

The Effects of Ether, Halothane, and Forane* on Apneic Thresholds in Man

Robert F. Hickey, M.D.,† Henry E. Fourcade, M.D.,† Edmond I. Eger, II, M.D.,‡
C. Philip Larson, Jr., M.D.,§ Steven H. Bahlman, M.D.,¶ Wendell C. Stevens, M.D.,‡
George A. Gregory, M.D.,† Norman Ty Smith, M.D.**

Apneic thresholds in man anesthetized with diethyl ether, halothane, and Forane were compared. Assisted ventilation to apnea lowered P_{aCO_2} by an average of 4.6 torr from P_{aCO_2} during spontaneous respiration. There was no difference between anesthetics or depths of anesthesia in the reduction of P_{aCO_2} needed to achieve apnea. Apneic thresholds were lower in subjects anesthetized with ether than in those anesthetized with halothane or Forane because P_{aCO_2} with spontaneous respiration was lower with ether than with either of the other two anesthetics. During ether anesthesia apneic threshold did not change significantly as end-tidal ether concentration was increased from 3.0 to 6.0 per cent. During halothane anesthesia apneic threshold and P_{aCO_2} during spontaneous ventilation increased by 9 torr as end-tidal halothane increased from 1.0 to 1.5 per cent. We conclude from these results that: 1) assisted ventilation can produce only a minor reduction in P_{aCO_2} ; 2) ether does not stimulate respiration independent of CO_2 . (Key words: Apneic thresholds; Ether; Halothane; Forane; Respiration; Carbon dioxide.)

GENERAL ANESTHETICS usually depress respiration, as evidenced by an increase in P_{aCO_2} and

a decrease in ventilatory response to inhaled CO_2 .¹ Diethyl ether is unique in that normal to slightly below-normal P_{aCO_2} values are maintained during light to moderately deep levels of ether anesthesia even though the ventilatory response to inhaled CO_2 is depressed at these anesthetic levels.² The effect of ether is not exerted at the lung, as evidenced by its persistence after vagotomy.³ Similarly, respiratory stimulation by ether is not peripheral, since high spinal anesthesia with or without vagotomy and carotid-body denervation fails to abolish it.³ Ether, then, must act within the central nervous system either to stimulate ventilation by some mechanism not related to CO_2 while depressing the ventilatory response to CO_2 or to maintain a near-normal ventilatory response to normal levels of CO_2 , but decrease the ventilatory response to increased levels of CO_2 . Either of these hypotheses suggests that as P_{aCO_2} is decreased below normal, there should be less depression of ventilation in humans anesthetized with ether compared with other anesthetics. That is, if ether itself stimulates ventilation, then during ether anesthesia, ventilation may be maintained despite a decrease in P_{aCO_2} . To test this hypothesis, we determined apneic thresholds for ether, halothane, and a new agent, Forane. Although apneic thresholds for some anesthetics have been reported, most studies have failed to measure P_{aCO_2} or the alveolar or arterial anesthetic partial pressure.^{2,4,5} In addition, no studies compare apneic thresholds to ventilatory responses to increased CO_2 in the same subjects. And finally, no study has examined the effect of duration of anesthesia on apneic thresholds. This report supplies these data.

* Trademark, Ohio Medical Products, Division of Air Reduction Company, Inc.

† Assistant Professor, University of California.

‡ Professor of Anesthesia, University of California.

§ Associate Professor of Anesthesia, University of California.

¶ Research Trainee and Resident in Anesthesia, University of California.

** Assistant Professor of Anesthesia, Stanford University School of Medicine.

Received from the Department of Anesthesia, University of California, San Francisco, California, and the Stanford University School of Medicine, Stanford, California. Accepted for publication March 10, 1971. Supported by Program Project Grant 1P01 GM 15571-02, Training Grant 5T1 GM 00063-12, Smith Career Development Award NIH GM 31757-05, and Ohio Medical Products.

Methods

Volunteers were accepted for study when medical history, physical examination, and laboratory evaluation indicated good health and no contraindications to general anesthesia. Laboratory evaluation consisted of roentgenogram of the chest, electrocardiogram, complete blood count, and urinalysis. Informed consent was obtained. Protocol and consent forms were approved by the human experimentation committees at the University of California and Stanford University. Subjects ranged in age from 22 to 26 years.

STUDIES WITH ETHER ANESTHESIA

We determined resting P_{aCO_2} values, ventilatory responses to increased CO_2 , and apneic thresholds in five volunteer subjects anesthetized at alveolar ether concentrations of 3.0 and 4.5 per cent. In addition, resting P_{aCO_2} and apneic threshold were determined at 6 per cent ether and resting P_{aCO_2} and ventilatory responses to increased CO_2 were determined while the subjects were awake.

On the morning of the study we inserted a plastic catheter into a radial artery and determined ventilation at four levels of P_{aCO_2} . Each subject breathed oxygen through a mouthpiece from a conventional anesthetic circle system with a CO_2 absorber which could be partially bypassed. P_{aCO_2} was measured continuously from the mouthpiece with a Beckman LB-1 microcatheter sampling cell and ventilation was measured with a recording ventilometer.⁸ End-tidal CO_2 was adjusted stepwise and held constant for a minimum of six minutes to allow for equilibration within the brain. After six minutes and when steady-state ventilation had been obtained, arterial blood was sampled for measurement of P_{aCO_2} , pH, and PaO_2 , using the appropriate electrodes. All values were corrected to the subject's body temperature. Body temperature was maintained between 36.4 and 37.5 C by adjustment of the room temperature.

Anesthesia with cyclopropane in oxygen was induced by mask and the trachea was intubated without muscle relaxants. Cyclopro-

pane was then discontinued and anesthesia maintained with ether in oxygen at total flow rates into the circle system in excess of 5 l/min. End-expired ether was measured with a Beckman LB-1 infrared ether analyzer, calibrated as previously described.⁷ Measurements were made after end-tidal ether concentrations had been stable for at least 15 minutes.

Apneic thresholds were determined by controlling ventilation to decrease P_{aCO_2} by the minimum amount necessary to maintain apnea when controlled ventilation was discontinued. All P_{aCO_2} values were maintained constant for a minimum of six minutes and arterial blood sampled immediately prior to stopping mechanical ventilation. P_{aCO_2} values at the apneic threshold were defined by two criteria: 1) when apnea persisted for at least six seconds but spontaneous ventilation returned by 20 seconds, the P_{aCO_2} obtained before stopping mechanical ventilation was considered to be the apneic threshold; or 2) when two P_{aCO_2} values were obtained no more than two torr apart, one at which spontaneous ventilation was maintained and the other producing apnea, then these P_{aCO_2} values were averaged and this value considered the apneic threshold.

STUDIES WITH HALOTHANE AND FORANE ANESTHESIA

The protocol used for ether studies was followed for halothane and Forane studies, with the following differences. Eight subjects were anesthetized with halothane and ten with Forane. Anesthesia was induced with the agent to be studied after determination of the ventilatory responses to inhaled CO_2 . In the halothane studies, apneic thresholds were determined at 1.0 per cent end-tidal halothane two to three and six hours after induction of anesthesia and at 1.5 per cent (seven subjects) five hours after induction. Ventilatory responses to increased CO_2 were also determined at these levels; the major details of this portion of the study are reported elsewhere.⁸ In the Forane studies, apneic thresholds and ventilatory responses to inhaled CO_2 were obtained at an end-tidal concentration of 1.30

Table 1. Ventilatory Responses to Increased and Decreased CO_2 in Subjects Awake and Anesthetized*

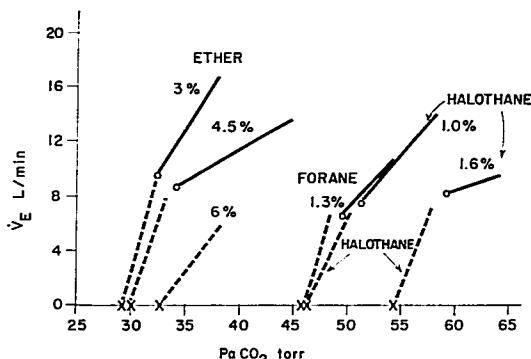
End-tidal Anesthetic Concentration (Per Cent)	Time Post-Induction (Hours)	\dot{V}_E (l/Min)	P_{aCO_2} (Torr)	P_{aCO_2} at Apnea (Torr)	ΔP_{aCO_2} (Torr)	CO_2 Response (l/Min/Torr)	Apneic Threshold Slope (l/Min/Torr)	Inne Excess (ml/kg/l)
Ether								
0 (awake)	—	6.1 ± 0.26	37.6 ± 0.4	—	—	2.00 ± 0.21	—	-0.9 ± 0.2
2.05 ± 0.10	5-6	9.5 ± 0.33	32.4 ± 0.7	29.4 ± 1.00	3.0 ± 0.3	1.29 ± 0.47	2.06 ± 0.32	-3.9 ± 1.0
4.51 ± 0.12	3-4	8.6 ± 1.5	34.2 ± 2.2	29.8 ± 2.6	4.4 ± 1.0	0.47 ± 0.17	2.18 ± 0.52	-3.3 ± 0.4
5.05 ± 0.10	1.0	7.3 ± 1.4	38.2 ± 2.7	32.7 ± 4.1	5.5 ± 1.0	—	1.06 ± 0.23	-3.5 ± 0.7
Halothane								
0 (awake)	—	7.4 ± 0.5	36.3 ± 1.2	—	—	2.69 ± 0.40	—	-1.0 ± 0.3
1.02 ± 0.02	2-3	7.3 ± 0.6	51.4 ± 1.4	46.1 ± 1.2	5.3 ± 0.7	0.99 ± 0.13	1.71 ± 0.38	-3.4 ± 0.7
1.1 ± 0.02	6	9.1 ± 1.0	48.0 ± 1.0	44.0 ± 1.2	4.2 ± 0.9	1.18 ± 0.16	3.02 ± 0.53	-3.3 ± 0.5
1.50 ± 0.02	5	8.1 ± 0.6	50.1 ± 2.1	54.4 ± 2.7	4.6 ± 0.8	0.27 ± 0.01	2.17 ± 0.47	-4.1 ± 0.8
Forane								
0 (awake)	—	7.0 ± 0.3	38.9 ± 0.8	—	—	2.00 ± 0.22	—	-0.6 ± 0.42
1.20 ± 0.10	2	6.4 ± 0.4	40.5 ± 1.7	46.1 ± 1.4	3.4 ± 2.2	0.83 ± 0.39	3.07 ± 0.43	-1.44 ± 0.60

* ΔP_{aCO_2} is the difference between resting P_{aCO_2} and P_{aCO_2} at apneic threshold. CO_2 response is the slope of the ventilatory response to CO_2 . Apneic threshold slope is the change in ventilation from apnea to spontaneous ventilation ($P_{\text{aCO}_2} = 0$) divided by ΔP_{aCO_2} .

† Significant difference from value at lightest level of anesthesia.

‡ Significant difference from value at 3 per cent ether.

FIG. 1. Ventilatory responses to increased carbon dioxide and apneic thresholds during ether, Forane and halothane anesthesia. X = apneic threshold; circle = resting ventilation; solid line = CO_2 response slope; dashed line = apneic threshold slope.



per cent. Both Forane and halothane were analyzed with an infrared halothane analyzer calibrated as previously described.⁷ Concomitant analysis of arterial blood samples confirmed the accuracy of the end-tidal infra-red analysis.

Regression lines for the ventilatory responses to CO_2 were determined for each subject by the method of least squares. The slopes thus obtained were averaged and compared. Statistical analysis was performed using the paired or unpaired *t* test as indicated. We accepted $P < 0.05$ as significant.

Results

Data obtained are shown in table 1 and figure 1. There were no significant differences between the awake values for subjects anesthetized with ether, halothane, and Forane. During anesthesia the average Pa_{CO_2} always exceeded 400 torr.

ETHER DATA

As reported by Larson *et al.*,² mean Pa_{CO_2} during spontaneous ventilation when inspired CO_2 equaled zero ($\text{P}_{\text{I}\text{CO}_2} = 0$) was significantly lower at 3 per cent ether than in the awake state. At 4.5 and 6.0 per cent ether resting mean Pa_{CO_2} was no different from awake Pa_{CO_2} . There was no significant difference between the values of apneic thresholds at 3.0, 4.5 and 6.0 per cent ether. The dif-

ference between the resting Pa_{CO_2} and the Pa_{CO_2} at the apneic threshold ($\Delta\text{Pa}_{\text{CO}_2}$) increased significantly between 3.0 and 6.0 per cent ether because of the increase in resting Pa_{CO_2} . This caused a decrease in apneic threshold slope (change in ventilation from apnea to spontaneous ventilation [$\text{P}_{\text{I}\text{CO}_2} = 0$] divided by $\Delta\text{Pa}_{\text{CO}_2}$). Note that the average slope value given in table 1 exceeds that obtained by dividing average \dot{V}_E by average $\Delta\text{Pa}_{\text{CO}_2}$. This results from weighting by individual high slope values. The responses of all subjects to inspired CO_2 decreased as anesthetic concentration was increased. Slopes of the CO_2 response curves at 3.0 and 4.5 per cent ether were significantly smaller than the apneic threshold slope.

HALOTHANE DATA

As reported previously,² we found that Pa_{CO_2} during spontaneous ventilation ($\text{P}_{\text{I}\text{CO}_2} = 0$) increased significantly with increasing depth of halothane anesthesia (1.5 value < 1.0 value > awake value). At 1.0 per cent halothane the resting Pa_{CO_2} values were significantly lower at six hours than at two hours. Pa_{CO_2} at apnea also was directly related to depth of anesthesia. $\Delta\text{Pa}_{\text{CO}_2}$ showed no change with depth of anesthesia, nor was there a significant change with duration of anesthesia. The apneic threshold slope did not vary with depth of anesthesia, but tended to increase

with duration of anesthesia. However, the change was not significant. All subjects had decreased ventilatory responses to CO_2 as anesthetic concentrations were increased. The slopes of the CO_2 response curves at 1.0 and 1.5 per cent end-tidal halothane were again significantly smaller than the apneic threshold slope.

FORANE DATA

As determined previously (Fourcade *et al.*⁸), Forane increased PaCO_2 and depressed the ventilatory response to CO_2 . In addition, the apneic threshold PaCO_2 values were significantly greater than the normal resting awake PaCO_2 's. The slopes of the CO_2 response curves were significantly smaller than the apneic threshold slope.

INTRA-ANESTHETIC COMPARISON

The lightest levels of halothane and Forane anesthesia produced higher apneic thresholds and resting PaCO_2 values than did ether. Still greater differences were revealed by a comparison of moderate depths of halothane anesthesia (1.5 per cent) with either moderate or deep levels of ether anesthesia. Apneic thresholds and ΔCO_2 values were significantly less at 3.0 per cent ether than at 1.0 per cent halothane. No other differences between either ΔCO_2 or apneic threshold slopes were found among the three anesthetics.

Discussion

Our study failed to demonstrate that ether stimulates respiration independent of CO_2 . Apnea always occurred when CO_2 was lowered and, furthermore, the reduction in CO_2 needed to produce apnea (ΔPaCO_2) during ether anesthesia was similar to that found by Bainton in studies in awake men.¹⁰ Similarly, ΔPaCO_2 with ether was either less than (3.0 per cent ether) or similar to those found with halothane and Forane. Table 1 suggests that a portion of the respiratory stimulation seen with ether may result from metabolic acidosis. However, an equal acidosis found during halothane anesthesia failed to protect against the respiratory depression produced by that anesthetic.

Our findings differ quantitatively from those

of other studies. In general, we found $\Delta\text{P}_{\text{CO}_2}$ smaller than reported by Larson or Fink.^{1,5} In addition, in our study $\Delta\text{P}_{\text{CO}_2}$ did not change with increasing depth of halothane anesthesia, whereas Larson and Fink reported an increase in $\Delta\text{P}_{\text{CO}_2}$ with increasing concentration of halothane.¹⁻⁵ Differences between our results and those reported by others could be attributed to different conditions of measurement. Previous studies did not measure end-tidal anesthetic concentration and measured end-tidal (rather than arterial) CO_2 , or measured arterial pH and calculated PaCO_2 .

Another of our observations remains unexplained. We found a discontinuity in ventilatory responses to increased CO_2 vs. apneic threshold slope. The magnitude of this discontinuity for each of the three agents is shown in figure 1. At light levels of ether, halothane, and Forane anesthesia, the slopes of the ventilatory responses to imposed increased CO_2 were 41, 24, and 27 per cent, respectively, of apneic threshold slopes. This discontinuity was related to depth of anesthesia; at deeper levels the percentages for ether and halothane were further reduced. (No studies were done at deeper levels of Forane anesthesia.) This contrasts with the awake state, in which apneic threshold slopes and slopes of the ventilatory responses to increased CO_2 do not differ.¹⁰ Another way of stating our finding is that the ventilatory response to inhaled CO_2 decreased with deepening anesthesia, whereas the response to reduced PaCO_2 remained constant. These data suggest that CO_2 may act in two ways: 1) to stimulate ventilation with increased CO_2 ; and 2) to inhibit ventilation by reduction in CO_2 . The first action is depressed by anesthesia, while the second remains unaffected. This second point, inhibition by decreased CO_2 , implies an active process, not merely the absences of stimulation. There is evidence for this suggestion: for example, Mitchell *et al.* have shown that despite the ventilatory stimulus of hypoxia, a sufficient reduction in CO_2 will produce apnea.¹¹

With all anesthetics studied, and at all depths, $\Delta\text{P}_{\text{CO}_2}$ averaged 4.6 torr. This finding implies that assisted ventilation is of limited value in lowering PaCO_2 . To lower PaCO_2 significantly, ventilation must be controlled.

The authors are indebted to Miss Dianne M. K. Impelman, Mrs. Anne White, and Mr. Richard Shargel for their assistance. Halothane (Fluothane) for this study was donated by Ayerst Laboratories, and Forane (compound 469) was provided by Ohio Medical Products.

References

1. Severinghaus JW, Larson CP Jr: Respiration in anesthesia, *Handbook of Physiology*. Volume II, Respiration. Baltimore, Williams and Wilkins, 1965, pp. 1219
2. Larson CP, Jr, Eger EI II, Muallem M, *et al.*: The effects of diethyl ether and methoxyflurane on ventilation. *ANESTHESIOLOGY* 30: 174-184, 1969
3. Muallem M, Larson CP Jr, Eger EI II: The effects of diethyl ether on P_{aCO_2} in dogs with and without vagal, somatic and sympathetic block. *ANESTHESIOLOGY* 30:185-191, 1969
4. Hanks, EC, Ngai SH, Fink BR: Respiratory threshold for carbon dioxide in anesthetized man. *ANESTHESIOLOGY* 22:393-397, 1961
5. Fink RB, Ngai SH, Hanks EC: The central regulation of respiration during halothane anesthesia. *ANESTHESIOLOGY* 23:200-206, 1962
6. Severinghaus JW: Continuously recording ventilometer. *ANESTHESIOLOGY* 23:582-583, 1962
7. Munson ES, Saidman LJ, Eger EI II: Solubility of fluorene in blood and tissue homogenates. *ANESTHESIOLOGY* 25:638-640, 1964
8. Fourcade HE, Stevens WC, Larson CP Jr, *et al.*: The ventilatory effects of Forane, a new inhaled anesthetic. *ANESTHESIOLOGY* 35:26-31, 1971
9. Munson ES, Larson CP Jr, Babad AA, *et al.*: The effects of halothane, fluorene and cyclopropane on ventilation: A comparative study in man. *ANESTHESIOLOGY* 27:716-728, 1966
10. Bainton CR, Mitchell RA: Posthyperventilation apnea in awake man. *J Appl Physiol* 21:411-415, 1966
11. Mitchell RA, Bainton CR, Edelist G: Posthyperventilation apnea in awake dogs during metabolic acidosis and hypoxia. *J Appl Physiol* 21:1363-1367, 1966

Drugs

METHOXYFLURANE AND RENAL FAILURE Methoxyflurane has been implicated in postoperative polyuric renal failure. Seven patients subjected to radical surgical operations under methoxyflurane anesthesia developed renal failure. A striking degree of renal tubular oxalate precipitation was found by renal biopsy in all seven patients, and methoxyflurane was implicated as a cause of secondary hyperoxaluria and intrarenal oxalate precipitation when renal function was compromised during or immediately following operation. Strict attention to postoperative fluid balances in all patients receiving methoxyflurane is important to prevent or minimize oxalate precipitation in the kidneys. (Fraschino, J. A., *et al.*: *Renal Oxalosis and Azotemia after Methoxyflurane Anesthesia*, *New Engl. J. Med.* 283: 676 (Sept.) 1970.) EDITOR'S COMMENT: What about the indications for use of methoxyflurane?

BETA-ADRENERGIC BLOCKADE AND ATRIAL ARRHYTHMIAS Alprenolol (Aptine), a new beta-adrenergic blocking agent, was administered intravenously on 25 occasions to 23 patients with atrial arrhythmias. Significant slowing of ventricular rates was achieved in 20 patients by decreasing atrioventricular conduction in those with atrial fibrillation and flutter and by slowing the rate of ectopic impulse formation in those with paroxysmal supraventricular tachycardia. In four patients the latter arrhythmia reverted to sinus rhythm following administration of alprenolol. In four patients with atrial fibrillation the chronotropic effect of isoproterenol was substantially abolished after treatment with alprenolol. Alprenolol appears to be a safe, effective beta-adrenergic blocking agent in the treatment of atrial arrhythmias. (Kerber, R. E., *et al.*: *Treatment of Atrial Arrhythmias with Alprenolol*, *J.A.M.A.* 214: 1849 (Dec.) 1970.)