The Central Regulation of Respiration During Halothane Anesthesia

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DEPRESSION of respiration during general anesthesia was regarded by Snow as a nonspecific effect of "narcotism" of the nervous system.[1] The work of Haldane and his school[2] led to the view that the depression is due to a decrease in the sensitivity of the respiratory center to carbon dioxide.[3] Such an explanation in essence restates the observation that anesthesia reduces the ventilatory response to carbon dioxide, but throws little light on how this is brought about.

A more specific explanation emerges from recent evidence that wakefulness-associated activity of the brain can maintain substantial ventilation despite the absence of any respiratory carbon dioxide drive.[4,5] Carbon dioxide in sufficient tension, it has been suggested, may stimulate respiration, partly by its augmenting action on this activity.[6] The results of the present study indicate that depression of this activity in general anesthesia may underlie the reduced ventilation observed during the administration of halothane.

Methods

The studies were carried out on 5 otherwise healthy patients scheduled for minor gynecological procedures. Preanesthetic medication consisted of atropine 0.5 mg. administered intramuscularly one and a half hours before induction of anesthesia. The studies were completed before operation.

Sleep was induced with thiopental (50 to 200 mg.), followed by succinylcholine 60 mg. intravenously, topical anesthesia of the larynx and trachea with 4 per cent lidocaine, and insertion of a cuffed endotracheal tube. Halothane from a Fluotec vaporizer was administered through a nonreturn system, at concentrations of 1 to 2.5 per cent in oxygen. The volume of expiration (ATBP) was measured for one minute before and one minute after taking blood samples, with a Wedge* recording spirometer coupled to a multichannel cathode-ray oscillograph. The spirometer tracing was calibrated with a 100 ml. syringe before each study. The carbon dioxide content of the endotracheal gas was monitored continuously with a recording infrared analyzer. Brachial arterial blood samples obtained through an indwelling Cournand needle were analyzed for pH at 37° C., with a Kopp meter standardized with pH 6.975 buffer, and for carbon dioxide content with a Natelson microgasometer. Pa_{CO_2} was calculated from the Henderson-Hasselbach equation. Analyses were made in duplicate, agreeing within 0.005 pH unit and 2 mm. Pa_{CO_2}. Samples were drawn during steady state spontaneous respiration and again during controlled ventilation at the threshold of rhythmic diaphragm electromyogram (EMG) activity. A respiratory steady state was assumed if the end-expiration CO_2 content measured by the infrared analyzer remained steady for at least five minutes. A relatively steady anesthetic state also existed, since otherwise the volume of ventilation and end-expiration CO_2 would not have remained steady. The method of recording the diaphragm EMG has been described in previous publications from this laboratory.[7,8]

Initial steady state observations of spontaneous respiration were begun one hour after induction of anesthesia. Graduated overventilation was then instituted with a mechanical

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* Manufactured by Custom Engineering Inc., St. Louis, Missouri.

ventilator.† Stroke volume remained fixed. Stroke frequency was adjusted to reduce and finally to abolish rhythmical diaphragm activity‡ over a period of about ten minutes. Following this, a slight decrease in stroke frequency allowed the rhythmical EMG to reappear. Having thus produced an approximately steady P_{CO_2} in the neighborhood of the threshold, mechanical ventilation was slowly increased until the EMG activity again ceased, when an arterial blood sample was drawn. Similarly, after once more decreasing the stroke frequency the rhythmical EMG activity returned, at which point another blood sample was drawn. These two samples thus bracketed the threshold. The ventilator was then disconnected, spontaneous respiration reestablished, and a steady state as defined above restored. This usually took about ten minutes, after which further blood and ventilation measurements were made. Next, the halothane concentration was reduced by 0.5 or 1 per cent. Half an hour was allowed for re-equilibration, following which the entire protocol of measurements was repeated.

Results

The complete results are presented in table 1, grouped for each patient according to the concentration of halothane administered. The four lines in a group document respectively: initial spontaneous respiration (S. 1), diaphragm EMG inactivation (D. I), diaphragm EMG reactivation (D. R.), and final spontaneous respiration (S. 2). The mean threshold and spontaneous respiration values of each group are tabulated separately in table 2, in order to facilitate comparisons between the levels of anesthesia. The differences between threshold and spontaneous respiration *p*H and P_{CO_2}, shown alongside, constitute the suprathreshold arterial acidity stimulus (ΔpH_a) and suprathreshold arterial carbon dioxide

† Manufactured by Stephenson Corporation, Shrewsbury, New Jersey.

‡ In this article the term "rhythmical activity" signifies a burst of action potentials present in only one phase of the respiratory cycle and recurring regularly in the same phase of successive cycles. "Nonrhythmical" refers to activity continuing throughout the respiratory cycle.

TABLE 1. Ventilation and Blood Acid-Base Balance in Unoperated Patients Anesthetized With Halothane

	Halothane Concentration (%)	Ventilation State	V (L/minute)	F	pH_a	P_{aCO_2} (mm. Hg)
A	1.5	S.1	4.74	34	7.307	46.5
		D.I.			7.365	40.9
		D.R.			7.342	46.4
		S.2	4.62	34	7.316	48.1
	2.5	S.1	3.89	31	7.284	50.7
		D.I.			7.350	44.0
		D.R.			7.332	46.2
		S.2	4.06	33	7.275	51.9
B	1	S.1	4.98	24	7.33	43.5
		D.I.			7.36	39.3
		D.R.			7.33	43.4
		S.2	4.40	24	7.32	45.7
	2	S.1	3.92	28	7.32	48
		D.I.			7.34	45.1
		D.R.			7.34	44.1
		S.2	4.21	28	7.28	50.2
C	1	S.1	6.42	30	7.265	51.6
		D.I.			7.357	37.1
		D.R.			7.343	40.0
		S.2	5.30	28	7.305	46.6
	2	S.1	3.53	26	7.258	57.8
		D.I.			7.312	45.8
		D.R.			7.281	52.5
		S.2	3.90	31	7.238	58.2
D	1	S	5.64	31	7.323	47.9
	1.5	S.1	4.39	32	7.298	51.2
		D.I.			7.353	42.6
		D.R.			7.341	46.8
		S.2	4.83	33	7.311	47.4
	2	S.1	4.27	35	7.255	59.1
		D.I.			7.300	49.4
		D.R.			7.301	48.5
		S.2	4.50	37	7.265	55.5
E	1.5	S.1	4.83	32	7.33	44.8
		D.I.			7.40	37.1
		D.R.			7.36	40.6
		S.2	4.83	33	7.36	42.5
	2.5	S.1	3.79	34	7.26	55.0
		D.I.			7.31	47.9
		D.R.			7.31	48.4
		S.2	3.70	33	7.26	53.6

S. = Spontaneous respiration. 1 = initial, 2 = final. D.I. = Inactivation of diaphragm. D.R. = Reactivation of diaphragm. V = Volume of expiration. F = Frequency of respiration per minute.

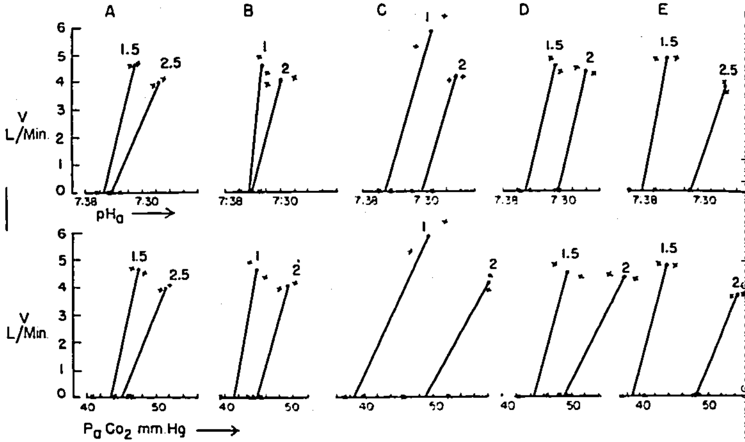

FIG. 1. Relation of ventilation to arterial blood acid-base balance in five patients anesthetized with halothane. *Top:* relation to pH_a; *bottom:* relation to Pa_{CO_2}. The crosses plot the data in table 1. The curves join the mean of each pair. The inhaled anesthetic concentration is indicated above each curve. At the higher anesthetic concentration the ventilatory response is reduced and the threshold alters in the direction of increased acidity and Pa_{CO_2}.

stimulus (ΔPa_{CO_2}) § respectively. In the final columns the ratio of minute volume to suprathreshold stimulus, also expressed by the slope of the curves in figure 1, indicates the "sensitivity" of the respiratory neural mechanisms to CO_2-H^+ stimulation.

Examination of table 2 reveals that increased concentration of anesthetic always depressed respiration. The depression was manifest both at the threshold and in spontaneous respiration. The threshold Pa_{CO_2} rose, 1.5–10 mm. of mercury at the same time as the threshold pH_a fell 0.005–0.07 pH units. Thus, as regards the threshold, with the higher halothane concentration a stronger arterial CO_2-H^+ stimulus was required to initiate respiration than with the lower concentration. As regards spontaneous respiration, the volume of ventilation was always decreased by deeper anesthesia, notwithstanding an increase in the suprathreshold P_{CO_2} and pH stimuli.

§ The term "suprathreshold carbon dioxide stimulus" is synonymous with but more descriptive than "effective carbon dioxide stimulus," defined by Lindhard [9] as the partial pressure of carbon dioxide effective in producing ventilation.

The relative respiratory depression in the individual patients is best evaluated from the ratio of the volume of ventilation to the suprathreshold stimulus. In patients *A*, *B*, and *E* increasing the halothane concentration one per cent reduced the combined ventilation response to arterial carbon dioxide ($V/\Delta Pa_{CO_2}$) and to arterial acidity ($V/\Delta pH_a$) by more than 40 per cent. In patient *D* a similar decrease in response to carbon dioxide occurred when the halothane concentration increased only 0.5 per cent. Patient *C* showed no change in sensitivity to CO_2 or acidity as far as the response per unit stimulus is concerned; in this patient increased depression of respiration was manifested only by the large shift in threshold Pa_{CO_2} and pH_a.

Discussion

It is well established that increasing anesthetic depression is characterized by decreased ventilation, carbon dioxide retention and acidosis, expressible graphically as a reduced ventilatory response to arterial CO_2. The ventilatory response to CO_2 is partly a specific effect

of the carbon dioxide and partly a result of the concomitant change in pH. According to Loeschke and co-workers [10] pH_a change is responsible for a little less than half the total response to carbon dioxide. The response over small ranges is linear in waking subjects,[11, 16, 22] and linearity is here assumed to prevail during anesthesia and down to the threshold (figure 1, bottom row). This assumption simplifies the presentation and does not affect the subsequent discussion. Total minute ventilation is plotted against pH_a (fig. 1, top row), for the purpose of comparing the magnitude of the suprathreshold pH_a stimuli at the two levels of anesthesia.

Accuracy of measurement requires that the level of anesthesia, the blood carbon dioxide tension and the volume of ventilation shall all be constant for about ten minutes before each measurement. This "steady state" is necessary because of the time lag between a change in one of these factors and its effect on the other two.[12] The relative merits of diverse methods of establishing the curves can be assessed in terms of how closely they approach this ideal. Rebreathing methods [13, 14, 15] depart from this ideal inasmuch as the P_{CO_2} is changing continuously throughout the test. On the other hand, inhalation of a fixed carbon dioxide mixture through a nonreturn circuit would produce the desired steady state,[18] but is inapplicable for determination of the threshold. In the present study a respiratory steady state was approximated during both threshold and spontaneous ventilation. However, our method suffers from the disadvantage that an unanesthetized control is not available, since a carbon dioxide threshold cannot ordinarily be demonstrated during wakefulness.[5]

The results seem significant in two respects. Firstly, they provide critical documentation of the progressive depression of the ventilatory response to CO_2-H^+ with increasing concentrations of halothane, suggested in an earlier report.[8] The ventilation volumes may seem unduly low, but it must be emphasized that

TABLE 2. Ventilation and Blood Acid-Base Balance During Halothane Anesthesia—Averages

	Halothane Concentration (%)	State of Ventilation	V (l./minute)	pH_a	P_{aco_2} (mm. Hg)	ΔpH_a	ΔP_{aco_2} (mm. Hg)	Response-Stimulus Ratio	
								$V/\Delta pH_a$ (%)	$V/\Delta P_{aco_2}$
A	1.5	S	4.50	7.311	47.3				
		Thr		7.353	43.6	.042	3.7	1.07	1.22
	2.5	S	3.98	7.280	51.3				
		Thr		7.341	45.1	.061	6.2	0.65	0.64
B	1	S	4.69	7.325	44.6				
		Thr		7.345	41.3	.020	3.3	2.35	1.42
	2	S	4.06	7.300	49.1				
		Thr		7.340	44.6	.040	4.5	1.01	0.90
C	1	S	5.86	7.285	49.1				
		Thr		7.350	38.6	.065	10.5	0.90	0.56
	2	S	4.21	7.248	58.0				
		Thr		7.296	49.1	.048	8.9	0.87	0.47
D	1.5	S	4.61	7.304	49.3				
		Thr		7.347	44.7	0.43	4.6	1.07	1.00
	2.0	S	4.38	7.260	57.3				
		Thr		7.301	49.0	.041	8.3	1.07	0.54
E	1.5	S	4.83	7.345	43.6				
		Thr		7.380	38.8	.035	4.8	1.40	1.15
	2.5	S	3.74	7.260	54.3				
		Thr		7.310	48.1	.050	6.2	0.75	0.60

S = Spontaneous respiration. Thr = Threshold.

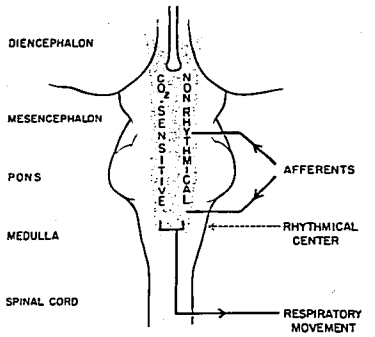

FIG. 2. Proposed functional scheme of respiratory regulating network. The rhythmical respiratory center of the brain stem is activated by excitation of a nonrhythmical network in the reticular core. The nonrhythmical excitation is increased by afferent impulses and, within limits, by carbon dioxide.

the observations were made preoperatively, in the absence of any surgical stimulation. The relative depression of the responses at two halothane concentrations can be appreciated by comparing the slopes in each pair of curves in figure 1. The reduced slope at the higher anesthetic concentration is quite clear.

Importance is also attached to the rise in the threshold Pa_{CO_2} as anesthetic depression increases. A similar rise has been seen with thiopental and with cyclopropane (unpublished observations). It appears that elevation of the rhythmic respiration threshold P_{CO_2} is a frequent accompaniment of anesthetic depression.

The mechanism of the change in threshold P_{CO_2} and *p*H with deeper anesthesia is not immediately obvious. It might be regarded as a sign of decreased sensitivity of the "respiratory center," but this concept requires qualification inasmuch as the sensitivity to carbon dioxide probably does *not* reside mainly in the rhythmically firing medullary neurons of the "respiratory center." The qualification arises out of work by von Euler and Söderberg with decerebrated cats.[17] They studied the results of 6.5 per cent CO_2 and of reflex stimulation before and after chloralose. Before anesthesia both CO_2 and reflex stimulation produced rhythmic discharges in the phrenic nerve. During anesthesia the response to CO_2 was strikingly reduced, whereas the effect of reflex stimulation was unaltered. They inferred that the CO_2-sensitive neurons inactivated by chloralose must lie outside the reflex coordination pathways. Further observations were made with microelectrodes in the completely denervated rhombencephalon. The behavior of rhythmical respiratory neurons of the medulla was compared with that of nonrhythmical randomly-firing reticular neurons in the same region. Both groups were inactivated by overventilation and both were reactivated by the addition of carbon dioxide. They concluded that "carbon dioxide acts by generating impulses in a special chemoreceptor system within the medulla oblongata, probably intermingled with respiratory neurons of the reticular formation." It may be pointed out that CO_2-sensitive neurons are not confined to this region. There is evidence for the existence throughout the length of the brain stem-including areas where rhythmical respiratory activity has never been observed—of reticular neurons sensitive to carbon dioxide.[19] There are thus grounds for suspecting in the brain stem an extensive nonrhythmical network sensitive to carbon dioxide, depressible by chloralose, and capable of triggering activity of the rhythmical respiratory neurons. Such nonrhythmical CO_2-sensitive neurons would have to be regarded as part of the respiratory regulating network (fig. 2).

In terms of this concept, the threshold P_{CO_2} observed in our studies is the carbon dioxide tension at which excitation of the nonrhythmical network becomes intense enough to trigger rhythmical neurons. This does not imply that the rhythmical neurons are themselves completely insensitive to CO_2. The implication is rather that whatever excitation these cells undergo from other causes is facilitated by the CO_2-induced excitation of the nonrhythmical network. Anesthetics can be conceived as reducing the number of excitable neurons in nerve nets, such as the respiratory network. Insofar as the nonrhythmical part of this network is concerned, greater stimulation would have to be applied to the remaining neurons to arouse the network collectively to the same activity as before anesthesia. In particular a stronger CO_2-H^+ stimulus would be required to raise the collective nonrhythmical excitation

to the triggering threshold of the rhythmical neurons.

The distribution limits of the nonrhythmical CO_2-sensitive neurons are not known, but there are several indications that these neurons may include much or all of the reticular activating system (R.A.S.). According to Dell [18] corticogram-activating neurons of the R.A.S. are just as sensitive to carbon dioxide as the respiratory neurons of the medulla. Stimulation of the R.A.S. by carbon dioxide [19] by direct electrical stimulation [20, 21] by adrenalin and noradrenalin,[19] chemoreflexly by hypoxia [19, 22] and physiologically in arousal from sleep [23] is in every instance accompanied by stimulation of respiration. Contrariwise, depression of the R.A.S. always depresses respiration, whether produced by anesthetics,[24, 25] injury [26, 27] or natural sleep.[22] Since carbon dioxide stimulates the R.A.S. and the R.A.S. stimulates respiration it seems quite feasible that the R.A.S. may mediate part of the stimulating effect of carbon dioxide on respiration.

Bülow and Ingvar [23] have reported that, in arousal from sleep, activation of the electroencephalogram and of ventilation occur simultaneously. They think that activation of the R.A.S. may be responsible for both. In anesthesic sleep depressed wakefulness activity of the brain is accompanied by partial R.A.S. deactivation. We suggest that such deactivation may be a major cause of the concomitant decrease in the ventilatory response to carbon dioxide.

Summary

Ventilation and arterial pH and P_{CO_2} were studied in 5 patients anesthetized successively with two different concentrations of halothane. Respiratory thresholds were determined by monitoring the diaphragm electromyogram during controlled overventilation. With increased concentration of anesthetic, stronger carbon dioxide and H^+ stimuli were required to initiate rhythmic activity in the diaphragm; ventilation per unit pH or P_{CO_2} change was generally diminished and spontaneous respiratory minute volume decreased.

The progressive rise of the respiratory carbon dioxide threshold with increasing anesthetic depression, and the absence of such a threshold during wakefulness, suggest a new functional scheme for the organization of the central respiratory regulating system. According to this scheme activity of the rhythmical respiratory neurons of the brain stem is triggered from a more extensive, nonrhythmical, CO_2-sensitive network which may include part or all of the brain stem reticular activating system. Deactivation of the nonrhythmical network by anesthetics may account for much of the observed reduction in ventilatory response to CO_2. Independent supporting evidence for these views is discussed.

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SURGICAL MORTALITY The records of 33,224 patients anesthetized in a ten-year period were analyzed to determine the contribution of anesthesia to death in surgical patients. Patients were divided into two groups, one given spinal anesthesia (18,737 patients) and the other given general anesthesia and a relaxant (14,487 patients). There were no deaths attributable to anesthesia in the 16,000 physically fit patients anesthetized by either technique. As the patients' physical condition worsened, deaths related to anesthesia increased in incidence. In the moribund patients, 1 in 16 patients given spinal anesthesia died of causes related to the anesthesia, and in 1 in 10 patients, general anesthesia could not be excluded as contributing to death. Of 6,000 physically fit patients who received a muscle relaxant, none died. No evidence of an inherent toxicity of muscle relaxants could be found. When deaths were related to the use of muscle relaxants, errors of omission or commission were always apparent. (*Dripps, R. D., and others: The Role of Anesthesia in Surgical Mortality, J. A. M. A. 178: 261 (Oct. 21) 1961.*)