Anesthesiology
V 36, No 1, Jan 1972

Effects of Time on Ventilation during Halothane and Cyclopropane Anesthesia

Henry E. Fourcade, M.D., C. Philip Larson, Jr., M.D.,†*
*Robert F. Hickey, M.D.,‡ Steven H. Bahlman, M.D.,**
Edmond I. Eger, II, M.D.§

The effects of duration of anesthesia upon spontaneous ventilation and ventilatory responses to inhaled CO_2 were studied in 14 volunteers. Six of the volunteers were anesthetized with 13 per cent end-tidal cyclopropane for three hours and eight with 1 per cent end-tidal halothane for six hours. Both anesthetics produced increases in resting Pa_{CO_2} values and decreases in ventilatory responses to CO_2, which remained unchanged during the first three hours of anesthesia. After six hours of halothane anesthesia, however, resting Pa_{CO_2} averaged 2.7 torr less than that after two hours of anesthesia, a return of 20 per cent toward the awake value. The ventilatory responses to CO_2 also showed a return toward the awake slopes in the volunteers anesthetized with halothane. Our data suggest that the ventilatory depression associated with constant-depth cyclopropane or halothane anesthesia occurs immediately and remains unchanged for as long as three hours of anesthesia. However, after longer periods of halothane anesthesia, ventilation tends to return toward the normal awake values. (Key words: Ventilation; CO_2; Halothane; Cyclopropane.)

INHALATION ANESTHETICS depress ventilation, the degree of depression depending upon the agent and its concentration.[1,2] The indices most commonly used to quantify ventilatory depression by anesthetics include spontaneous resting arterial carbon dioxide tension (Pa_{CO_2}) and the ventilatory responses to inhaled carbon dioxide (CO_2 response curves). With progressively larger doses of inhalation anesthetics, resting Pa_{CO_2} increases, the ventilatory response curve shifts to the right, and the slope of the curve decreases. Although these indices are often used to compare the depressant effects of different anesthetics, it has not been shown that either remains constant in man during long periods of constant-depth anesthesia. Furthermore, "recovery" from circulatory depression during halothane anesthesia has been reported, and it is conceivable that ventilation may recover also.[3]

Methods

Fourteen young, healthy volunteers were studied after informed consent had been obtained. The mean age of the volunteers was 22 ± 2 years and body size was 1.94 ± 0.2 m^2. Each volunteer arrived in the laboratory on the morning of the study after a minimum of eight hours of fasting. No premedicant drugs were given. Catheters were placed into a peripheral vein for the infusion of fluid and into a brachial or radial artery for recording of blood pressure and analysis of blood gases. In the eight volunteers anesthetized with halothane, a catheter was also placed into the right atrium (localized by recording right ventricular pressure and then withdrawing) for use in measuring cardiac output by the dye-dilution technique. Ventilation was measured with the volunteer breathing from a circle system containing a Neff circulator distal to the inspiratory valve to minimize the resistance of the circuit. A recording ventimeter was substituted for the reservoir bag for monitoring of ventilation.[4] Expired CO_2 was recorded continuously by means of a Beckman LB-1 infrared analyzer.

Measurements of ventilation prior to anesthesia were made in each volunteer scheduled to receive halothane. After the volunteer had

* Resident and Research Trainee, Department of Anesthesia.
† Associate Professor of Anesthesia.
‡ Assistant Professor of Anesthesia.
§ Professor of Anesthesia.
Received from the Department of Anesthesia, University of California, San Francisco, California. Accepted for publication August 27, 1971. Supported in part by USPHS Grants 5T1GM00063-12 and IP01GM15571-02. Presented in part at the Annual Meeting of the American Society of Anesthesiologists, New York, N. Y., October 19, 1970.

TABLE 1. Effects of Time on Resting Ventilation during Constant-depth Anesthesia

	Awake	One Hour	Two Hours	Three Hours	Six Hours
Halothane, 1.02 per cent*					
P_{aCO_2} (torr)	36.5 ± 1.0†	—	51.1 ± 1.5†	53.0 ± 2.3†	48.4 ± 0.9
$\dot{V}_E$ (l/min/m²)	3.9 ± 0.2†	—	3.7 ± 0.3†	4.3 ± 0.4	4.8 ± 0.4
V_T (ml)	489 ± 31†	—	230 ± 25†	250 ± 25†	280 ± 20
f (/min)	16 ± 1†	—	31 ± 2	32 ± 2	32 ± 2
Cyclopropane, 13.4 per cent‡					
PA_{CO_2} (torr)	—	48.1 ± 2.1	47.1 ± 1.4	49.1 ± 1.8	—
$\dot{V}_E$ (l/min/m²)	—	2.7 ± 0.4	2.6 ± 0.1	2.5 ± 0.1	—

* Mean ± SE for eight volunteers.
† Significantly different from the six-hour value.
‡ Mean ± SE for six volunteers.

breathed oxygen for 10 minutes, measurements of arterial P_{O_2}, P_{CO_2}, and *p*H, minute ventilation ($\dot{V}_E$), and cardiac output ($\dot{Q}$) were made and repeated at least three times. The inspired CO_2 concentration was then increased in increments of 4 torr until end-tidal P_{CO_2} (P_{ACO_2}) was 8 to 14 torr (mean 11.8 torr) above the resting value. After P_{ACO_2} had been kept constant for at least 6 minutes, the ventilatory measurements were repeated at two or more levels above the resting value.

Eight of the volunteers were then anesthetized with halothane–oxygen and six with cyclopropane–oxygen. When an adequate depth of anesthesia had been obtained, the trachea was intubated without muscle relaxants or topical anesthesia. Halothane was vaporized from a Copper Kettle vaporizer and the alveolar concentration monitored with an ultraviolet halothane analyzer.

After an alveolar halothane concentration of 1.02 ± 0.02 per cent had been maintained for a minimum of 30 minutes, measurements of resting ventilation and $\dot{Q}$ and ventilatory responses to CO_2 were made in the same way as the awake measurements. The measurements were repeated after two hours (116 ± 8 min), three hours (193 ± 5 min), and six hours (393 ± 14 min) of constant-depth halothane anesthesia.

Six volunteers were studied during cyclopropane anesthesia, using the same techniques except that awake measurements were not made and cardiac outputs were not determined. Cyclopropane concentration was maintained at 13.4 ± 0.2 per cent as measured by a Beckman Model D oxygen analyzer with the system arranged to return the gas sample to the expiratory limb of the circle. The measurements were made after approximately one

TABLE 2. Effects of Time on the Ventilatory Responses to Inhaled CO_2 during Constant-depth Anesthesia

	Awake	One Hour	Two Hours	Three Hours	Six Hours
Halothane, 1.02 per cent*					
P_{aCO_2} shift†	39.7 ± 1.2§	—	60.3 ± 2.0§	60.4 ± 3.1§	53.1 ± 1.3
Slope‡	1.45 ± 0.22§	—	0.52 ± 0.07§	0.57 ± 0.07	0.63 ± 0.08
Cyclopropane, 13.4 per cent¶					
P_{aCO_2} shift	—	57.2 ± 3.2	60.7 ± 4.8	58.7 ± 3.2‖	—
Slope	—	0.60 ± 0.12	0.49 ± 0.12	0.59 ± 0.10	—

* Mean ± SE for eight volunteers.
† Mean P_{aCO_2} (torr) necessary to produce a minute ventilation of 8 l/min/m².
‡ Mean slope of CO_2 response curves (l/min/m²/torr P_{aCO_2}).
§ Significantly different from the six-hour value.
¶ Mean ± SE for six volunteers.
‖ Significantly different from the one-hour value.

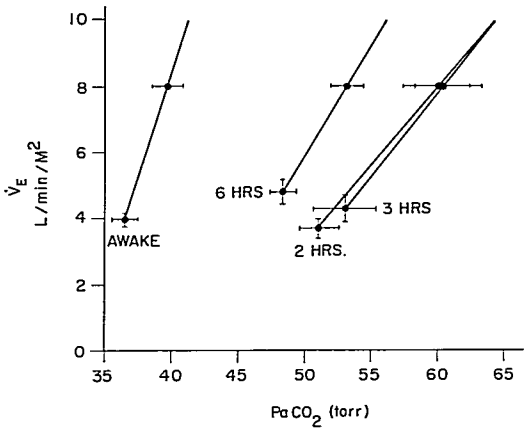

FIG. 1. Effects of time on the ventilatory responses to inhaled CO_2 during constant-depth halothane anesthesia (means of eight volunteers ± SE).

hour (56 ± 3 min), two hours (119 ± 7 min) and three hours (187 ± 9 min) of constant-depth cyclopropane anesthesia. Ventilation was expressed as l/min/m². Esophageal temperatures were recorded (range 36.2–37.5 C) and the blood–gas values were corrected to the volunteer's temperature. The slopes of the CO_2 response curves were calculated by the method of least squares and expressed as l/min/m²/torr Pa_{CO_2}.[5] In addition, we calculated the lateral displacement of the CO_2 response curves at a standard ventilation of 8 l/min/m². This ventilation was chosen because all of the volunteers had $\dot{V}_E$ values of this magnitude during the course of all of the CO_2 response curves.[6] All differences were then analyzed by Student's paired t test, and differences were considered significant when $P < 0.05$.[5]

Results

Resting Ventilation

After two hours of halothane anesthesia, mean Pa_{CO_2} was 15 torr greater than during the awake state, although minute ventilation was not significantly changed (table 1). The values obtained after three hours of anesthesia were not significantly different from the two-hour values. However, after six hours of halothane anesthesia, resting Pa_{CO_2} values averaged 2.7 torr less than after two hours of anesthesia ($P < 0.05$), representing a 20 per cent return of resting Pa_{CO_2} toward the awake value. Mean resting minute ventilation increased by 1.1 l/min/m² from the second to the sixth hour, entirely as a result of an increase in tidal volume.

During the three hours of cyclopropane anesthesia, there were no significant changes in resting Pa_{CO_2} or minute ventilation (table 1).

Ventilatory Responses to Inhaled CO_2

After two hours of halothane anesthesia, the positions of the CO_2 response curves were invariably displaced compared with the awake values (table 2, fig. 1). After three hours of anesthesia, there was no further significant change, but by six hours the CO_2 response curve had shifted 35 per cent back towards the awake position ($P < 0.001$), and the slope had returned 12 per cent towards the awake value ($P < 0.05$ (table 2).

After three hours of cyclopropane anesthesia, there was a statistically significant mean shift of the CO_2 response curve to the right compared with the mean curve obtained after one hour of anesthesia ($P < 0.01$), but this difference was less than 2 torr Pa_{CO_2} at a minute ventilation of 8 l/min/m² (fig. 2, table 2). There were no significant differ-

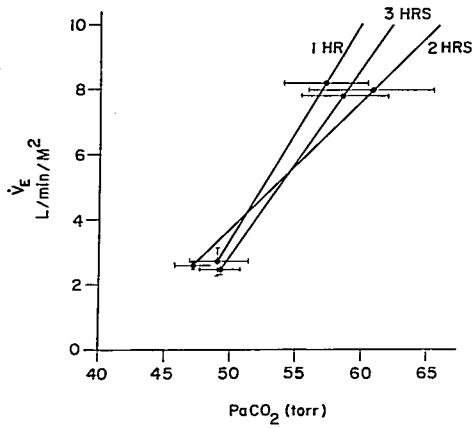

FIG. 2. Effects of time on the ventilatory responses to inhaled CO_2 during constant-depth cyclopropane anesthesia (means of six volunteers ± SE).

ences among the slopes at any of the time intervals during cyclopropane anesthesia.

Discussion

Both halothane and cyclopropane increased resting Pa_{CO_2} and depressed the ventilatory responses to inhaled CO_2. The values found in this study are similar to those reported by Munson, who reported increases in resting Pa_{CO_2} to 48 and 60 torr during anesthesia with 0.81 and 1.11 per cent halothane, respectively, and to 45 and 52 torr during 11 and 17 per cent cyclopropane anesthesia.[2] In this earlier study, the mean slope of the CO_2 response curves during halothane anesthesia decreased to 35–48 per cent of the control slopes and during cyclopropane to 67–92 per cent of the control slopes.

The present study establishes that once the initial ventilatory depression has occurred, both resting Pa_{CO_2} and CO_2 responses remain relatively unchanged for as long as three hours of constant-depth anesthesia with halothane or cyclopropane. Thereafter, however, there was a distinct tendency toward improvement of ventilation in the volunteers anesthetized with halothane.

Eger *et al.* have reported recovery of cardiac output during prolonged, constant-depth halothane anesthesia.[3] This study documents that there is a similar tendency for recovery from ventilatory depression, an observation not

TABLE 3. Variables during Prolonged Halothane Anesthesia (Means ± SE)

	Study	Two Hours	Three Hours	Six Hours
Anesthetic depth	End-tidal halothane (%)	1.02 ± 0.02	1.06 ± 0.01*	1.01 ± 0.02
Metabolic acidosis	pH_a (units)	7.27 ± 0.01*	7.25 ± 0.02*	7.29 ± 0.01
	Base excess (mEq/l)	−3.4 ± 0.7	−3.4 ± 0.7	−3.3 ± 0.5
	Cardiac index (l/min/m^2)	2.8 ± 0.1	2.9 ± 0.2	3.1 ± 0.2
Oxygenation	Pa_{O_2} (torr)	461 ± 23	477 ± 15	441 ± 23
Body temperature	Esophageal temperature (C)	36.7 ± 0.1*	36.7 ± 0.1*	36.9 ± 0.1

* Significant difference from the six-hour value.

made previously. These findings indicate that future studies of ventilatory or circulatory function during anesthesia must take into consideration the possible modifying effects that duration of anesthesia may have.

Why recovery of ventilation and circulation occurs during prolonged halothane anesthesia is not known. There are several possible mechanisms, including decreased depth of anesthesia, an increase in MAC, the development of metabolic acidosis, hypoxemia or hyperthermia, or an increased effect of norepinephrine. Mean end-tidal halothane concentration after six hours of anesthesia was not significantly different from that after two hours (table 3). Whether MAC changes in man during prolonged exposure to anesthesia is not known, but Eger found no change of MAC in dogs during eight hours of anesthesia.[7] However, Munson *et al.* have recently reported circadian variations in MAC in rats, MAC being greater in the evening (active) hours than in the morning (inactive) hours.[8] This may help to explain the lesser effect of halothane on ventilation, when we consider that the late (six-hour) measurements in this study were made in the afternoon. Metabolic acidosis may displace the CO_2 response curve to the left and increase the slope.[9] However, in our studies there were no significant changes in base excess *in vivo* after six hours. A decrease in cardiac output might bring about the same result, but mean cardiac output was greater after six hours than after two hours. The increase in ventilation with time actually resulted in a significant increase in arterial *p*H. Hypoxemia may displace the curve to the left and increase the slope,[10] but the high Pa_{O_2} maintained in this study excludes this possibility. Likewise, an increase in body temperature of more than 1 degree C may result in a shift of the CO_2 response curve to the left and an increase in its slope.[11] Our volunteers did have esophageal temperatures 0.2 C higher after six hours than after two hours of anesthesia, but this increase is too small to explain the results. Moreover, two of the eight had no increase or decreases in esophageal temperature, yet had the same shift to the left and increase in slope of the CO_2 response curve.

Perhaps the most plausible explanation for the recovery phenomenon would be a change in chemical or hormonal levels of substances known to stimulate ventilation. For example, norepinephrine stimulates ventilation.[12] As previously reported, urinary catecholamine excretion during halothane anesthesia was not significantly different from control values in these volunteers, but there was a sudden increase in plasma corticosteroids after two to five hours of anesthesia.[13] Although their effect has not been studied specifically with respect to ventilation, corticosteroids do have a "permissive" effect on all the many actions of norepinephrine which have been studied.[14] It is possible, therefore, that ventilation increased because of an increased effect of norepinephrine due to a permissive action of the increased level of corticosteroids. It has also been speculated that one of the metabolites of halothane might be responsible for the circulatory recovery seen during halothane anesthesia.[2] What the metabolite might be and its site of action are unknown.

References

1. Bellville W, Seed JC: The effect of drugs on the respiratory response to carbon dioxide. ANESTHESIOLOGY 21:727–741, 1960
2. Munson ES, Larson CP Jr, Babad AA, *et al.*: The effect of halothane, fluroxene and cyclopropane on ventilation: A comparative study in man. ANESTHESIOLOGY 27:716–728, 1966
3. Eger EI II, Smith NT, Stoelting RK, *et al.*: Cardiovascular effects of halothane in man. ANESTHESIOLOGY 32:396–409, 1970
4. Severinghaus JW: Continuously recording ventimeter. ANESTHESIOLOGY 23:582, 1962
5. Snedecor GW, Cochran WG: Statistical Methods. Sixth edition. Ames, Iowa, State University Press, Iowa, 1967, pp 91, 135
6. Seed JC, Wallenstein SL, Haude RW, *et al.*: A comparison of the analgesic and respiratory effects of hydrocodeine and morphine in man. Arch Int Pharmacodyn 116:293–339, 1958
7. Eger EI II, Saidman LJ, Brandstater B: Minimum alveolar anesthetic concentration: A standard of anesthetic potency. ANESTHESIOLOGY 26:756–763, 1965
8. Munson ES, Martucci RW, Smith RE: Circadian variations in anesthetic requirement and toxicity in rats. ANESTHESIOLOGY 32: 507–514, 1970
9. Fencl V, Vale JR, Broch JA: Respiration and cerebral blood flow in metabolic acidosis and alkalosis in humans. J Appl Physiol 27:67–76, 1969

10. Lloyd BB, Jukes MGM, Cunningham DJC: The relation between alveolar oxygen pressure and the respiratory response to carbon dioxide in man. Quart J Exp. Physiol 43: 214–227, 1958
11. Cunningham DJC, O'Riordan JLH: The effect of a rise in the temperature of the body on the respiratory response to carbon dioxide. Quart J Exp Physiol 42:329–345, 1957
12. Cunningham DJC, Hey EN, Patrick JM, *et al.*: The effect of noradrenaline infusion on the relation between pulmonary ventilation and the alveolar P_{O_2} and P_{CO_2} in man. Ann NY Acad Sci 109:2, 756–771, 1963
13. Von Werder K, Stevens WC, Cromwell TH, *et al.*: Adrenal function during long-term anesthesia in man. Proc Soc Exp Biol Med 135:854–858, 1970
14. Ramey ER, Goldstein MS: The adrenal cortex and the sympathetic nervous system. Physiol Rev 37:155–195, 1957

Respiration

LEFT VENTRICULAR FUNCTION IN CHRONIC OBSTRUCTIVE LUNG DISEASE Left ventricular function was studied during cardiac catheterization of 15 patients hospitalized for chronic obstructive lung disease. No patient had clinical, electrocardiographic or radiographic evidence of left ventricular disease. Performance of the left ventricle was assessed during cardiac catheterization either by a transseptal approach or by a retrograde technique from a peripheral artery. Abnormal left ventricular function was considered present when at least two of the following criteria were met: left ventricular end-diastolic pressure higher than 12 mm Hg; abnormal LV function curve (plot of stroke volume index *vs.* end-diastolic pressure during graded infusion of angiotensin); increased LV wall thickness or chamber size (ventriculography); impairment of the rate of change of area during systole as compared with normal disappearance of contrast material from the ventricle. Of ten patients with hypercapnia, seven had RV failure (Pa_{CO_2} 56 ± 8 torr). No patient had a hematocrit above 52 per cent. The mean forced expiratory volume in one second ($FEV_{1.0}$) was 0.64 liter. Although Pa_{O_2} was lower in patients with right-sided failure than those without, the difference was not statistically significant. Ventricular function curves were abnormal in 14 of 15 patients. Other abnormalities included increased LV wall thickness and impaired LV performance. LV end-diastolic pressure (LVED) showed a significant correlation with Pa_{CO_2}, *i.e.*, patients with the highest Pa_{CO_2}'s had the highest LVED's. Only two of ten patients had definite evidence of coronary-artery narrowing on coronary angiography. (*Baum, G. L., and others: Left Ventricular Function in Chronic Obstructive Lung Disease, New Eng. J. Med. 285: 361, 1971.*) EDITOR'S COMMENT: The presence of left ventricular failure must always be suspected in a patient with chronic obstructive lung disease admitted to the hospital in acute respiratory failure. It should cause us to temper our enthusiasm for "adequate hydration with intravenous fluids" when the classic clinical signs of overt congestive heart failure are absent.