± 1	44 ± 2	261 ± 5	282 ± 6
Controlled respiration	31 ± 1*	52 ± 2*	310 ± 11*	303 ± 13
Halothane concentration (per cent)				
Spontaneous respiration	1.02 ± 0.02	1.59 ± 0.03	1.04 ± 0.01	1.55 ± 0.10
Controlled respiration	1.01 ± 0.03	1.55 ± 0.02	0.95 ± 0.03*	1.58 ± 0.01
$Paco_2$ (torr)				
Spontaneous respiration	46.6 ± 1.3†§	59.7 ± 1.8†	53.2 ± 2.0†‡§	60.6 ± 2.4†
Controlled respiration	38.5 ± 1.2*	—	38.2 ± 0.8*	—
Cardiac output				
Spontaneous respiration	94 ± 3	91 ± 5	118 ± 5†‡	116 ± 5†‡
Controlled respiration	78 ± 2	68 ± 4*	107 ± 9	91 ± 4*
Mean arterial pressure				
Spontaneous respiration	86 ± 3†§	77 ± 3†	76 ± 4†‡	76 ± 4†
Controlled respiration	76 ± 2*	67 ± 4	73 ± 3	63 ± 3*
Heart rate				
Spontaneous respiration	114 ± 4†	119 ± 4†	135 ± 6†‡§	145 ± 7†‡
Controlled respiration	102 ± 3*	101 ± 4*	109 ± 3*	115 ± 3*
Total peripheral resistance				
Spontaneous respiration	88 ± 4†§	78 ± 5†	65 ± 5†‡	62 ± 3†‡
Controlled respiration	92 ± 4	92 ± 7	74 ± 3	67 ± 3
Left ventricular minute work				
Spontaneous respiration	81 ± 4†§	70 ± 4†	89 ± 6	88 ± 6‡
Controlled respiration	64 ± 3*	44 ± 4*	68 ± 4*	63 ± 5*
Left ventricular stroke work				
Spontaneous respiration	71 ± 3†§	59 ± 3†	67 ± 4†	61 ± 2†
Controlled respiration	63 ± 3	44 ± 5*	63 ± 4	53 ± 5
Mean right atrial pressure (torr change from control)				
Spontaneous respiration	3.2 ± 1.0†§	5.2 ± 0.8†	0.7 ± 0.9‡§	2.5 ± 1.4‡
Controlled respiration	2.5 ± 0.6	3.7 ± 1.3	0.7 ± 0.5	1.7 ± 0.4
Stroke volume				
Spontaneous respiration	83 ± 3†	77 ± 4†	89 ± 5	80 ± 3†
Controlled respiration	78 ± 2	68 ± 5	91 ± 4	80 ± 3
IJ-wave amplitude				
Spontaneous respiration	73 ± 8† (n = 6)	79 ± 7† (n = 5)	111 ± 26 (n = 5)	98 ± 26 (n = 6)
Controlled respiration	70 ± 3 (n = 14)	57 ± 6*	84 ± 4	70 ± 4
Oxygen consumption				
Spontaneous respiration	94 ± 8§	88 ± 9	113 ± 15	108 ± 12‡
Controlled respiration	76 ± 5 (n = 11)	—	88 ± 15 (n = 10)	—
Muscle blood flow				
Spontaneous respiration	154 ± 25†	104 ± 10	227 ± 29†	205 ± 30†‡
Controlled respiration	100 ± 10* (n = 10)	88 ± 14	140 ± 28* (n = 9)	153 ± 41 (n = 8)
Venous compliance				
Spontaneous respiration	88 ± 22	123 ± 43	164 ± 65	130 ± 53
Controlled respiration	78 ± 8 (n = 12)	93 ± 15 (n = 5)	101 ± 28 (n = 11)	75 ± 13 (n = 9)

TABLE 2. *(Continued)*

	Early		Late	
	1 Per Cent	1.6 Per Cent	1 Per Cent	1.6 Per Cent
Base excess (mEq/l change from control)				
Spontaneous respiration	0.7 ± 0.9§	−1.3 ± 1.1	−0.4 ± 1.1	−1.8 ± 0.6
Controlled respiration	−0.4 ± 0.5	—	−1.7 ± 0.7	—
Pa_{O_2} (torr)				
Spontaneous respiration	431 ± 22	384 ± 28	444 ± 18	439 ± 25
Controlled respiration	466 ± 17	—	465 ± 20	—
Ratio of cardiac output to oxygen consumption				
Spontaneous respiration	104 ± 10	111 ± 16	116 ± 14	116 ± 12
Controlled respiration	110 ± 10 (n = 11)	—	118 ± 11 (n = 9)	—
Body temperature (degrees C)				
Spontaneous respiration	36.7 ± 0.1	36.8 ± 0.1	36.8 ± 0.1§	36.9 ± 0.1†
Controlled respiration	36.8 ± 0.1	—	37.0 ± 0.3	—
*p*H (units)				
Spontaneous respiration	7.31 ± 0.02†§	7.21 ± 0.11†	7.26 ± 0.01†§	7.23 ± 0.01†
Controlled respiration	7.37 ± 0.01*	—	7.35 ± 0.01*	—

* Significant difference (5 per cent level) from comparable value during spontaneous respiration.
† Significant difference from awake value for spontaneous-respiration group.
‡ Significant difference compared with early value at the same anesthetic level.
§ Significant difference comparing 1 per cent level with 1.6 per cent level either early or late.

trations but in whom ventilation was controlled to keep Pa_{CO_2} normal.[1] The groups were compared utilizing Student's t test. We accepted the 5 per cent level as significant. Linear-regression analysis was used to define the slopes of the CO_2 response curves.

Results

Several control cardiovascular variables were significantly lower in our volunteers than in those in whom respiration was controlled (table 1). These included hemoglobin, cardiac output, Pa_{CO_2}, heart rate, base excess, left ventricular minute work, and oxygen consumption.

During spontaneous respiration halothane anesthesia increased Pa_{CO_2} (table 2). The only immediate evidence of cardiovascular stimulation was an increase in heart rate. Cardiac output was sustained at normal levels, while arterial pressure decreased in proportion to halothane concentration. The decrease in pressure resulted from a decrease in total peripheral resistance, which in turn lowered left ventricular minute work and stroke work.

As found in previous studies during controlled respiration, we found that duration of anesthesia produced cardiovascular stimulation, as evidenced by progressive increases in cardiac output and heart rate and a decrease in mean right atrial pressure (table 2). The IJ-wave amplitude of the ballistocardiogram increased to control levels. Total peripheral resistance and arterial pressure decreased with time.

As we had expected, when compared with the group subjected to controlled respiration, our group had less cardiovascular depression (table 2, figs. 1, 2). Cardiac output, arterial pressure, left ventricular work, stroke work, and IJ-wave amplitude were less depressed in our group at 1.6 per cent end-tidal halothane. Other evidences of differences in cardiovascular stimulation were heart rate and muscle blood flow, which increased more during spontaneous ventilation than during controlled ventilation.

The cardiovascular response to carbon dioxide was depressed by halothane anesthesia

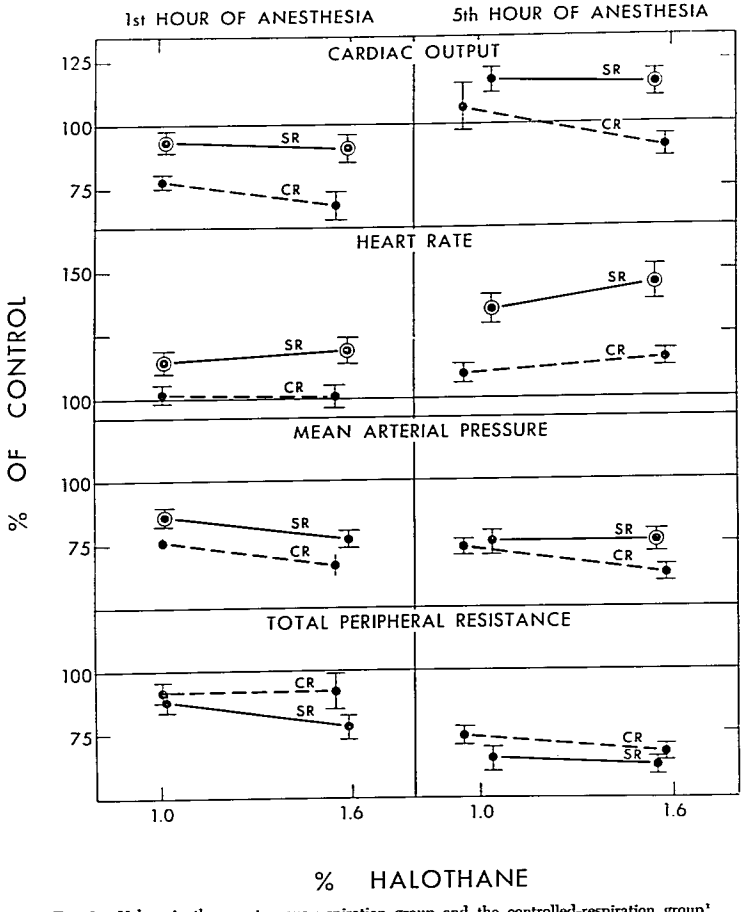

FIG. 1. Values in the spontaneous-respiration group and the controlled-respiration group[1] in the first and fifth hours of anesthesia. Per cent control versus per cent end-tidal halothane is plotted for each variable.

(table 3). Cardiac output, mean arterial pressure, and heart rate responses to imposed increases in CO_2 were all depressed at one or more levels of halothane anesthesia. In addition, the slope of the CO_2 response curve of mean right atrial pressure became more positive with anesthesia.

Duration of anesthesia had variable effects on the responsiveness to CO_2 at 1.0 per cent alveolar halothane. There were no significant changes in responsiveness between the first and second determinations except a change in heart rate, which showed increased responsiveness. Comparison of the first and last CO_2 re-

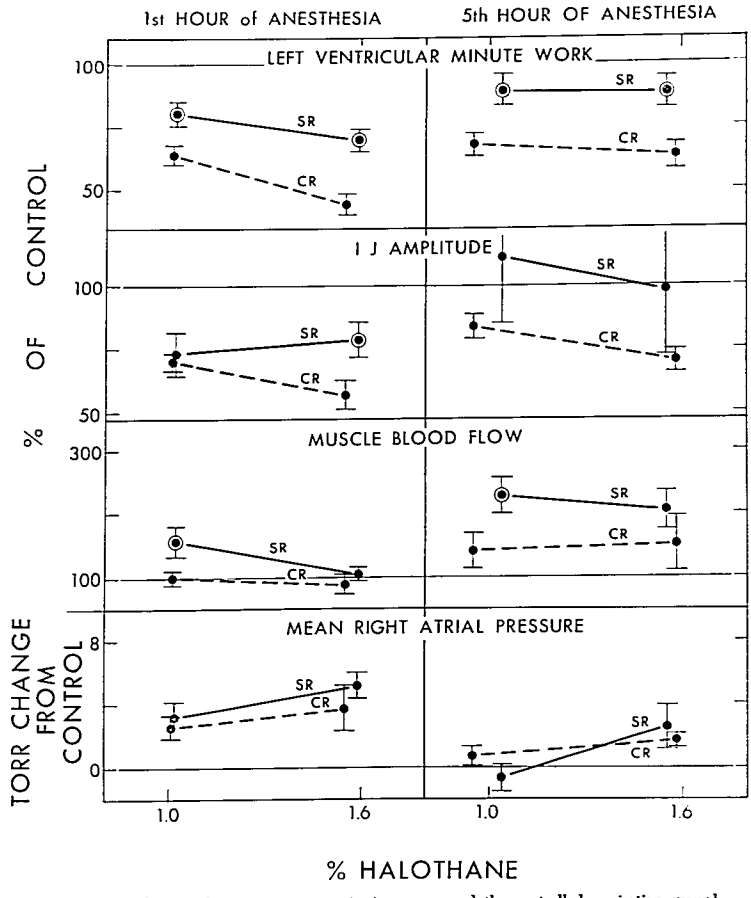

FIG. 2. Values in the spontaneous-respiration group and the controlled-respiration group[1] in the first and fifth hours of anesthesia. Per cent control (or for mean right atrial pressure, torr change from control) versus per cent end-tidal halothane is plotted for each variable.

sponses at 1.0 per cent suggests that prolonged anesthesia is associated with depressed cardiac output, arterial pressure, heart rate, and total peripheral resistance responses to changes in carbon dioxide.

There was no significant change in blood volume with time.

Discussion

Our data show that less cardiovascular depression attends halothane anesthesia during spontaneous respiration than during controlled respiration (table 2). We suppose, from the results of previous studies, that this difference reflects the effect of CO_2 and lack of positive

TABLE 3. Linear Regression Slopes versus Duration and Depth of Halothane Anesthesia*

	Duration (Min)	Cardiac Output Δ Liters/ Min/ Δ torr CO_2	Mean Arterial Pressure Δ torr/ Δ torr CO_2	Heart Rate Δ Beats/ Min/ Δ torr CO_2	Stroke Volume Δ ml/ Δ torr CO_2	IJ-wave Amplitude Δ cm/ Δ torr CO_2	Mean Right Atrial Pressure Δ torr/ Δ torr CO_2	Total Peripheral Resistance Δ dynes/ sec/cm^{-5}/ Δ torr CO_2
1) Awake	0	0.170 ±0.039	0.900 ±0.155	1.743 ±0.375	0.300 ±0.273	0.357 ±0.152 (n = 6)	−0.113 ±0.023	−22.50 ± 7.04
2) 1 per cent halothane	108 ±2	0.119 ±0.015	0.463 ±0.086	0.817 ±0.110	0.667 ±0.211	0.263 ±0.179 (n = 6)	−0.002 ±0.027	−10.78 ± 3.14
3) 1 per cent halothane	194 ±4	0.165 ±0.025	0.422 ±0.148	1.155 ±0.141	0.934 ±0.268	−0.099 ±0.157 (n = 6)	−0.085 ±0.073	−12.67 ± 4.08
4) 1.6 per cent halothane	318 ±17	0.034 ±0.021 (n = 4)	−0.053 ±0.235 (n = 4)	0.311 ±0.071 (n = 4)	0.152 ±0.202 (n = 4)	0.132 ±0.069 (n = 3)	0.106 ±0.038 (n = 4)	− 6.38 ± 2.66 (n = 4)
5) 1 per cent halothane	395 ±14	0.063 ±0.017	0.170 ±0.042	0.326 ±0.113	0.471 ±0.242	0.172 ±0.076 (n = 6)	−0.013 ±0.066	− 4.97 ± 2.48
Significant difference at 5 per cent level	1–2 2–3 2–5 3–4 1–4	2–5 1–4	1–2 2–5 1–4	1–2 1–4 2–3 2–5 3–4	N.S.	N.S.	1–2 3–4 1–4	2–5

* n = 8 unless otherwise indicated. Change in variable/increase in Pa_{CO_2} ± SE. N.S. = not significant.

intrathoracic pressure. Differences between the spontaneous-respiration and controlled-respiration groups due to control of respiration and the consequent positive intrathoracic pressure may have been minimized by the use of controlled ventilation for the awake studies in the controlled-respiration group. However, this was not reflected in the cardiovascular values for the awake controlled-respiration subjects. In fact, control of respiration in the awake state seems to have stimulated the volunteers (table 1). We think the differences during anesthesia are largely due to changes in CO_2. The maintenance of cardiac output and myocardial function in the face of a known cardiovascular depressant—halothane—and the decrease in total peripheral resistance and increases in heart rate and muscle blood flow all bespeak beta-sympathetic stimulation, a known result of an increase in Pa_{CO_2}.[8]

If maintenance of normal cardiovascular variables is desirable during halothane anesthesia, then the use of spontaneous respiration may be advantageous. Furthermore, the differences in effect between spontaneous and controlled respiration may be exaggerated in patients with limited cardiovascular reserve. This assertion, however, remains untested and thus has not been proven.

Spontaneous respiration and the accompanying increase in Pa_{CO_2} do not prevent the cardiovascular stimulation seen accompanying prolonged anesthesia. Moreover, as found with controlled respiration,[1] the effect of increasing depth of anesthesia after five hours is less. Early in anesthesia, arterial pressure, total peripheral resistance, left ventricular minute work, left ventricular stroke work, and oxygen consumption all decreased with increasing depth of anesthesia, whereas after five hours none of these changed significantly with increasing depth. Surprisingly, the cardiovascular responsiveness to CO_2 was less after six and a half hours of anesthesia. Several factors

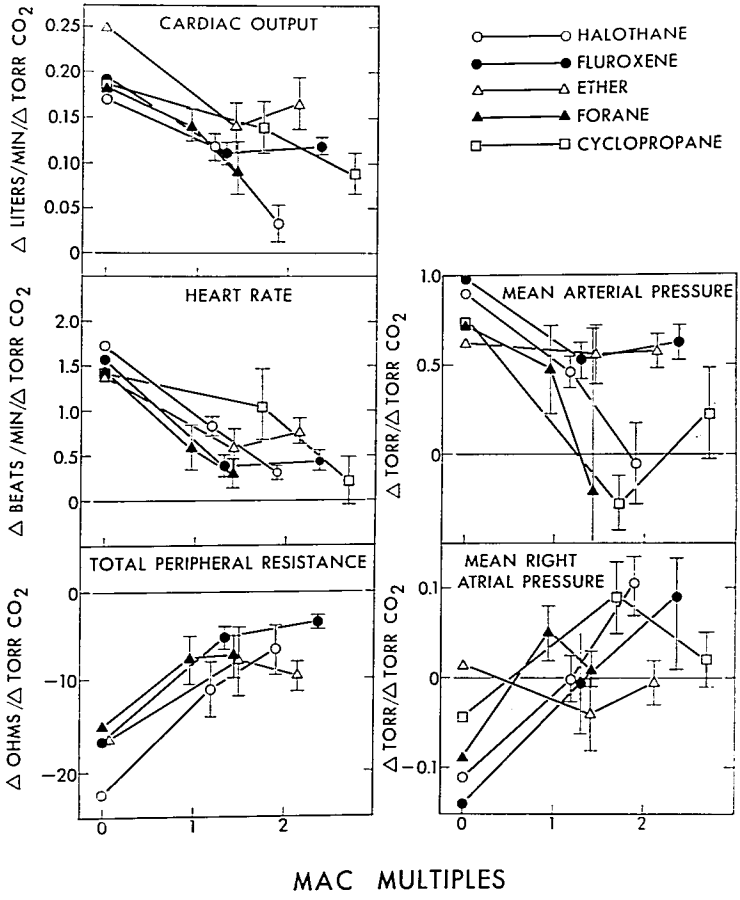

FIG. 3. CO_2 response slopes versus MAC multiples compared for halothane, fluroxene,[11] ether,[10] Forane,[12] and cyclopropane.[9] Depth of anesthesia is indicated by the "MAC multiple." Spontaneous respiration was used in all studies.

may influence these last responses, including the prior (though more than one hour earlier) deep anesthesia level, repeated carbon dioxide stimulation, and duration of anesthesia. Our data do not allow us to discriminate among those or other factors.

Although our data correspond closely to those of Hornbein *et al.*,[3] in several instances, their values are intermediate between our early-anesthesia and late-anesthesia values. For example, at 0.8 to 1.0 per cent end-tidal halothane, they found a heart rate which was 126

per cent of control, whereas we found 114 per cent early (first hour of anesthesia) and 135 per cent late (after five hours of anesthesia). They found a mean arterial pressure of 76 per cent of control, whereas we found 86 per cent early and 76 per cent late. Likewise, they found a total peripheral resistance of 80 per cent of control and we found 88 per cent early and 65 per cent late. At 1.5 to 1.6 per cent end-tidal halothane, they found a cardiac output of 95 per cent of control, whereas we found 91 per cent early and 116 per cent late. At this level, they found a total peripheral resistance of 73 per cent of control, and we found 78 per cent early and 62 per cent late. These data suggest that their results apply to the cardiovascular responses during maintenance of anesthesia rather than early in anesthesia. However, the differences between our results and theirs are small.

Finally, because of previous studies done in this laboratory with cyclopropane,[9] ether,[10] fluroxene,[11] and Forane ‡‡ [12] and spontaneous ventilation, it is possible to place halothane within the spectrum of these inhalational anesthetics with respect to their responsiveness to carbon dioxide challenge with increasing depths of anesthesia (fig. 3). For example, the slope of the CO_2 response curve for cardiac output versus depth of anesthesia (MAC multiple) reveals that increasing the depth of Forane or halothane anesthesia produces decreasing slopes, whereas the slopes are maintained with deeper ether, cyclopropane, or fluroxene anesthesia. This pattern is also seen for heart rate and mean arterial pressure, where once again ether and fluroxene, and to a lesser extent, cyclopropane, maintain better responsiveness to CO_2 challenge with increasing depths of anesthesia than do halothane and Forane.

Review of the manuscript by C. Philip Larson, Jr., M.D., and technical assistance with this work by Mr. Richard Shargel, Miss Dianne Impelman, Mrs. Anne White, Miss Jacqueline Smith, Miss Eunice Lim, and Mrs. Linda Howard were greatly appreciated. The halothane (Fluothane) for this study was donated by Ayerst Laboratories.

‡‡ Trademark, Ohio Medical Products, Division of Airco, Inc.

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