

Ventilatory Responses to Hypoxia and Hypercapnia during Halothane Sedation and Anesthesia in Man

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To elucidate the effects of halothane on chemical regulation of ventilation in man, the authors studied the ventilatory responses to isocapnic hypoxia and hyperoxic hypercapnia in 33 human subjects while fully conscious and during sedation or anesthesia with halothane, .1, 1.1, or 2 MAC. In each group, the ventilatory effect of intravenous administration of doxapram, .4 mg/kg, was also measured. Halothane, 1.1 and 2 MAC, totally abolished the hypoxic response and nearly abolished the response to doxapram, while leaving the response to CO₂ relatively brisk. Halothane, .1 MAC, decreased the responses to hypoxia and doxapram to less than a third of control, but did not alter the response to CO₂. It is concluded that halothane selectively impairs two ventilatory responses mediated by peripheral chemoreceptors in man. (Key words: Anesthetics, volatile: halothane. Receptors: chemoreceptors. Ventilation: carbon dioxide response; oxygen response; regulation.)

NUMEROUS STUDIES have established that halogenated hydrocarbon anesthetics decrease ventilation and the ventilatory response to inhaled carbon dioxide, in a dose-related fashion. However, there is no information about the influence of these drugs on the ventilatory responses to hypoxia and metabolic acidosis in man. Animal studies have suggested that peripheral chemoreceptor-mediated reflexes are relatively durable and resistant to the depressant effects of anesthetic drugs,¹ although recent studies of the hypoxic chemoreflex in dogs anesthetized with halothane, enflurane, or isoflurane contradict that prediction.^{2,3} In this study we measured the ventilatory effects of brief periods of isocapnic hypoxia and hyperoxic hypercarbia and the ventilatory responses to injection of a small dose of doxapram in human subjects while conscious and sedated or anesthetized with halothane.

Methods

We studied 24 patients and nine physicians. The former were outpatients scheduled for elective dental surgical procedures, and the latter were either anesthesiologists or trainees in anesthesia. All were healthy, taking no medication, and without characteristics known to

influence ventilatory control.⁴ Mean value (\pm SD) for age was 24 ± 5 years, weight 70 ± 9 kg, and height 171 ± 9 cm. The patients were naive with respect to respiratory physiology. Excepting two physicians, no subject had previously served as an experimental subject. Each was informed of the experimental design, including a full explanation of the nature, purpose, and risks of each study, as a prerequisite for informed consent.

The 33 subjects were divided into three groups, each group to be studied at one dose of halothane, .1, 1.1, or 2 MAC. The 15 subjects in the 1.1 MAC group and ten subjects in the 2 MAC group consisted mainly of patients. The eight subjects in the .1 MAC group were mainly physicians.

Halothane studies were always first and, to avoid long periods of fasting, early in the day. We studied the patients during a period of anesthesia prior to their planned surgical procedures; we studied the physicians at a time of convenience. None received any premedicant drugs.

Subjects in the 1.1 and 2 MAC groups were positioned supine. With an intravenous catheter and, in some instances, an arterial catheter in place, anesthesia was induced with either halothane or sodium thiopental, 3-4 mg/kg. Following succinylcholine, 1 mg/kg, and topical application of lidocaine, 4 per cent, to the glottis and upper trachea, the trachea was intubated with an 8- or 9-mm cuffed endotracheal tube. Halothane and oxygen were administered by a nonrebreathing system with inspired halothane concentrations appropriate for the end-tidal concentration desired (*i.e.*, concentrations equivalent to 1.1 or 2 MAC). A 30-min administration was allowed to achieve both an unvarying end-tidal halothane concentration, which would be a reasonable index of anesthetic depth,⁵ and a new steady state for CO₂ elimination.

To evaluate the potential effects of the thiopental-succinylcholine sequence on the 1.1 and 2 MAC responses, in one subject at each depth anesthesia was induced with halothane, and following intubation, maintained with halothane alone. The usual testing was performed and then the subject was given thiopental, 4 mg/kg, while halothane administration continued. In the period following thiopental, tests of responses to CO₂ were repeated every 10 or 15 min. To evaluate the influence of endotracheal intubation, in five subjects anesthesia was induced with thiopental

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and maintained with halothane, 1.1 MAC; these subjects were tested in the usual fashion while they breathed through a mask. The tracheas of these subjects were then intubated and testing was repeated.

Subjects for study at halothane, .1 MAC, were seated comfortably in a chair with a mouthpiece and a nose clip in place. Sedation was induced and maintained with halothane in oxygen, administered by a nonbreathing system. Inspired halothane concentrations were set to achieve .1 MAC end-tidal, allowing 30 min for equilibration.

In all groups, a period of resting ventilation was measured while the subject inspired oxygen from a nonbreathing circuit. End-tidal CO₂ was recorded. Subsequently, individual chemical challenges were administered (the order of presentation varying from subject to subject) and the ventilatory response to each was determined. After each challenge, the subject was allowed to breathe unstressed for approximately 10 min, insuring that ventilation and end-tidal CO₂ values were again steady before commencing the next test.

Hypoxia was produced by a progressive and nonbreathing technique. Beginning with an F_IO₂ greater than .95, air and then nitrogen were progressively added to the inspired gas, such that end-tidal oxygen tension values decreased to approximately 40 torr over an 8–10-min period. End-tidal carbon dioxide tension values were held constant throughout by adding carbon dioxide to the inspired gas as necessary. Ventilation and end-tidal gas values were recorded continuously. In eight subjects at halothane, 1.1 MAC, the hypoxic response was also assessed at two or three additional steady-state CO₂ levels, created by the addition of carbon dioxide to the inspired gas for a period of at least 10 min.

Hypercarbia was produced by the method of Read.⁶ The subject's airway was connected to a 6–7-l rebreathing circuit that initially contained CO₂, 7 or 8 per cent in oxygen, along with an appropriate concentration of halothane to maintain sedation or anesthesia constant. After four or five large tidal volume exchanges with the circuit, the subject breathed spontaneously while his CO₂ levels progressively increased. In most subjects, there was a plateau of inspired and expired CO₂ concentrations when the circuit initially contained 7 per cent CO₂; however, in some anesthetized subjects an initial CO₂ concentration of 8 per cent was necessary. The test was terminated at a circuit CO₂ concentration of 9–9.5 per cent, which was usually achieved within 6 min. Ventilation and gas concentrations in the circuit were continuously recorded. In eight subjects at halothane, 1.1 MAC, responses to CO₂ were also assessed by the classic steady-state method. Three or four levels of hypercarbia were created by adding

various concentrations of CO₂ (3 to 8 per cent) to the inspiratory limb of a nonbreathing circuit, each for a 10- or 12-min period. With a new end-tidal CO₂ stable over 2 min, a sample of arterial blood was drawn for blood-gas analysis and ventilation was recorded.

The ventilatory effects of doxapram, .4 mg/kg, were determined for 60 sec following its injection as a bolus in four subjects breathing halothane–oxygen at .1 MAC, six subjects at 1.1 MAC, and five subjects at 2 MAC.

Throughout the studies in the sedated and anesthetized states, attention was paid to maintaining end-tidal halothane concentrations constant. Pulse rate, blood pressure and EKG were continuously monitored. Subjects at 1.1 and 2 MAC halothane received an infusion of dextrose, 5 per cent, in .2 per cent saline solution, to as much as 1,000 ml over the study period, and occasionally more when necessary to keep systolic blood pressure within 30 torr of the awake value. Nasopharyngeal temperature was measured during anesthesia and remained above 36 C in all subjects.

We studied 30 subjects in the awake state. Those who had had operations were tested only when their incisions had completely healed and they were without discomfort. On the day of conscious testing, the subjects were allowed to eat, but instructed to avoid caffeine-containing drinks. Tests were conducted with the subject seated in a comfortable chair, quiet music playing on the radio, and the laboratory lights dim. Initially 30 min were spent familiarizing the subject with the sensations of a nose clip and mouthpiece, hypoxia and hypercarbia. We found these practice periods to be essential for obtaining normal resting end-tidal CO₂ values, as well as reproducible hypercarbic and hypoxic responses. Procedures for producing the various chemical challenges were identical to those used during anesthesia. In most cases, ventilation was recorded and the isocapnic hypoxic response tested at the CO₂ level that had been present during steady-state anesthesia. This level was recreated in the awake state by adding CO₂ to inspired gas for a 10–12-

ABBREVIATIONS

PET _{CO₂}	= end-tidal carbon dioxide tension
PET _{O₂}	= end-tidal oxygen tension
\dot{V}_I	= inspired minute ventilation
$\Delta\dot{V}_I$	= change of inspired minute ventilation
\dot{V}_I at P _{CO₂} 55 torr	= inspired minute ventilation at a PET _{CO₂} of 55 torr
$\Delta\dot{V}_I$ 45	= isocapnic change of inspired minute ventilation from hyperoxia to a PET _{O₂} of 45 torr
"A"	= calculated variable of hypoxic responsiveness (see Methods)
F _I O ₂	= inspired oxygen concentration

min equilibration period. In five subjects who had been studied at halothane, 2 MAC, higher anesthetic CO₂ levels were not well tolerated in the conscious state, and awake hypoxic responses could be reliably determined only at the resting conscious CO₂ value.

In all studies, expired gases were continuously sampled and analyzed by a Perkin Elmer 1100 mass spectrometer for carbon dioxide, oxygen, and halothane concentrations. The carbon dioxide and oxygen signals were calibrated each testing day with Canadian Liquid Air Specialty Gases; the halothane signal was regularly checked against the calculated vapor concentrations of measured amounts of halothane injected into a closed chamber. During testing, the three signals were simultaneously and continuously fed to a strip-chart recorder, from which end-tidal plateau concentrations could be read. End-tidal halothane was the index of anesthetic depth; end-tidal carbon dioxide and oxygen concentrations, converted to tensions, were the indices of Pa_{CO₂} and Pa_{O₂}.

In the hypoxic test, our measured index of hypoxemia was usually the end-tidal oxygen tension. In simultaneous measurement of end-tidal and arterial blood oxygen tensions in three subjects tested awake and anesthetized, we found that arterial blood tension values were always less than end-tidal, but in the range of oxygen tension values below 80 torr this difference was always less than 6 torr. Thus, where ventilation was changing (*i.e.*, Pa_{O₂} less than 70 torr), the end-tidal oxygen tension value underestimated the arterial blood oxygen stimulus slightly.

During the Read rebreathing test, changes in the end-tidal (or circuit) CO₂ tension were taken to represent the CO₂ stimulus. With adequate equilibration of alveolar and circuit CO₂ at the beginning of this test, the change in circuit CO₂ tension—the “meas-

ured” stimulus—approximates the change of brain or medullary CO₂ tension—the “actual” stimulus.⁷

When arterial blood-gas analysis was needed, *i.e.*, for steady-state responses and some hypoxic responses, blood was drawn anaerobically through a radial arterial cannula into previously heparinized syringes. These were immediately capped and placed on ice, and the blood was analyzed within 30 min with a Radiometer Copenhagen BMS 3 system, which was calibrated with tonometered blood daily. Values of dried end-tidal gas concentrations were converted to tensions, using the measured barometric pressure of the day of testing.

In all studies, inspired ventilation was measured with a pneumotachograph head incorporated into the inspiratory limb of each circuit, and both the flow signal and its integral (*i.e.*, volume) were recorded. Volume was regularly calibrated with an air calibration syringe, and correction factors were applied for the density and viscosity of the various gas mixtures inspired. Instantaneous ventilation was calculated from the averaged respiratory cycle lengths and inspired volumes of three consecutive breaths. All ventilatory volumes are expressed at BTPS.

Hypoxic responses were analyzed in two ways. First, we measured the change in instantaneous inspired ventilation between P_{O₂} 400 torr and P_{O₂} 45 torr, calling this the “Δ $\dot{V}_{I_{45}}$.” Second, data points relating inspired ventilation to P_{O₂} were fitted to the following regression equation, a modification of that proposed by Weil *et al.*⁸:

$$\dot{V}_I = \dot{V}_{I_0} + \frac{A}{P_{O_2} - 30}$$

This equation assumes a hyperbolic relationship between the increment of ventilation and P_{O₂}, where the constant 30 represents the P_{O₂} at which the extrap-

TABLE 1. Ventilation and Responses (Mean ± SEM) to Stimuli at Various Depths of Halothane Anesthesia

	Halothane, .1 MAC		Halothane, 1.1 MAC		Halothane, 2 MAC	
	Awake	Sedated	Awake	Anesthetized	Awake	Anesthetized
Ventilation l/min PET _{CO₂} (torr)	(n = 8) 6.9 ± .7* 39 ± 1.9	(n = 8) 6.7 ± .6 39 ± 1.3	(n = 13) 11.2 ± 1.1* 43 ± 1.4†	(n = 15) 5.8 ± .5§ 43 ± 1.2	(n = 9) 12.4 ± 1.5* 43 ± 2.0†	(n = 10) 5.4 ± .5§ 47 ± 1.4
Hypoxic response Δ $\dot{V}_{I_{45}}$ (l/min) “A” (l·torr/min)	(n = 8) 9.5 ± 2.1 153 ± 35	(n = 8) 2.9 ± .9§ 43 ± 16§	(n = 13) 11.5 ± 2.1 210 ± 36	(n = 15) -.3 ± .3§ -7 ± 4§	(n = 9) 9.4 ± 2.6 153 ± 57	(n = 10) -.3 ± .3§ -2 ± 6§
Doxapram response Δ \dot{V}_I (l/min)	(n = 5) (16.1 ± 2.9)‡	(n = 4) 4.8 ± 3.3§	(n = 5) (16.1 ± 2.9)‡	(n = 6) 1.1 ± .8§	(n = 5) (16.1 ± 2.9)‡	(n = 5) 1.4 ± .3§
CO ₂ response Slope (l/min/torr) \dot{V}_I at P _{CO₂} 55 torr (l/min)	(n = 8) 1.9 ± .2 23.0 ± 2.8	(n = 8) 1.9 ± .2 22.5 ± 2.2	(n = 13) 2.2 ± .3 28.0 ± 3.5	(n = 15) .8 ± .3§ 10.4 ± .8§	(n = 9) 2.3 ± .4 28.1 ± 3.8	(n = 10) .4 ± .1§ 8.1 ± 1.0§

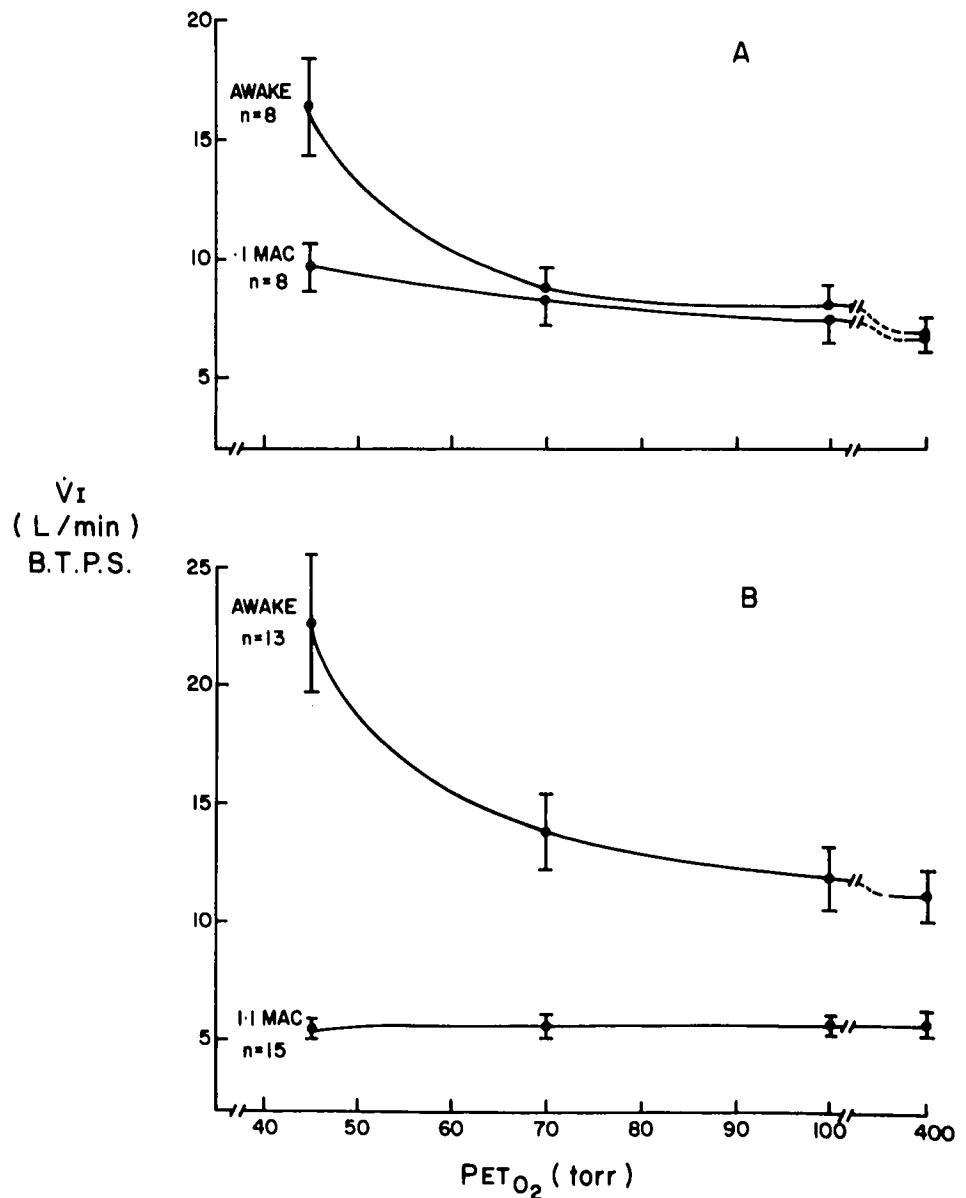
* Values of ventilation at PET_{CO₂} indicated.

† PET_{CO₂} matched to anesthetic value by inhaling CO₂.

‡ Doxapram response of an independent sample of awake normo-capnic subjects.

§ Significantly different from awake value, P < 0.05.

FIG. 1. Graphic representations of mean ventilatory responses to progressive hypoxia for all subjects at halothane .1 MAC (A) and 1.1 MAC (B). Control responses in the awake isocapnic states are also shown. Each response is represented by four points, mean inspired ventilation values (\pm SEM) at $P_{ET}O_2$ 400, 100, 70, and 45 torr. Lines approximating the usual responses are handdrawn through these points. Halothane sedation (.1 MAC) depressed the awake hypoxic response; halothane anesthesia (1.1 MAC) totally abolished it.



olated slope of the $\dot{V}_I:P_{O_2}$ curve approaches infinity and the \dot{V}_{I_0} represents the \dot{V}_I at high P_{O_2} where the extrapolated slope approaches zero. The computed variable "A" has the units $l \cdot \text{torr}/\text{min}$. It represents the shape of the hyperbolic curve and therefore also the hypoxic response, such that the greater the response, the higher the "A" value. Whether ventilation increased or decreased during hypoxia, our data points fit this equation well. (This equation does not necessarily have physiologic meaning, and the "A" value should be considered no more than a convenient representation of the hypoxic response). The recorded response to doxapram was the maximum change in instantaneous ventilation following injection. Analysis of the responses to CO_2 was by least-squares linear regression of ventilation as a function of P_{CO_2} . We

report the slope of the regression and, to indicate the position of the curve, the actual ventilation at P_{CO_2} 55 torr.

Statistical evaluation of most of our data employed the two-tailed t test for paired samples. The awake subjects for the doxapram response were different from those sedated and anesthetized; accordingly, the doxapram data were analyzed with a t test for independent samples. P values of 0.05 or less were regarded as significant.

Results

There was no untoward effect of the studies we are reporting. At halothane, 1.1 and 2 MAC, all subjects were unconscious; at halothane, .1 MAC, sub-

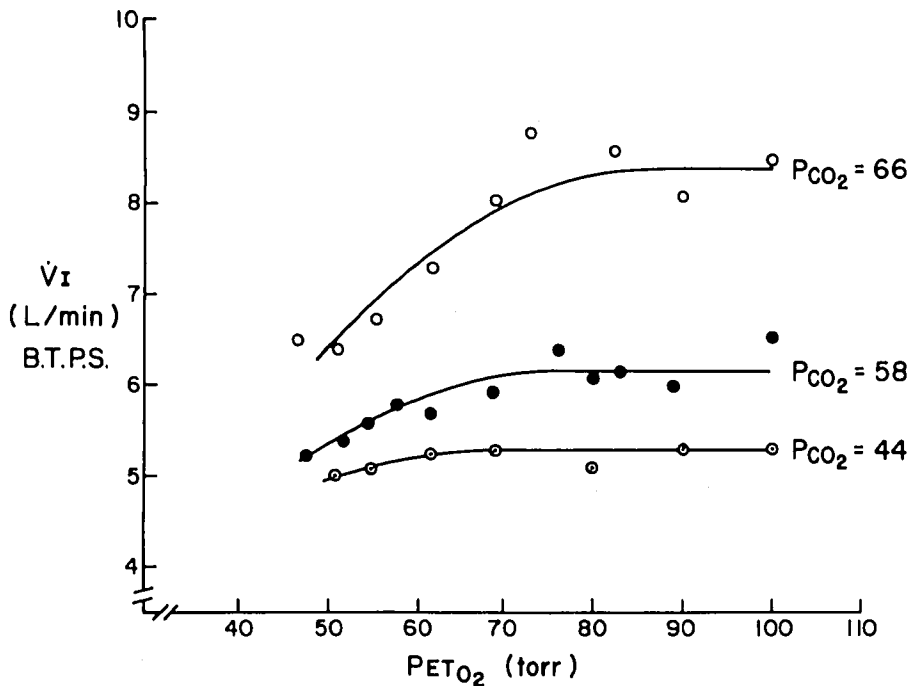


FIG. 2. Relation of inspired ventilation to P_{ETO_2} at three steady-state P_{aCO_2} levels for a halothane-anesthetized subject (1.1 MAC). Ventilatory depression during hypoxia, which was slight at P_{aCO_2} 44 torr, became greater as P_{aCO_2} increased. The ventilatory increase produced by a P_{aCO_2} change of 44 to 66 torr during normoxia was greater than the ventilatory change effected by the same change in P_{aCO_2} during hypoxia. Hypoxia decreased the ventilatory response to carbon dioxide.

jects were sedated but well-oriented and had full recollection of the study afterwards.

Halothane, .1 MAC, had no discernible effect on resting ventilation and end-tidal P_{CO_2} (table 1). Halothane, 1.1 and 2 MAC, decreased mean resting ventilation and increased mean end-tidal CO_2 . As the main purpose of this work was to compare hypoxia responses at identical CO_2 levels, we recorded awake ventilation at CO_2 levels similar to those present during anesthesia (Table 1). Halothane, 1.1 or 2 MAC, nearly always abolished the ventilatory response to isocapnic hypoxia, and .1 MAC greatly decreased it (fig. 1, table 1). In 13 of 15 subjects at 1.1 MAC and in seven of 10 at 2 MAC, halothane also unmasked a slight ventilatory depression during hypoxia, accounting for the mean negative $\Delta\dot{V}_{I_{15}}$ and "A" values of these groups. The ventilatory depressant effect of hypoxia in 1.1 MAC subjects became relatively greater at higher P_{aCO_2} values (fig. 2). The mean slope of the normoxic steady-state CO_2 responses of eight subjects at halothane, 1.1 MAC, was $.25$ l/min/torr $\pm .06$ (SEM), and the mean slope of their hypoxic steady-state CO_2 responses was $.18$ l/min/torr $\pm .04$. Thus, during halothane anesthesia, hypoxia decreased both ventilation and the ventilatory response to CO_2 .

The ventilatory response to CO_2 was unchanged from awake at halothane, .1 MAC (table 1). At 1.1 MAC, the mean slope of the responses to CO_2 was 38 per cent of the awake slope; at 2 MAC it was only 17 per cent of control. The mean steady-state CO_2 response of eight subjects at halothane, 1.1 MAC, was

$.25$ l/min/torr $\pm .06$, a value significantly lower than this group's mean Read CO_2 response of $.59$ l/min/torr $\pm .07$.

The ventilatory response to doxapram was decreased to a third of the awake value by halothane, .1 MAC, and halothane 1.1 and 2 MAC nearly eliminated it (table 1).

There was no discernible difference between the hypoxic and hypercapnic responses of anesthetized subjects induced with and without thiopental and succinylcholine. In the two who received an induction dose of thiopental during a steady state of halothane anesthesia, there was a transient depression of ventilation and a decreased CO_2 response for approximately 25 min. Subsequently, the hypercapnic responses were virtually identical to those prior to thiopental. Responses of anesthetized subjects with and without endotracheal intubation were nearly the same.

To compare the relative activity of each chemoreflex in each halothane state, we calculated the mean response to each chemical challenge as a percentage of the awake response (fig. 3). The variables used for this comparison were: for hypoxia, the $\Delta\dot{V}_{I_{15}}$ for doxapram, the maximum increase in ventilation following injection; for CO_2 , the slope of the ventilation: P_{CO_2} relationship. At each halothane dosage, responsiveness to hypoxia and doxapram was decreased approximately in parallel and out of proportion to the change in hyperoxic CO_2 response. The selectivity of this effect was most obvious at halothane, .1 MAC, where the response to CO_2 was unchanged from the

awake response, but the other two were clearly depressed.

Discussion

During periods of hypoxemia, normal awake man rapidly increases his pulmonary ventilation. The principal new findings of this work are that during halothane sedation, this hypoxic chemoreflex is very much less active, and during halothane anesthesia, it is usually nonexistent.

While there has been considerable investigation into the medullary chemoreceptor-mediated response to carbon dioxide in anesthetized man, very little has been known of the effects of anesthetic drugs on ventilatory responses mediated by the peripheral chemoreceptors, the carotid bodies. These tiny arterial receptors sense arterial oxygen tension and pH. Normally, they contribute only 15 per cent of the overall drive to ventilation. However, during hypoxemia or acute systemic metabolic acidosis, their contribution to ventilatory drive is greatly augmented, to effect the increase in ventilation that helps to compensate for these states. In the past, laboratory testing of these reflexes during anesthesia has suggested that they are rather durable and resistant to anesthetic depression.⁹⁻¹¹ The results of more recent studies are at variance with this general hypothesis. The studies of Hirshman and co-workers in dogs indicate that barbiturates, ketamine, halothane, enflurane, and isoflurane decrease the hypoxic and hypercarbic reflexes more or less in parallel.^{3,12} Weiskopf's data from dogs anesthetized with halothane suggest a relatively greater depression of the hypoxia than the CO₂ chemoreflex.² One must be cautious in extrapolating any of these findings to man, since species may vary considerably in both the proportions of their chemical drives originating from peripheral chemoreceptors¹³ and the susceptibilities of peripheral chemoreceptor-mediated responses to pharmacologic stimulation and depression.¹⁴

Our findings of a loss of the ventilatory response to isocapnic hypoxia at surgical levels of halothane anesthesia, along with a marked depression at a sedating dose of the drug, must be interpreted with respect to man alone and with respect to the particular conditions we studied. In man, halothane, 1.1 and 2 MAC, generally abolished the hypoxic reflex; in dogs, the effects of similar doses of halothane were not so complete.^{2,3} The subjects of this study were anesthetized only, *i.e.*, there was no surgical stimulation. Surgical stimulation obviously augments ventilation; whether it also affects the hypoxic response is not known. The episodes of hypoxia we studied were progressive and

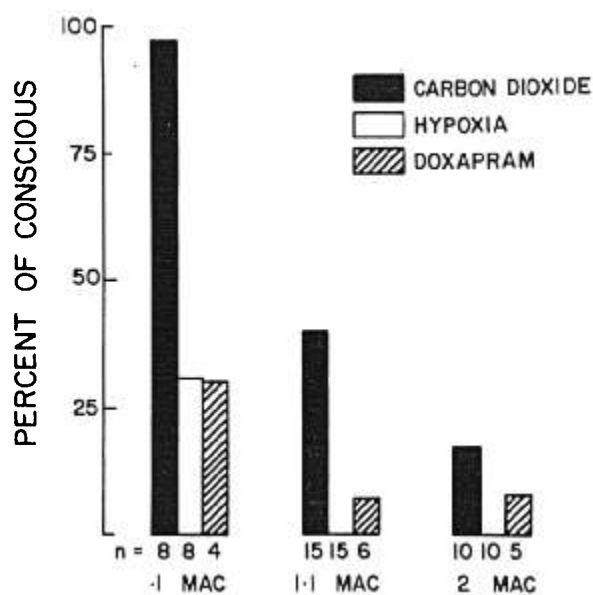


FIG. 3. Relative activity of each chemoreflex at each halothane dosage studied. Bar heights represent the mean responses as percentages of control or awake. The index of each response used is stated in the text. In each halothane state, there was a disproportionate depression of responses to hypoxia and doxapram. Hypoxic responses at halothane, 1.1 and 2 MAC, were absent.

brief. Our results cannot necessarily be applied to longer periods of hypoxia, where secondary effects such as chemoreceptor adaptation, increased circulating levels of catecholamines, and lactic acid formation may assume some importance in ventilatory control.

In most of our anesthetized subjects, anesthesia was induced with a thiopental-succinylcholine-tracheal intubation sequence. Our findings indicate that these factors did not influence the anesthetic hypoxic response. In man, thiopental-induced changes in hypoxic response parallel changes in response to CO₂.¹⁵ We found that the CO₂-response effect of thiopental was dissipated 30 min following its administration, and that the hypoxic response was no different with or without these additional drugs or stimulus.

There are few human studies with which data on hypoxic responsiveness during anesthesia can be compared. The corollary of an absent ventilatory response to hypoxia would be an absent response to hyperoxia, *i.e.*, no ventilatory depression following the inhalation of two breaths of oxygen (Dejour's test). Duffin *et al.* examined this response in man anesthetized with halothane and undergoing surgical procedures and reported it to be virtually absent.¹⁶ Our finding of a selective depression of the hypoxic response at subanesthetic doses of halothane is analogous to what Yacoub *et al.* observed with subanesthetic doses of nitrous oxide.¹⁷

Three features of the absent hypoxic response during anesthesia were of particular interest. First, although there was usually no increase in overall ventilation during hypoxia, there was always an increase in respiratory frequency (at 1.1 MAC 4 ± 1 breaths/min and at 2 MAC 5 ± 2 breaths/min), with tidal volume simultaneously decreasing. Second, the decrease in tidal volume was often relatively greater than the increase in frequency, such that their product was decreased slightly (table 1). Third, the decrease in ventilation was proportionately greater when hypoxia was induced at increased CO₂ levels, meaning that hypoxia decreased the ventilatory response to carbon dioxide (fig. 2). These hypoxia-induced changes in pattern of ventilation, overall ventilation, and responsiveness to CO₂ are reminiscent of what has been observed in both animals and man deprived of peripheral chemoreceptor function.¹⁸⁻²⁰ Assuming that halothane was desensitizing peripheral chemoreceptors, we wondered whether this effect would be specific for hypoxia or might include other peripheral chemoreceptor-mediated responses.

Doxapram drives ventilation in man exclusively through a peripheral chemoreceptor action; Severinghaus has proposed this as a test of peripheral reflex function.²¹ Halothane sedation decreased the response to this stimulant, and anesthesia virtually abolished it (table 1). Moderate acute systemic metabolic acidosis also drives ventilation through peripheral chemoreceptor activation; Duffin *et al.* have pointed out that this response (which they studied by an indirect method) may be markedly obtunded by halothane in man.¹⁶ Our preliminary results in work on the effect of halothane on ventilatory responses to isocapnic metabolic acidosis (induced moderately and briefly with intravenous ammonium chloride) support Duffin's hypothesis. Together, these data hint that halothane in man may be a potent depressant of several peripheral chemoreceptor-mediated ventilatory reflexes.

For comparative purposes, we also examined the ventilatory response to hyperoxic hypercapnia. Sedation with halothane did not alter this response, while anesthesia decreased it in a dose-related fashion. (The magnitude of this depression depended upon the method of creating the hypercarbic stimulus. During anesthesia, the mean slope of the Read ventilation: P_{CO₂} relationship was more than twice as great as that obtained by the more classic steady-state technique, a finding which is at variance with results of studies of conscious man,^{6,22} but is consistent with what has been observed in human subjects sedated with lorazepam²³). Comparing the effect of halothane on this central chemoreceptor-mediated CO₂ response with

its effects on the two peripheral chemoreflexes tested (*i.e.*, responses to hypoxia and doxapram), it is clear that at each halothane dosage, the depression of the peripherally mediated response was proportionately greater (fig. 3). Indeed, at halothane, .1 MAC, this depressant effect was selective.

Our data suggest a potent action of halothane on one or more components of the peripheral chemoreflex arc that are distinct from the central CO₂ reflex, *i.e.*, peripheral chemoreceptors, their immediate central neural connections, or neural circuits that modulate chemoreceptor input. Further speculation as to site or mechanism of action can be based only on limited evidence from animals. In cats, Biscoe found that halothane decreased the resting activity of afferent fibers from the carotid bodies, as well as their response to induced hypoxia.²⁴ If, as these data suggest, halothane depresses the peripheral chemoreceptors, its action could be a direct one on the sensing mechanism of the receptor (*e.g.*, metabolic changes allowing aerobic metabolism at a lower P_{O₂}) or an indirect one on some factor influencing the transfer function of the receptor (*e.g.*, altered sympathetic control of the organ and/or its blood flow).²⁵ Many investigators have held that blood flow to the chemoreceptors is most important in its activity, with decreased flow augmenting activity (by allowing a build-up of natural stimulants) and increased flow decreasing it.²⁵ Several different substances with the common property of vasodilation have the common effect of decreasing peripheral chemoreceptor discharge, *e.g.*, nitrites, dopamine and epinephrine, as well as halothane.^{14,24,26,27} Could receptor vasodilation and relative hyperfusion be the mechanism by which halothane decreases the hypoxic chemoreflex? Such an explanation would be consistent with Biscoe's observation that the decrease of chemoreceptor discharge associated with halothane is partly reversed by a decreased perfusion pressure and presumably, blood flow.²⁴ A vascular hypothesis would also explain the animal findings that the predominantly vasoconstricting anesthetics, ether and cyclopropane, preserve (or even enhance) both chemoreceptor discharge and the hypoxic chemoreflex,^{9,24} while the predominantly vasodilating anesthetic, halothane, decreases both peripheral chemoreceptor discharge and the hypoxic chemoreflex.^{2,24}

The findings of this study have clinical implications during halothane anesthesia and recovery. The absence of a normal ventilatory response to hypoxia during halothane anesthesia increases the danger of hypoxic episodes; this is especially so when hypoxia causes ventilatory depression (the latter being most apparent when subjects are simultaneously hyper-

carbic). Furthermore, the absence of hyperpnea during hypoxia represents the loss of a useful clinical sign.

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