The Effects of Methoxyflurane on Ventilation in Man

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Minute volume, tidal volume, respiratory frequency, end-tidal carbon dioxide, and ventilatory response to carbon dioxide inhalation were studied during anesthesia at three different concentrations of end-tidal methoxyflurane, 0.19, 0.37, and 0.82 per cent, in 12 unpremedicated patients prior to surgery. Minute volume rose during light anesthesia and fell with increasing concentrations. Tidal volume decreased progressively from 0.49 liters awake, to 0.22 liters at the highest concentration, while respiratory rate rose from 11 to 22 per minute. End-tidal carbon dioxide rose progressively from 38.6 torr while awake, to 43.4 torr during deep anesthesia. More striking was the change in slope of the carbon dioxide response curve, which decreased progressively with increasing depth of anesthesia from 56 per cent of the control response in light anesthesia, through 28 to 9 per cent during deep anesthesia. An estimate of MAC for methoxyflurane in this study was 0.17 per cent, which agrees with previous reports despite employment of different criteria.

IN THE COMPARISON of respiratory data during various anesthetics, Munson has called attention to the importance of: (1) controlled stable anesthetic concentration; (2) stable arterial and cerebral CO_2 tensions (hence stable cerebral blood flow); (3) control of afferent stimuli unaffected by premedication or surgery; and (4) minimized dead space and resistance in anesthetic apparatus.[1] Using these criteria Larson and his co-workers have reported the effects of methoxyflurane in six anesthetized men.[2] We report here similar measurements in 12 normal volunteers, made prior to surgical intervention, covering a wider range of anesthetic concentrations. We found both agreement and disagreement in our results with those of Larson *et al.*

Methods

Twelve patients (without premedication), free of cardiopulmonary disease, their characteristics summarized in table 1, agreed to an extra period of anesthesia prior to operation. They rested for one half hour in a quiet, dimly lit laboratory. After control measurements of respiratory minute volume, $\dot{V}_E$, respiratory frequency, f, end-tidal carbon dioxide tension, $P_{ET}CO_2$, and steady state ventilatory response to inspired carbon dioxide, atropine (0.4–0.6 mg.) was given intravenously. Anesthesia was induced with a single dose of intravenous thiopental. Inhalation of 75 per cent nitrous oxide was begun, and methoxyflurane was added to the inspired gas from a Vernitrol vaporizer and a number 8 Ohio Wick vaporizer as rapidly as the patient would tolerate it. Nitrous oxide was discontinued within ten minutes. Oxygen and methoxyflurane (3 per cent) were given in a non-rebreathing system for the next 30 minutes. No drugs except methoxyflurane were given after discontinuing nitrous oxide. Spontaneous ventilation was allowed throughout. The trachea was not intubated, but an oro-pharyngeal airway was used to maintain an unobstructed airway in 9 of the 12 patients.

Experimental Design. All subjects were deeply anesthetized within the first 30 minutes. Thereafter, three depths of anesthesia

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were studied in each patient; the order of study of the three depths was randomly chosen.

Usually 20 minutes, rarely longer than 40 minutes, elapsed between the initial one-half hour of deep anesthesia and the first study, and between subsequent studies. When a stable desired end-tidal concentration of methoxyflurane was achieved, resting ventilation, respiratory rate, and ventilatory response to inspired carbon dioxide were recorded. Statistical significance was determined with the F ratio of Fisher at the 5 per cent level. When indicated, further analyses were done with the *t* statistic of Dunnet to compare measurements after anesthesia with the control.[3]

Breathing Circuits. Two different breathing circuits were used. Ventilation of the first six patients, both awake and anesthetized, was measured with a Collins nine liter spirometer which replaced the bag of a standard Air-Shields Ventimeter mounted in a standard Ohio 2000 Series Jumbo Circle System. The resistance to inspiration was 0.6 cm. $H_2O \times L.^{-1} \times sec.^{-1}$ and to exhalation, 0.7. This system proved suitable for recording ventilation during anesthesia. It was less satisfactory for maintaining a steady state of alveolar anesthetic concentration, since with augmented ventilation owing to carbon dioxide stimulation it was necessary to change the setting of the number 8 vaporizer to keep P_{ET} methoxyflurane constant. For the second group of six subjects a non-rebreathing system with a Rahn end-tidal sampler and a recording Tissot gasometer was used both for the control and the measurements during anesthesia. The resistance to breathing was approximately 0.6 cm. $H_2O \times L.^{-1} \times sec.^{-1}$. The smallest mask which gave a gas-tight fit was used to minimize dead space.

Gas Analysis. Carbon dioxide concentration in end-tidal gas was measured with a Liston-Becker infra-red carbon dioxide analyzer. Gas was sampled at the rate of 500 cc. per minute from a catheter with the tip placed beneath the face mask between the nares and lips, or within the oro-pharyngeal airway. In the first six cases the sample gas was returned to the breathing circuit in the expiratory limb of the circle; in the second six it was returned to the central cavity of the Rahn end-tidal sampler. Mixed venous carbon dioxide tensions were estimated by the rebreathing method [4] in 8 of the patients before anesthesia, and in 10 of the 12 patients at the end of the study.

Concentration of methoxyflurane in end-tidal samples was measured by an F&M gas chromatograph using a silicone gum rubber column and flame ionization gauge, calibrated with air saturated with methoxyflurane at four accurately controlled temperature, from 0° to 20° C. End-tidal aliquots of 10 to 20 breaths were analyzed. In the second group of six patients, in addition to gas chromatographic analyses of end-tidal samples, an infra-red halothane analyzer (charged with carbon dioxide and sensitive to methoxyflurane) was

TABLE 1. Physical Characteristics of Subjects

Subject	Sex	Age (Yrs.)	Height (cm.)	Weight kg.	Body Surface Area (m^2.)	Physical Status	Induction Dose of Thiopental (mg.)	Minimum Anesthetic Concentration (%)
1	F	42	168	75	1.84	I	100	<0.22
2	M	17	193	85	2.08	I	100	0.16
3	F	15	173	65	1.77	I	250	<0.37
4	F	35	152	56	1.49	I	200	<0.28
5	M	31	188	89	2.13	I	300	0.14
6	M	33	183	108	2.28	I	500	0.19
7	M	30	178	75	1.90	I	350	0.17
8	F	26	165	63	1.69	I	300	0.10
9	F	26	158	56	1.55	I	250	0.20
10	F	58	175	51	1.62	I	200	0.21
11	F	59	158	62	1.61	II	200	0.17
12	M	28	178	89	2.06	I	300	0.17

TABLE 2. Individual Measurements and the Means for 12 Patients

Subject	Anesth. Alv. Conc. (%)	Resp. Rate Per Min.	Min. Vol. (L/min.)	End-Tidal P_{CO_2} Torr.	Slope of Vent. Resp. to CO_2 ($L \cdot min.^{-1} \cdot Torr^{-1}$)	Fraction of Awake Slope	Time After Induct. (Min.)
Awake							
1	0	8	3.39	40.2	0.46	100	0
2		6	6.53	37.6	1.72		
3		11	5.06	37.0	2.76		
4		12	5.20	38.0	0.77		
5		12	8.18	35.2	1.39		
6		8	7.60	38.0	0.98		
7		17	7.11	38.4	0.82		
8		18	5.22	35.2	1.32		
9		11	2.45	40.0	0.77		
10		12	4.69	41.0	0.72		
11		10	4.41	40.8	0.90		
12		12	7.30	42.2	0.97		
Mean		11.4	5.60	38.63	1.13		
S. D.		3.4	1.77	2.25	0.63		
S. E.		1.0	0.51	0.65	0.18		
Lightly Anesthetized							
1	0.23	31	6.84	41.6	0.282	0.61	280
2	0.17	21	7.65	41.0	0.59	0.31	38
3	—	—	—	—	—	—	—
4	0.28	18	5.20	40.0	0.43	0.56	70
5	0.14	23	6.54	30.0	1.12	0.81	138
6	0.27	20	12.64	36.5	0.52	0.53	45
7	0.17	19	7.43	39.0	1.01	1.23	107
8	0.10	24	6.84	37.0	1.13	0.86	50
9	0.20	16	6.86	39.2	0.42	0.55	163
10	0.21	18	5.68	41.2	0.41	0.57	80
11	0.17	14	6.33	39.2	0.74	0.82	101
12	0.17	13	7.17	49.2	0.33	0.31	186
Mean	0.192	19.7*	7.198*	39.45	0.635*	0.65	114
S. D.	0.053	5.1	1.942	4.58	0.32	0.267	73
S. E.	0.016	1.5	0.590	1.38	0.10	0.081	22
Moderately Anesthetized							
1	0.32	21	3.28	35.0	0.18	0.39	88
2	—	—	—	—	—	—	—
3	0.43	24	7.28	38.8	0.22	0.08	94
4	—	—	—	—	—	—	—
5	0.26	23	8.39	31.0	0.98	0.70	94
6	0.34	20	10.64	38.0	0.29	0.30	55
7	0.44	20	5.76	42.8	0.10	0.12	85
8	0.33	24	4.77	36.4	0.52	0.40	87
9	0.35	19	5.75	36.6	0.37	0.48	113
10	0.41	26	4.97	44.2	0.07	0.10	206
11	0.46	16	4.84	39.6	0.25	0.28	165
12	0.41	17	5.94	55.2	0.19	0.19	105
Mean	0.374	21.0*	6.161	39.76	0.317*	0.304	109
S. D.	0.061	3.2	2.110	6.60	0.33	0.195	44
S. E.	0.019	1.0	0.667	2.09	0.11	0.062	14

* Represent significant change from control values as assessed by analysis of variance using a 5 per cent level of probability.

TABLE 2. (*Continued*)

Subject	Aneath. Alv. Conc. (%)	Resp. Rate Per Min.	Min. Vol. (L./min.)	End-Tidal P_{CO_2} Torr.	Slope of Vent. Resp. to CO_2 (L·min.$^{-1}$·Torr^{-1})	Fraction of Awake Slope	Time After Induct. (Min.)
Deeply Anesthetized							
1	0.58	24	2.60	41.6	0.04	0.08	56
2	0.47	22	7.41	43.0	0.30	0.17	81
3	0.82	20	4.01	43.8	0.10	0.04	51
4	0.58	23	3.90	44.4	0.18	0.23	110
5	1.00	28	5.24	35.6	0.03	0.02	60
6	0.77	25	8.20	38.2	0.09	0.09	115
7	1.42	23	3.53	45.6	0.03	0.03	60
8	0.53	26	4.85	42.0	0.10	0.08	185
9	0.88	14	6.25	42.0	0.11	0.14	163
10	0.94	26	3.90	46.0	0.07	0.10	133
11	0.82	12	4.13	43.0	0.14	0.16	60
12	1.05	19	5.42	55.7	0.01	0.01	230
Mean	0.821	21.9*	4.954*	43.39*	0.100*	0.096	101
S. D.	0.268	4.8	1.65	4.87	0.08	0.068	57
S. E.	0.077	1.4	0.48	1.41	0.02	0.020	17

used to continuously monitor the end-tidal methoxyflurane. Gas was sampled at 50 ml./min. from the Rahn end-tidal sampler and returned to the expiratory limb of the breathing system. The sampler was modified with teflon tubing and a mylar bag to prevent contamination from diffusion of inspired methoxyflurane through the rubber bag. The response of this instrument was too slow to give a breath by breath analysis with respiratory rates of 20 or more per minute. All concentrations reported below were from gas chromatographic analysis of end-tidal samples.

Ventilatory Response to Carbon Dioxide. After stable ventilation was recorded, the ventilatory response to carbon dioxide was measured. A constant flow of carbon dioxide was added to the inspired gas. Within three to eight minutes steady ventilation resulted, as shown by a constant inspired carbon dioxide tension. Ventilation and end-tidal carbon dioxide were recorded during the next minute. The inspired carbon dioxide flow was then changed, and a second steady state reached and recorded. Carbon dioxide was discontinued and when ventilation became stable a fourth period of ventilation was recorded. The flow rates of carbon dioxide used for stimulation produced an increase in $P_{ET_{CO_2}}$ of either 5 to 10 torr, or 10 to 15 torr above the unstimulated value. If carbon dioxide challenge caused movement of the patient, anesthesia was deepened slightly and resting ventilation determined again. The line relating ventilatory response to carbon dioxide was drawn from the average of the two resting ventilations with a slope which minimized the deviation of the two stimulated points from the line.

Minimum Anesthetic Concentration (MAC). In 9 of 12 patients, at some time during the study, anesthesia was decreased until spontaneous movements of the limbs occurred. The stimulus of either carbon dioxide challenge or manpulation of the oral airway apparently caused the limb movement. Concentration of methoxyflurane in end-tidal gas sampled at this time was considered to represent minimum anesthetic concentration (MAC) for that patient.

Results

Individual measurements and the means for the 12 subjects are given in table 2. The control respiratory frequency varied from 6 to 17 with a mean of 11.4 ± 1.0 S.E. After anesthetization, mean frequency was 19.7 ± 1.53 S.E., 21.0 ± 1.02 S.E., and 21.9 ± 1.39 S.E. at average end-tidal concentrations of 0.19, 0.37, and 0.82 per cent, respectively. Re-

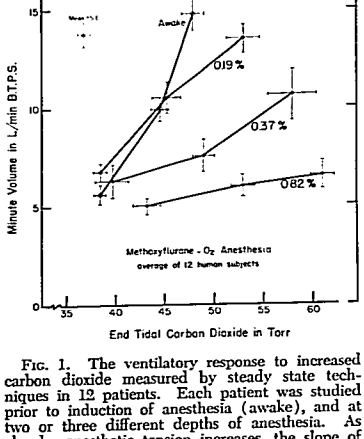

FIG. 1. The ventilatory response to increased carbon dioxide measured by steady state techniques in 12 patients. Each patient was studied prior to induction of anesthesia (awake), and at two or three different depths of anesthesia. As alveolar anesthetic tension increases, the slope of the ventilatory response is progressively decreased.

spiratory frequency increased in every subject during induction of anesthesia and remained high at every depth studied. No significant increase in frequency could be detected after induction, as anesthesia was deepened.

Tidal volume, V_T, decreased progressively as anesthetic concentration increased. Analysis of variance in the ten subjects in whom measurements were made at all three levels of anesthesia, showed a significant decrease in V_T with each increase in depth of anesthesia. At 0.82 per cent methoxyflurane, V_T was less than one-half the awake value.

Resting control minute ventilation, V_E, was 5.60 ± 0.51 S.E. L./min. During light anesthesia it was 7.20 ± 0.59 and varied inversely with anesthetic concentration. This variation was not related to the order of study of the three depths or the duration of anesthesia. V_E was increased above control in three of four subjects in whom light anesthesia was studied last, an average of 172 minutes after induction.

Control values for end-tidal carbon dioxide tensions, $P_{ET_{CO_2}}$, averaged 38.6, ranging between 35 and 41 torr. Anesthesia caused an increase in $P_{ET_{CO_2}}$ which varied directly with the anesthetic concentration. However, in four instances during the study of light anesthesia and in four during the study of moderate anesthesia, $P_{ET_{CO_2}}$ was lower than the control value. During deep anesthesia there was a significant and consistent increase to an average value of 43.4 ± 1.4 S.E.

The average values for ventilation and end-tidal carbon dioxide during the steady state measurements of ventilatory response to carbon dioxide are plotted in figure 1. The control value for the slope of the response line was an increase in ventilation of 1.13 L./min., ± 0.18 S.E. for each rise in torr of $P_{ET_{CO_2}}$. During anesthesia the slope was 0.64 L. $\times$ min.$^{-1}$ $\times$ torr^{-1} ± 0.10 S.E. at 0.19 per cent methoxyflurane; 0.32 ± 0.11 at 0.39 per cent; and 0.10 ± 0.02 at 0.82 per cent. With but a single exception the slope was steeper when patients were awake than when lightly anesthetized: it was always decreased at the higher

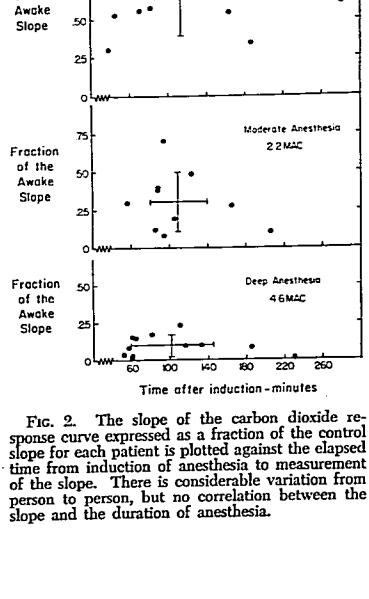

FIG. 2. The slope of the carbon dioxide response curve expressed as a fraction of the control slope for each patient is plotted against the elapsed time from induction of anesthesia to measurement of the slope. There is considerable variation from person to person, but no correlation between the slope and the duration of anesthesia.

concentrations of anesthesia. In the deeply anesthetized patients the slope was nearly flat, with an extreme of 0.01 L. × min.$^{-1}$ × torr^{-1}. There was no correlation between the slope and the duration of anesthesia as shown in figure 2. The mean elapsed time for observations during light anesthesia was 114 minutes (range 40 to 280); for moderate, 109 minutes (range 55 to 190); and for deep anesthesia, 101 minutes (range 50 to 230). The average duration from induction to the first study period (light, moderate, or deep anesthesia chosen randomly) was 65 minutes. The average duration from induction to the second and third study periods was 102 and 132 minutes, respectively.

The mean concentration at which carbon dioxide inhalation or oro-pharyngeal stimulation produced limb movement was 0.169 with a range of 0.10 to 0.21 per cent methoxyflurane and a coefficient of variation of 12 per cent. Patients would tolerate an airway at lighter levels of anesthesia, provided it was not moved vigorously.

Discussion

The effects of methoxyflurane-oxygen anesthesia on the respiration of man consisted primarily of a decrease in the slope of the carbon dioxide response curve. This depression of slope was dose related as shown in Figure 1. Deep levels of anesthesia were associated with a carbon dioxide response curve having a slope approaching 0, indicating that ventilation was nearly constant over the measured range for P_{CO_2}. Effects on the displacement of the curve were inconsistent and unrelated to the depth of anesthesia.

A report in preliminary form of the respiratory effects of methoxyflurane in man has been presented by Larson and co-workers.[2] Essential similarities in the experimental design include: the establishment of a stable anesthetic level and carbon dioxide tension; the assessment of respiratory depression by the method of steady state carbon dioxide response curves; the use of unpremedicated patients prior to surgical intervention; the use of apparatus with low resistance and dead space and the evaluation of anesthetic depth in terms of the minimum anesthetic concentration. Similarity in the results is shown

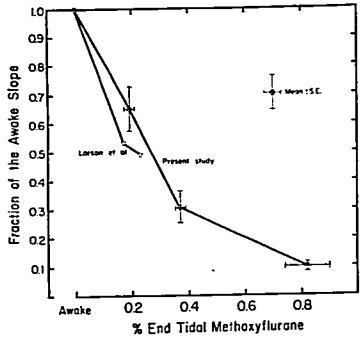

FIG. 3. The slope of the ventilatory response to carbon dioxide expressed as a fraction of the control slope as determined in each patient is plotted against the end-tidal methoxyflurane concentration. The circles and bars indicating a standard error of the mean are from the present study, while the open triangles are from the preliminary report of Larson *et al.* The slope progressively decreases as alveolar concentration of methoxyflurane is increased. Measurement of alveolar concentration is very difficult in deep anesthesia due to small tidal volumes and a large inspired to alveolar gradient. Because of this, it is likely that the deeply anesthetized point is over-estimated and should lie further to the left.

in Figure 3, where the change in slope of the carbon dioxide response curves reported by Larson *et al.* for 1.06 MAC, and 1.44 MAC is close to our measurements at 1.1 MAC.

Another similarity in results is their value for MAC of 0.16 per cent for methoxyflurane. Saidman and Eger have proposed that the criteria for minimum anesthetic concentration in man be the alveolar concentration at or below which 50 per cent of the patients move when a skin incision is made.[5] Larson *et al.* use this statistical assessment for their determination of MAC. We found a value of 0.17 per cent methoxyflurane using the criterion of movement following airway stimulation, either mechanical or with inspired carbon dioxide concentration above 10 per cent.

The differences in the two studies include a different technique of induction (cyclopropane vs. thiopental), a different airway (oro-tracheal vs. oro-pharyngeal), the use of a calculated vs. observed interval for determination

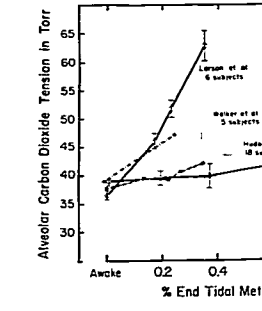

FIG. 4. The relation of alveolar carbon dioxide tension during spontaneous unassisted respiration to the alveolar concentration of methoxyflurane. The data of Larson *et al.* are from arterial blood analysis for P_{CO_2} and end-tidal gas analysis for methoxyflurane. The present study used end-tidal gas samples for both carbon dioxide and methoxyflurane. The data of Walker and his co-workers estimated P_{CO_2} from the Henderson-Hasselbach relationship, and the depth of anesthesia from EEG signs. Hudon *et al.* measured P_{CO_2} in arterial blood directly. We have estimated the depth of anesthesia from their data of inspired concentration and duration of anesthesia.

of a steady ventilatory state, and the technique for measuring alveolar carbon dioxide (arterial blood versus end-tidal gas). The major difference in results between the two studies is the relation between carbon dioxide tension during spontaneous breathing and the depth of anesthesia. In the 6 patients reported by Larson, carbon dioxide tension of arterial blood rose rapidly with increase in depth of anesthesia. In contrast, we found that although end-tidal carbon dioxide increased with depth of anesthesia, the increase was moderate as shown in figure 4.

It is unlikely that the difference in results can be attributed to the development of a large arterial-alveolar carbon dioxide tension difference during anesthesia, $a\text{-}AD_{CO_2}$. Such a difference would tend to be corrected by increasing depth of breathing associated with carbon dioxide challenge, producing a marked increase in slope of the response at higher inspired CO_2. Additionally, the resting end-tidal carbon dioxide measured after challenge would be expected to exceed that measured before challenge, if deep breathing partially corrects an aA difference for carbon dioxide. Such was not observed. The mixed venous dioxide tension was measured in eight of the subjects while awake, and measured 14 times in ten of the subjects after one and a half to two hours of anesthesia. The mixed venous to end-tidal difference was 6.7 torr ± 1.8 S.E. with subjects awake, and 7.0 ± 1.7 S.E. anesthetized. Since mixed venous to end-tidal difference must always exceed the $a\text{-}AD_{CO_2}$, the latter must be of the order of one to two torr. This is the magnitude of $a\text{-}AD_{CO_2}$ we regularly find during other studies in normal man.[6]

Measurement of alveolar concentration of methoxyflurane in deep anesthesia is subject to considerable error owing to the large inspired to alveolar difference with soluble anesthetics, and due to the decreasing V_T. A small amount of contamination of "end-tidal" samples with dead space or inspired gas gives a large error. For light anesthesia this can be minimized by an initial period of deep anesthesia, which results in an appreciable mixed venous content of methoxyflurane. We employed a 30 minute or longer period of 3 per cent methoxyflurane inhalation for this purpose. When the concentration is later decreased to provide light or moderate anesthesia, a lesser inspired concentration is needed and a more stable alveolar level results. The vapor pressure of methoxyflurane limits the inspired concentration to about 3 per cent. Our reported concentration of methoxyflurane after 50 to 60 minutes of deep anesthesia averaged 0.92 per cent and after more than 100 minutes was 0.76. Using Mapleson's computer simulation of uptake of methoxyflurane,[7] and assuming a 3 per cent inspired concentration, the calculated alveolar concentration are 0.60 and 0.78 per cent. This suggests that our reported alveolar concentrations in deep anesthesia are in error by up to 50 per cent. For moderate and light anesthesia maximal errors of 10 and 0 per cent are suggested. This error is probably the cause of the curvature in figure 3 with deeper anesthesia.

There are only two published reports of arterial P_{CO_2} during methoxyflurane anesthesia which include data on depth of anesthesia. Walker, Eggers, and Allen studied methoxyflurane-oxygen anesthesia at electroencephalo-

graphic levels 2 to 3.[8] If EEG signs of methoxyflurane and diethyl ether bear the same relationship as do the minimum anesthetic concentrations of the two agents, we calculate that Walker's patients were anesthetized at 1 to 1.5 times MAC. The average carbon dioxide tension of arterial blood, calculated from the Singer-Hastings nomogram, is shown in figure 4 and approximates the data of Larson and his co-workers. Hudon and his co-workers have reported direct measurements for arterial carbon dioxide tension, the inspired concentration of methoxyflurane and the duration of anesthesia at that tension.[9] Using Mapleson's computer solution for the approach of alveolar concentration of the inspired methoxyflurane,[7] we calculate that Hudon's patients had anesthetic concentration between 1.2 and 2.25 times MAC. These values with their respective carbon dioxide tensions are very close to the data presented in this study.

In short, we find depression of the respiratory response to carbon dioxide similar to that reported by Larson and his co-workers in similar patient groups at similar depths of anesthesia. However, they found a different P_{CO_2} during anesthesia without CO_2 challenge. Previously published values for carbon dioxide tensions during spontaneous respiration at equivalent depths of anesthesia (the starting points of the response curves) lie between Larson's results and our own. Despite the apparent divergence, the actual difference is not great. From the analysis of Bellville and Seed relating ventilation and alveolar carbon dioxide clearance,[10] and from the assumption of similar metabolic carbon dioxide production for Larson's subjects and our own, we calculate that an increase of 60 ml. per breath would suffice to lower carbon dioxide tensions from those reported by Larson, to those we have found during anesthesia at two times MAC.

There is a qualitative difference in the respiratory response to carbon dioxide challenge in awake man when compared with anesthetized man. In awake man the response to carbon dioxide is shifted in parallel fashion to the right with narcotics or sleep,[10, 11] and to the left with stimulants[12] or reversal of the depression. The appropriate measure of a parallel shift is the change in alveolar carbon dioxide at some specific carbon dioxide excretion rate. Commonly, the alveolar carbon dioxide at ventilations of 10 to 20 liters per minute is chosen since the hyperbola of carbon dioxide excretion is quite flat at normal $P_{ET_{CO_2}}$. The resting alveolar carbon dioxide is as good in theory if the carbon dioxide response is a straight line; however, in practice it is less precise. Figure 4 from four different studies of ventilation and carbon dioxide is in essence such a measure of shift using the resting alveolar carbon dioxide, and shows the scatter of the observed results.

When the slope of the carbon dioxide curve is affected by a drug under study, the usual criteria of displacement of the curve becomes meaningless because its value changes with the level of ventilation selected to express the displacement. It may, in fact, have a negative value. Mathematically the appropriate measure of displacement of a straight line which is independent of the slope of the line is the intercept on the ordinate. Unfortunately, this value would require extensive extrapolation of respiratory response curves and would further provide a negative value in normal man. Since the concept of a negative ventilation is unlikely to have physiologic significance, this strictly mathematical expression is not used. Since the slope bears a reproducible relation to concentration of methoxyflurane, but measures of displacement do not (fig. 3), we consider our results basically confirmatory of the preliminary report of Larson.

A marked change in slope of the respiratory response to carbon dioxide has been reported after every general anesthetic agent studied to date. It also results from the combined effects of sleep and narcotics,[13] although either alone causes simple displacement. The change in slope produced by such dissimilar agents as nitrous oxide-Innovar,[14] methoxyflurane, diethyl ether,[2] cyclopropane, and halothane,[1, 15] is surprisingly similar when expressed at equipotent alveolar concentrations. In contrast, the unstimulated carbon dioxide tension, or tension at any selected ventilatory level, varies widely not only from agent to agent but from report to report. We interpret these findings as strong evidence that more than one mecha-

nism controls the level of ventilation in man, and that loss of consciousness creates a change in the relative balance of such mechanisms.

Conclusions

Methoxyflurane anesthesia decreases the respiratory response to carbon dioxide so that spontaneous ventilation cannot be relied upon to prevent respiratory acidosis during anesthesia. The depression increases with depth of anesthesia. The relationship of alveolar carbon dioxide tension to depth of anesthesia in the present study is different from that previously reported, although the change in slope of the response is nearly identical. Whatever the resting unstimulated ventilation and alveolar carbon dioxide tension might be, methoxyflurane clearly limits the ability of an anesthetized patient to respond to an increase in carbon dioxide which might result from such challenges as airway obstruction, abnormal body position, or surgical interference with diaphragmatic motion.

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