The Effects of Diethyl Ether and Methoxyflurane on Ventilation:

II. A Comparative Study in Man

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We measured the effects of diethyl ether and methoxyflurane on resting spontaneous ventilation and ventilatory response to CO_2 in healthy unpremedicated human subjects and compared the results with those we previously reported for patients anesthetized with halothane, fluroxene and cyclopropane. Comparisons were made at equipotent anesthetic concentrations and equal multiples of these concentrations using the MAC concept. With all five agents, ventilatory response to CO_2 progressively decreased with increasing anesthetic depth. Mean Pa_{CO_2} values remained at or below the conscious value to relatively deep levels of ether anesthesia (2.9 MAC), whereas mean Pa_{CO_2} values increased early and rapidly with methoxyflurane anesthesia. We conclude that at equipotent anesthetic concentrations and equal multiples of equipotent concentrations, halothane and methoxyflurane produce the greatest, and diethyl ether the least, depression of ventilation.

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DIETHYL ETHER is generally regarded as a ventilatory stimulant. At light-to-moderate surgical levels of ether anesthesia in unpremedicated man, alveolar ventilation is usually either increased, as evidenced by a reduction in arterial carbon dioxide partial pressure (Pa_{CO_2}) below the conscious value, or at least maintained at the conscious value.[1] However, this conclusion is not uniformly supported by results of studies of ventilatory response to inhaled CO_2. Both a displacement in ventilatory response slope to the left,[2] indicating respiratory stimulation, and a decrease in slope, indicating respiratory depression, have been reported in man [3] and animals [4-5] during ether anesthesia.

Review of ventilatory studies during methoxyflurane anesthesia yields equally variable results. Tidal volume and minute ventilation are usually reduced during methoxyflurane anesthesia in both man [6, 7, 8] and dog.[8, 9] In man, these reductions in ventilation may [10, 11] or may not [12, 13] be associated with appreciable increases in Pa_{CO_2}. Hypercarbia and respiratory acidosis are usually observed in dogs anesthetized with methoxyflurane while breathing spontaneously.[8, 9] Ventilatory response to CO_2 is depressed in decerebrate cats breathing 0.5 to 1.0 per cent methoxyflurane.[14] Despite the absence of conclusive evidence of depression of alveolar ventilation in man, most,[6, 8, 15] but not all,[13] investigators advocate assisted or controlled ventilation during methoxyflurane anesthesia.

Possible explanations for the striking differences in ventilation and blood gas values obtained by various investigators have been considered by Munson *et al.*[16] These include: (1)) partial pressure of anesthetic, unknown

or unstable; (2) variable sensory input; (3) ventilatory adequacy based on determinations of $P_{A_{CO_2}}$ in the presence of an inconstant and unknown arterial–alveolar difference; and (4) variable mechanical deadspace and air-flow resistances of test apparatus. Minimizing these factors, we determined the effects of diethyl ether anesthesia on ventilation in eight patients and the effects of methoxyflurance anesthesia on ventilation in six patients, and compared these results with those previously obtained for halothane, fluroxene and cyclopropane.[16] Anesthetic effects on ventilation were compared at equipotent anesthetic doses and multiples of equipotent doses using the minimum (alveolar) anesthetic concentration (MAC) as the standard of equipotency.

Method

$P_{a_{CO_2}}$ and ventilatory responsiveness to inhaled carbon dioxide were determined awake and anesthetized in 14 healthy, unpremedicated patients before operation. The patients' ages ranged from 19 to 43 years (table 1). Each patient was informed of all investigative procedures involved and consent was obtained prior to study. The equipment and protocol were essentially identical to those used by Munson.[16] Briefly, on the morning of surgery, the patient was brought to a quiet, dimly-lit operating room and the ventilatory response to a CO_2 challenge was determined during oxygen breathing from a mouthpiece connected to a modified, low-resistance anesthetic apparatus. Carbon dioxide was added stepwise to the system and ventilation was measured at five to seven levels of $P_{A_{CO_2}}$. The total increase in $P_{A_{CO_2}}$ was at least 10 mm Hg above the resting value. The slope of the response in l/min/mm Hg was calculated by the method of least squares. At each level, $P_{A_{CO_2}}$ was held constant for an interval of at least six minutes to allow for CO_2 equilibration between alveoli and brain. In each instance, ventilation was stable at the time of measurement. Ventilation was recorded with a modified recording ventimeter and $P_{A_{CO_2}}$ with a Beckman LB-1 microcatheter sample cell infrared analyzer sampling from the mouthpiece.

Anesthesia was then induced in all patients with cyclopropane–oxygen, and following succinylcholine, 40 to 100 mg intravenously, a 36 or 38 French, cuffed orotracheal catheter was inserted. Prior to intubation, the larynx was anesthetized either with a topical spray or with a bilateral superior laryngeal nerve block, using 4 ml of 2 per cent lidocaine. Cyclopropane was discontinued and anesthesia maintained with diethyl ether–oxygen in eight patients and methoxyflurane–oxygen in six patients. Total gas inflow exceeded 3 l/min for at least 30 minutes to eliminate cyclopropane from the patient and system. Thereafter, inflow was maintained at 1 to 1.5 l/min. Alveolar anesthetic concentration was determined at two- or three-minute intervals by sampling end-expired gas through a nylon catheter passed to the tracheal end of the orotracheal tube. To obtain adequate samples of alveolar gas during shallow breathing, the airway above the sampling catheter was occluded at end-expiration and continuous suction applied to the sampling catheter for three to five seconds. Methoxyflurane was analyzed with a Beckman LB-1 infrared halothane analyzer and diethyl ether with the corresponding ether analyzer. The analyzer heads were filled with carbon dioxide and calibration curves prepared

TABLE 1. Physical Characteristics of the Patients Studied during Diethyl Ether or Methoxyflurane Anesthesia

Diethyl Ether

Patient	Age	Sex	Height (cm)	Weight (kg)
1	30	M	175	62.2
2	31	M	165	55.5
3	23	F	165	67.2
4	19	M	183	72.7
5	20	M	185	72.7
6	25	M	170	59.1
7	20	M	190	88.7
8	21	M	185	80.2

Methoxyflurane

Patient	Age	Sex	Height (cm)	Weight (kg)
9	23	M	178	76.5
10	20	M	158	63.7
11	43	M	178	84.0
12	29	M	178	89.2
13	29	M	180	63.7
14	39	M	171	74.2

as previously described.[17] They were intermittently calibrated with standards from pressurized tanks. Analysis was performed at ambient pressure and zero flow through the analyzer. $P_{A_{CO_2}}$ was continuously monitored from a 25-ml extension tube inserted between the orotracheal tube and the Y piece of the circle. Esophageal temperature, monitored in each patient, was held between 35 and 37.5 C.

Effects of diethyl ether or methoxyflurane on ventilation were compared at constant and equivalent depths of anesthesia using the concept of minimum (alveolar) anesthetic concentration (MAC). MAC in man for ether is 1.92 per cent; for methoxyflurane, 0.16 per cent.[18] A constant alveolar anesthetic concentration was established and held for a minimum of 15 minutes before resting ventilation and Pa_{CO_2} were measured. Ventilatory response to CO_2 was then determined at three or more alveolar CO_2 concentrations. In each instance, the arterial blood sample was drawn and ventilation measured during the sixth minute of constant $P_{A_{CO_2}}$ and ventilation. This procedure was then repeated at random multiples of MAC ranging from 1.14 to 3.39 for ether (2.2 to 6.5 per cent alveolar ether) or from 0.89 to 2.42 for methoxyflurane (0.14 to 0.42 per cent alveolar methoxyflurane). Time from the start of anesthesia to the first set of ventilatory determinations was 50 to 60 minutes in the ether-anesthetized patients and 70 to 90 minutes in the methoxyflurane-anesthetized patients. For both agents, the interval between determinations ranged from 30 to 60 minutes as anesthetic concentrations were increasing and from 15 to 25 minutes as anesthetic concentrations were decreasing.

The MAC concept assumes that anesthetic partial pressures in alveolar gas, arterial blood and brain tissue are in equilibrium, and that a steady state exists. However, with soluble anesthetics, a problem arises in obtaining alveolar gas samples which accurately reflect the partial pressure of anesthetic in arterial blood.[19] To determine whether effective alveolar gas (alveolar gas in communication with pulmonary capillary blood) was being contaminated by gas (airway or alveolar) not in communication with pulmonary capillary blood, we monitored inspired–end-tidal anesthetic partial pressure difference.[18] To minimize this difference, we administered high inspired anesthetic concentrations; that it, 20 to 30 per cent ether and 3 per cent methoxyflurane, before the first set of ventilatory determinations and in the intervals preceding measurements at higher multiples of MAC. In addition, we gave four patients, anesthetized with ether, additional ether by intravenous infusion (5 volumes per cent in 5 per cent dextrose in water) in a quantity sufficient to eliminate the inspired–end-tidal difference.

We maintained an unvarying alveolar anesthetic concentration at each MAC level for an interval calculated to be necessary to establish equilibrium between alveolar gas and cerebral tissue.[16] Assuming a brain–blood partition coefficient for ether of 1.1,[20, 21] and for methoxyflurane of 1.7,[21, 22] and a cerebral blood flow of 44 ml/100 g brain/min,[23] equilibrium of the brain with a given alveolar anesthetic partial pressure can be considered virtually complete after ten minutes with ether and after 12 minutes with methoxyflurane.

Pa_{CO_2} and *p*H were determined with a Severinghaus CO_2 electrode and Radiometer *p*H electrode. Arterial partial pressure of oxygen (Pa_{O_2}) was determined with a modified Clark oxygen electrode. All blood gas values were corrected to the patient's esophageal temperature and a calculation of base excess made with the Severinghaus slide rule.[24] Pa_{O_2} values ranged from 92 to 561 mm Hg (mean = 418 mm Hg), excluding the possibility that any of the ventilatory responses obtained were the results of hypoxemia. Paired analysis of data was performed using Student's *t* test. Unless otherwise stated, significant differences are reported at the 5 per cent level ($P < 0.05$).

Results

All ventilation data obtained are listed in table 2.

Pa_{CO_2}

In patients anesthetized with ether and breathing spontaneously, resting Pa_{CO_2} remained essentially unchanged from the awake alveolar value to an alveolar ether concentration of 5.6 per cent (2.9 MAC) (fig. 1). Above this ether concentration, Pa_{CO_2} rose rapidly. No significant difference was found when Pa_{CO_2} values at 1.3 to 2.9 MAC were

TABLE 2. Effects on Ventilation of Anesthesia with Diethyl Ether or Methoxyflurane

Diethyl Ether

Patient	Alveolar Anesthetic Concentration (volumes per cent)	Inspired Anesthetic Concentration (volumes per cent)	f	$\dot{V}_E$ (l/min)	P_{CO_2}	pH	S	Fraction Conscious S	Base Excess (mEq/l)
1	conscious		9.5	5,420	37	—	1.06	1.0	—
2	conscious		18	4,950	33.1	—	1.30	1.0	—
3	conscious		14	4,850	34	—	2.28	1.0	—
4	conscious		12	8,240	34.6	—	1.85	1.0	—
5	conscious		13	4,130	38	—	1.73	1.0	—
6	conscious		11	4,070	32.3	—	1.21	1.0	—
7	conscious		11	6,700	36.3	—	0.76	1.0	—
8	conscious		12.5	7,090	39.6	—	1.24	1.0	—
Mean			12.6		35.6		1.43	1.0	
± S.D.			2.6		2.5		0.43		
1†	2.2	2.3	20	7,000	38.4	7.42	1.37	1.29	0
2	2.5	3.6	18	5,660	38	7.39	0.54	0.42	−3
3	2.1	2.4	20	4,420	37.6	7.38	1.44	0.63	−2
4	2.3	2.8	21	10,000	43	7.35	1.03	0.56	−3
5	2.3	2.8	18	6,700	41.2	7.39	0.63	0.36	0
6†	2.3	2.7	17.5	4,290	36.2	7.42	1.13	0.93	0
7†	2.5	2.1	32.5	11,390	31.6	7.41	—	—	−4
8†	2.8	3.4	17.5	6,900	33.7	7.43	—	—	−1.6
Mean	2.4	2.8	20.6		37.5		1.02	0.70	−1.7
± S.D.	0.2	0.5	5.0		3.7		0.37	0.35	1.6
2	3.4	—	26.5	8,350	34	7.44	—	—	−1
4	3.4	3.5	30.5	14,100	42.2	7.34	0.88	0.48	−2
5	3.3	3.5	23.5	8,700	39.8	7.34	—	—	−2
7	3.2	3.8	40	16,400	33.1	7.39	—	—	−4
8	3.8	4.0	22	9,800	32.0	7.40	0.79	0.64	−4
Mean	3.4	3.7	28.5		36.2		0.84	0.56	−2.6
± S.D.	0.2	0.2	7.2		4.5				±1.3
1	4.1	4.4	25	7,500	35.3	7.44	0.51	0.48	0
2	4.8	6.6	32	5,750	41	7.35	0.18	0.14	−2
3	4.5	5.7	25	8,560	31.1	7.43	0.67	0.29	−3
4	4.5	5.6	30	12,800	43.9	7.33	0.41	0.22	−3
5	4.8	6.1	26	7,900	46.2	7.34	0.50	0.29	−2
6	4.6	5.0	23.5	5,880	33.5	7.44	0.57	0.47	−2
7	4.5	4.6	44	7,080	44.9	7.32	0.32	0.42	−3.5
8	4.9	5.3	28	8,400	30.3	7.45	—	—	−1.6
Mean	4.6	5.4	29.2		38.3		0.45	0.33	−2.1
± S.D.	0.3	0.7	6.6		6.5		0.16	0.13	±1.1

* Conversion of alveolar anesthetic concentration to multiplies of the minimum anesthetic concentration (MAC) can be accomplished by division of the alveolar concentration by the appropriate MAC value (diethyl ether, 1.92; methoxyflurane, 0.16). Values represent alveolar determinations (P_{ACO_2}) during consciousness and arterial determinations (P_{aCO_2}) during anesthesia. S = slope of ventilatory responses to inhaled carbon dioxide in l/min/mm Hg P_{CO_2}. Fraction conscious S = anesthetic slope divided by conscious slope. Mean values and one standard deviation (± S.D.) given.

† Intravenous ether administered.

TABLE 2.—*Continued*

Diethyl Ether

Patient	Alveolar Anesthetic Concentration (volumes per cent)	Inspired Anesthetic Concentration (volumes per cent)	f	V_E (l/min)	P_{CO_2}	pH	S	Fraction Conscious S	Base Excess (mEq/l)
2	5.6	—	30	3,750	37	7.36	—	—	−4
3	5.8	8.0	23	5,520	34.3	7.41	—	—	−3
6	5.4	6.0	30	10,500	30.6	7.44	0.24	0.20	−2
7	5.2	5.2	50	8,000	50.8	7.16	—	—	−6
8	5.8	6.1	48	7,200	31.7	7.41	—	—	−3.3
Mean	5.6	6.3	36		36.9				−3.7
± S.D.	0.2	1.2	10		8.2				±1.5
1	6.1	6.7	46	6,900	40.9	7.39	0.23	0.21	0
4	6.5	—	37	5,900	59.8	7.19	—	—	−7
5	6.2	—	30	6,300	46.2	7.33	—	—	−2
7	6.2	6.6	57	3,430	74.3	7.15	—	—	−7
Mean	6.3		43		55.3				−4.0
± S.D.	0.2		12		14.9				±3.6

Methoxyflurane

Patient	Alveolar Anesthetic Concentration (volumes per cent)	Inspired Anesthetic Concentration (volumes per cent)	f	V_E (l/min)	P_{CO_2}	pH	S	Fraction Conscious S	Base Excess (mEq/l)
1	conscious		13	5,525	35.9	—	1.47	1.0	—
2	conscious		13	5,530	39.4	—	1.53	1.0	—
3	conscious		14	5,880	33.9	—	.92	1.0	—
4	conscious		18	7,200	37.5	—	1.94	1.0	—
5	conscious		16	6,315	36.6	—	1.27	1.0	—
6	conscious		14	4,550	36.1	—	1.29	1.0	—
Mean			14.5		36.5		1.40	1.0	
± S.D.			2.0		1.8		0.34		
1	0.14	0.16	18	5,840	44.5	7.33	—	—	−3.1
2	0.16	0.14	20	3,700	44.1	7.37	0.94	0.61	−0.3
3	0.20	0.27	24.5	7,350	41.2	7.40	—	—	+0.3
4	0.18	0.35	28	7,700	51.2	7.30	—	—	−1.9
5	0.16‡§	0.44‡	32‡	6,000‡	47.5‡	7.26‡	0.66	0.52	−6.0‡
6	0.18‡	0.27‡	16‡	5,200‡	46.1‡	7.38‡	0.61‡	0.47	+1.9‡
Mean	0.17	0.27	21.4		45.8		0.74	0.53	−1.5
± S.D.	0.02	0.11	4.4		3.4		0.19	0.07	±2.8
1	0.23	0.27	20.5	5,640	49.4	7.30	0.94	0.64	−2.6
2	0.24‡	0.38‡	19‡	3,380‡	52.5‡	7.34‡	0.68	0.44	+1.0‡
3	0.21‡	0.30‡	26‡	9,200‡	49.2‡	7.33‡	0.55	0.60	−0.6‡
4	0.26‡§	0.68‡	29‡	6,750‡	48.7‡	7.31‡	0.67	0.35	−2.1‡
5	0.22§	—	23	3,450	51.6	7.25	—	—	−5.5
6	0.22‡§	0.70‡	16.5‡	3,882‡	58.6‡	7.29‡	0.54	0.42	−0.5‡
Mean	0.23	0.47	22.3		51.7		0.68	0.49	−1.7
± S.D.	0.02	0.21	4.6		3.7		0.16	0.12	±2.3

TABLE 2.—*Continued*

			Methoxyflurane						
Patient	Alveolar Anesthetic Concentration (volumes per cent)	Inspired Anesthetic Concentration (volumes per cent)	f	V_E (l/min)	P_{CO_2}	pH	S	Fraction Conscious S	Base Excess (mEq/l)
1	0.34‡§	0.8	20‡	3,280‡	66.8‡	7.23‡	—	—	−2.2*
2	0.38	0.62	18	1,980	67.0	7.24	—	—	−1.0
4	0.42‡	0.8	31‡	4,480‡	51.8‡	7.27‡	0.49	0.25	−3.3‡
5	0.32§	0.8	26	3,900	60.0	7.24	—	—	−3.0
6	0.32§	0.8	27	2,620	68.0	7.26	—	—	−0.3
Mean	0.30	0.76	24.4		62.7				−1.8
± S.D.	0.08		5.3		6.9				±1.5

‡ Values averaged from multiple determinations.
§ Suction end-tidal sample.

compared with conscious values. Pa_{CO_2} values at 3.3 MAC were significantly greater than conscious values. In contrast, patients anesthetized with methoxyflurane had early and progressive increases in Pa_{CO_2} with increasing anesthetic depths. The single exception was patient 4, who showed a slight drop in Pa_{CO_2} as alveolar methoxyflurane concentration was increased from 0.17 to 0.22 per cent. However, this patient also had the highest resting Pa_{CO_2} at the lightest level of methoxyflurane studied (1.1 MAC). Pa_{CO_2} values at all MAC levels of methoxyflurane were significantly greater than the conscious values ($P < 0.01$).

We compared Pa_{CO_2} values obtained in this study with those previously reported for halothane, fluroxene and cyclopropane [16] (fig. 2). At all MAC levels, mean Pa_{CO_2} values were significantly lower during ether anesthesia than during halothane or cyclopropane anesthesia. Mean Pa_{CO_2} values for ether and fluroxene showed no difference until the depth of anesthesia reached 2.4 MAC. No significant differences in mean Pa_{CO_2} existed between methoxyflurane and halothane cyclopropane or fluroxene at any MAC level.

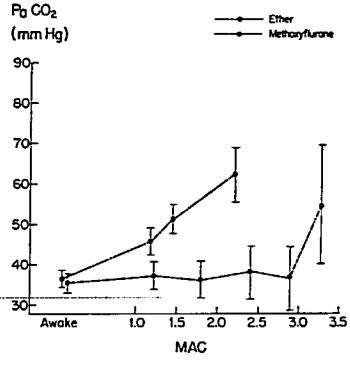

FIG. 1. Mean Pa_{CO_2} values during spontaneous, resting ventilation conscious and at multiples of MAC in eight patients anesthetized with ether and six patients anesthetized with methoxyflurane. Awake values in this and all subsequent figures represent P_{ACO_2} determinations. Vertical bars in this and subsequent figures represent one standard deviation from the mean. Lines connecting conscious values with those during anesthesia for this and all succeeding figures are added for graphic representation and do not necessarily indicate the direction of values taken at anesthetic levels less than 1.0 MAC. Regression equations are: ether, $P_{ACO_2} = 4.71$ (MAC) + 29.5; methoxyflurane, $P_{ACO_2} = 13.03$ (MAC) + 32.99.

CO_2 RESPONSE

With one exception (patient 1 at 2.2 per cent alveolar ether concentration), all patients had progressive reductions in ventilatory response to inhaled CO_2 with increasing depths

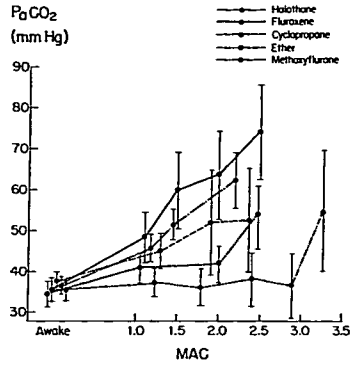

FIG. 2. Comparison of mean P_{ACO_2} values in this study of patients anesthetized with ether or methoxyflurane with values reported by Munson *et al.*[16] for patients anesthetized with halothane, fluroxene or cyclopropane. All values were obtained during resting, spontaneous ventilation, awake and at multiples of MAC.

of anesthesia (fig. 3). Although there was considerable variation among patients, ventilatory response to CO_2 averaged 70 per cent of the conscious value at the lightest mean level of ether anesthesia (1.25 MAC). Mean ventilatory response was 53 per cent of the conscious value at the lightest mean level of methoxyflurane anesthesia (1.06 MAC). Despite this divergence, we found no significant difference between these two slopes. Likewise, no significant differences were observed when we compared these slopes with those obtained in patients anesthesized with halothane, fluroxene or cyclopropane[16] (fig. 4).

Respiratory Frequency and Volume

Tidal volume decreased and respiratory frequency increased with increasing anesthetic depths in patients anesthetized with ether and methoxyflurane, similar to the results of the previous study with halothane, fluroxene and cyclopropane[16] (figs. 5–6). However, the magnitude of the reduction in tidal volume was significantly less with ether than halothane at all anesthetic levels up to 2.4 MAC. Paired analysis of respiratory frequency between the conscious state and the lowest MAC value showed a significant difference for both ether and methoxyflurane ($P < 0.01$). Intergroup comparison of respiratory frequency revealed that both ether and methoxyflurane produced significantly greater increases in respiratory rate than did cyclopropane with increasing anesthetic depth.

Acid–Base Changes

Mean values of base excess obtained in patients anesthetized with ether or methoxyflurane were compared with values obtained in our earlier study in patients anesthetized with halothane, fluroxene or cyclopropane.[16] No significant changes in base excess occurred with increases in anesthetic depth for any agent, and there were no significant differences in base excess among any of the agents.

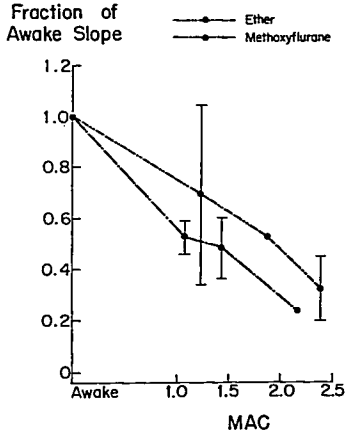

FIG. 3. Mean slopes of the ventilatory response to inhaled CO_2 plotted against multiples of MAC in eight patients anesthetized with ether and six patients with methoxyflurane. Values on the ordinate are expressed as fractions of awake slope (FAS) or anesthetic slope divided by conscious slope. Standard deviation was not calculated if only one or two slope values were available. FAS regression equations are: ether, -0.29 (MAC) $+1.05$; methoxyflurane, -0.22 (MAC) $+0.79$. Comparison of regression slopes showed no significant difference between these agents.

Discussion

Both diethyl ether and methoxyflurane depressed the ventilatory response to CO_2. The magnitudes of depression were dose-related and not significantly different for the two drugs at equipotent concentrations. In contrast, the effects of diethyl ether and methoxyflurane on resting Pa_{CO_2} were dissimilar. Pa_{CO_2} rose early and progressively with increasing methoxyflurane concentration, whereas with ether, Pa_{CO_2} remained essentially unchanged from the awake value until the level of anesthesia exceeded an alveolar ether concentration slightly under 6 per cent (3 MAC). Above this concentration, Pa_{CO_2} rose rapidly.

The ventilatory effects of diethyl ether observed in this study corresponded, in general, to what would be predicted from previous studies. Our results with methoxyflurane agreed with those recently published by Dunbar, Ovassapian and Smith,[25] with one important exception. We observed a much more marked increase in resting Pa_{CO_2} with increasing anesthetic depth than they reported. Reasons for this discrepancy in results are probably twofold and relate to the accuracy of determinations of CO_2 and anesthetic concentrations. Our evaluation of resting ventilation during anesthesia is based upon determinations of arterial P_{CO_2} (Pa_{CO_2}), whereas end-tidal P_{CO_2} ($P_{ET}{}_{CO_2}$) was used in Dunbar's study. We question whether $P_{ET}{}_{CO_2}$ accurately reflects mean alveolar or arterial P_{CO_2} when tidal volume is less than 200 ml and respiratory frequency is greater than 20 per minute. This situation prevailed at the deepest level of anesthesia in seven of 12 patients in Dunbar's study. We suggest that $P_{ET}{}_{CO_2}$ seriously underestimated Pa_{CO_2} in these patients at deeper levels of anesthesia. Furthermore, the a–A CO_2 differences of 1 to 2 mm Hg, *predicted* by Dunbar to exist in his patients, are con-

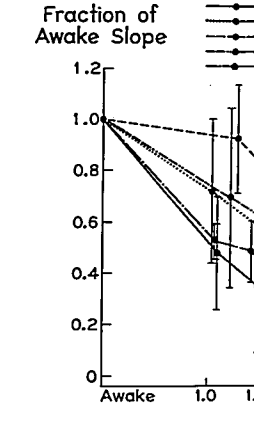

FIG. 4. Comparison of mean slopes of ventilatory response to inhaled CO_2 at multiples of MAC obtained in this study in patients anesthetized with ether or methoxyflurane with those reported by Munson et al.[16] obtained in patients anesthetized with halothane, fluroxene or cyclopropane. Values on the ordinate are expressed as fraction of awake slope. Intergroup comparison of regression slopes of ether and methoxyflurane with all other agents showed no significant difference. However, halothane cyclopropane slopes were significantly different.[16]

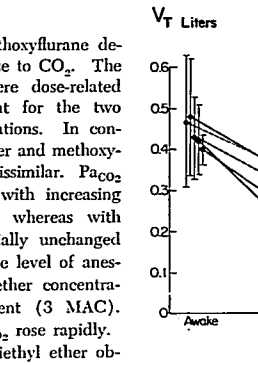

FIG. 5. Comparison of mean changes in tidal volume at multiples of MAC obtained in this study in patients anesthetized with ether or methoxyflurane with those obtained in our earlier study in patients anesthetized with halothane, fluroxene or cyclopropane.[16] Tidal volume (V_T) in liters. Intergroup comparison showed reduction in tidal volume to be significantly greater for halothane than ether at all levels of MAC ($P < 0.01$). Comparison of ether and cyclopropane showed a significant difference only at 1.8 MAC.

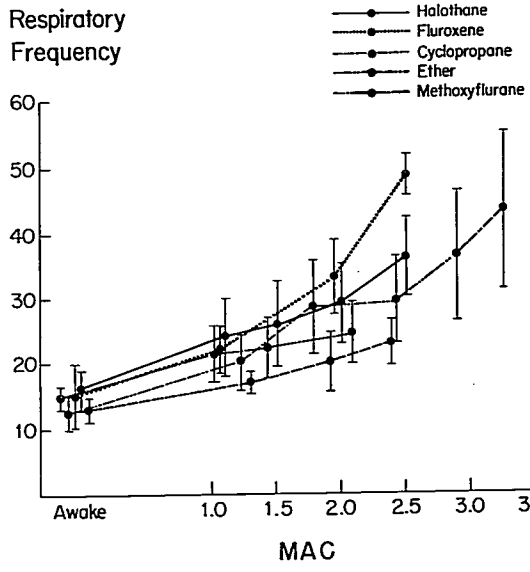

FIG. 6. Comparison of mean changes in respiratory frequency at multiples of MAC obtained in this study in patients anesthetized with ether or methoxyflurane with those reported in our earlier study in patients anesthetized with halothane, fluroxene or cyclopropane.[16] Ordinate in breaths per minute. Regression equations are: ether, f = 9.05 (MAC) + 10.0; methoxyflurane, f = 3.04 (MAC) = 18.0. Comparison of regression slopes showed significant differences between ether and fluroxene and between methoxyflurane and fluroxene.

siderably smaller than the usual differences obtained in anesthetized man.[26-29]

Any errors which result in an overestimation of anesthetic depth would simultaneously result in an underestimation of the magnitude of ventilatory depression. It is generally recognized that measurement of alveolar tensions of soluble agents is subject to considerable error. Small volumes of inspired gas or alveolar gas from ventilated but nonperfused areas of the lungs (alveolar wasted ventilation) may elevate the measured alveolar (end-tidal) anesthetic concentration significantly above that existing in arterial blood. Holiday *et al.*[29] found significant differences in methoxyflurane partial pressures between alveolar gas and arterial blood throughout periods of anesthesia in man lasting more than four hours. Using computer simulation of uptake of methoxyflurane, Dunbar *et al. estimated* that their maximal error in determination of alveolar methoxyflurane concentration was 0 to 10 per cent at light and moderate levels of anesthesia and 50 per cent at deep levels of anesthesia.

In our study, we *determined* the relative magnitudes of the alveolar–arterial differences for both diethyl ether and methoxyflurane by monitoring the inspired–end-tidal partial-pressure difference. For diethyl ether, the inspired–end-tidal difference was small (6 to 18 per cent) over a wide range of anesthetic concentrations (1.2 to 3.3 MAC). In contrast, the inspired–end-tidal difference for methoxyflurane was 59 per cent at 1.06 MAC, 100 per cent at 1.44 MAC, and greater than 100 per cent (inspired concentration not measurable on our calibration curve) at 2.1 MAC. From these measurements, we conclude that Dunbar overestimated the alveolar methoxyflurane concentration by several hundred per cent at the moderately deep and deep levels of anesthesia.

The observation of greatest consequence in this and our previous study[16] is that inhalation anesthetics vary significantly in the degrees to which they alter the various indices of ventilatory adequacy. Ether and methoxyflurane, like halothane, fluroxene and cyclo-

propane, depress ventilatory responsiveness to CO_2, the magnitude of the depression increasing with increasing anesthetized depth (fig. 4). However, the ability to augment ventilation when faced with a CO_2 challenge is significantly greater in patients anesthetized with cyclopropane than in patients anesthetized with any of the other agents studied This difference may be due to the liberation of endogenous catecholamines during cyclopropane anesthesia.[16]

Ether is unique among the five inhalation agents studied in that resting Pa_{CO_2} remains at the conscious value until deep levels (2.9 MAC) of anesthesia are attained (fig. 2). In contrast, Pa_{CO_2} rises progressively with increasing alveolar concentrations of methoxyflurane or halothane, no differences between these two anesthetics appearing at equipotent anesthetic doses. Resting Pa_{CO_2} values with fluroxene and cyclopropane anesthesia are intermediate between halothane and methoxyflurane at one extreme and ether at the other. Considering only the influence of the anesthetic on ventilation, our findings indicate that it is usually unnecessary to assist or control ventilation during ether anesthesia to maintain a normal Pa_{CO_2}. With methoxyflurane or halothane, assisted or controlled ventilation is mandatory in most patients anesthetized beyond 1.5 MAC (0.24 per cent alveolar methoxyflurane or 1.1 per cent alveolar halothane concentration) if an elevation in Pa_{CO_2} above the normal range is to be avoided. It must be emphasized, however, that all of our anesthetic dose–ventilatory response relations were obtained in an environment where factors tending to modify the primary pharmacologic actions of inhalation anesthetics on ventilation were minimized. Any changes in this environment, that is, the use of premedicant drugs, addition of nitrous oxide, presence of surgical stimulation, etc., may alter these relations. For example, we found that during halothane anesthesia surgical stimulation lowered Pa_{CO_2} by an average of 5 mm Hg.[16] This stimulatory effect was not enough to restore mean Pa_{CO_2} to normal. Presumably the same would be true during methoxyflurane anesthesia. One can usually predict in a directional or qualitative sense how the commonly encountered clinical factors, such as those cited above, may modify ventilation. However, for accurate quantitation in the clinical setting, ventilatory measurements of the type used in this study must be made in each patient.

Tidal volume decreased markedly with increasing MAC with all agents, making this a useful clinical sign of relative anesthetic depth (fig. 5). Although respiratory frequency increased with all agents, the magnitude of the changes over a wide range of cyclopropane and methoxyflurane concentrations was small, making rate changes a less useful clinical sign of anesthetic depth with these agents than with halothane, fluroxene or ether (fig. 6). Only with diethyl ether did the increase in breathing frequency offset the decrease in tidal ventilation sufficiently to maintain alveolar ventilation, and hence Pa_{CO_2}, within the normal range. Ether may also have reduced the volume of wasted ventilation by reducing airway volume (bronchoconstriction) and/or by improving the distribution of pulmonary capillary blood flow, thereby reducing alveolar deadspace volume. We have no data bearing on this question. Marshall and Grange found no change in wasted ventilation (physiologic deadspace) from the preoperative value in ten patients anesthetized with ether in air and allowed to breathe spontaneously.[30]

This study prompted us to evaluate the proposed mechanism whereby ether maintains a normal Pa_{CO_2}, even though ventilatory responsiveness to CO_2 is depressed as with other inhalation anesthetics.[31] In a separate report, Muallem [32] documents in dogs that the stimulant effect of ether probably originates within the central nervous system.

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