

Effects of Halothane on Canine Respiratory Responses to Hypoxia with and without Hypercarbia

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The ventilatory response to hypoxia was studied in three dogs in the awake state and during 1.1 per cent end-tidal halothane anesthesia, at three levels of constant P_{aCO_2} (40, 44 and 48 torr). Halothane depressed $\Delta\dot{V}_{t0}$ (the increase in ventilation at P_{aO_2} 40 torr above the normocarbic, hyperoxic ventilation) by 52 per cent at P_{aCO_2} 40 torr, by 65 per cent at P_{aCO_2} 44 torr, and by 59 per cent at P_{aCO_2} 48 torr, compared with the awake state at the same levels of CO_2 . Computer analysis of our data demonstrated a better fit to logarithmic or power functions than to the traditional hyperbolic form. Halothane depressed the ventilatory response to carbon dioxide by 41 per cent at P_{aO_2} 160 torr, by 29 per cent at P_{aO_2} 74 torr, by 65 per cent at P_{aO_2} 52 torr, and by 92 per cent at P_{aO_2} 40 torr, in comparison with the awake responses. The increasing depression of the ventilatory response to carbon dioxide as P_{aO_2} decreased below normoxic levels indicates that, in addition to depressing the ventilatory responses to hypoxia and CO_2 , halothane also interferes with the interaction of hypoxia and hypercarbia in driving ventilation.

(Key words: Anesthetics, volatile: halothane; Hypoxia; ventilatory response; Carbon dioxide; hypercarbia; Ventilation: hypoxic and hypercarbic responses.)

THE RESPIRATORY RESPONSE to carbon dioxide decreases during anesthesia in both man and dog.²⁻⁵ The ventilatory response to hypoxia during anesthesia has been thought to be preserved,⁶ although almost no experimental evidence has been obtained in support of this concept. We therefore studied the ventilatory responses to hypoxemia at several levels of constant P_{aCO_2} , in three dogs, awake and at constant, predetermined alveolar concentrations of halothane. Our findings indicate that halothane anesthesia impairs the ventilatory response to hypoxia to a greater extent than it impairs the ventilatory response to carbon dioxide.

Methods

Three dogs (two beagles and one mongrel) were prepared with chronic tracheostomies and subcutaneous right carotid artery loops,⁷ and trained to sit or lie quietly, without panting, during these studies. The dogs breathed through cuffed tracheostomy tubes attached by a nonbreathing Sierra valve to a closed-circle system. Carbon dioxide within the system was controlled by a variable-bypass CO_2 absorber placed within the circle. A percutaneous catheter was placed in the exteriorized carotid artery (using 1 per cent lidocaine local anesthesia for awake animals), permitting arterial blood sampling and blood pressure recording. Ventilation was recorded using a bellows-driven potentiometer.⁸ End-expiratory oxygen, carbon dioxide and halothane were also recorded.

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Oxygen was determined by a relatively rapidly-responding polarographic oxygen electrode with a stretched ¼-mil teflon membrane (electrode time constant approximately 0.5 seconds), placed in the expired gas line just beyond the nonrebreathing valve. Airway CO₂ was monitored continuously from the tracheostomy tube by an infrared analyzer. End-tidal halothane concentration was frequently determined by manually opening a stopcock between the tracheal catheter and an infrared analyzer. All of the above were recorded on a Gilson 8-channel recorder.

Blood for gas tension and pH analysis was sampled from the carotid-artery catheter and measured by the appropriate electrodes. A special problem noted here and during another study in this laboratory was the instability of P_{O₂} readings in those bloods containing halothane.⁹ Halothane is polarographically reduced at the anode of the oxygen electrode and thus is falsely read as oxygen.¹⁰ During the studies with halothane-anesthetized dogs, the oxygen electrode was carefully ground with an Arkansas stone and the polarizing voltage of the electrode was maintained at 0.55 v. Blood oxygen tensions were read only when we failed to demonstrate a P_{O₂} reading other than zero with halothane vapor in N₂ in the oxygen cuvette. Calibrating gas was read immediately prior to and following each blood analysis and the blood oxygen tensions were corrected for the blood-gas factor (ϕ_b) as described by Hultands, Nunn and Paterson.¹¹ Pa_{CO₂}, Pa_{O₂}, and pH were also corrected for electrode drift and body temperature.

In the anesthetized animals rectal temperature was controlled at 37.5–38.5 C. In the awake animals, periodic checks of rectal temperature were obtained, the observed range being 37.5–38.5 C. Anesthetized animals were studied prone, while the awake animals were allowed to maintain their position of choice, which was usually prone or sitting, but occasionally standing.

Measurements were made following no less than 6 minutes after a change in Pa_{CO₂}, and no less than 3 minutes following a change in Pa_{O₂}. For purposes of data analysis, measurement periods of 1–3 minutes during

a time of stability were used. Each dog was studied on three separate occasions for each of the three conditions: awake; 1.1 per cent end-tidal halothane; 1.7 per cent end-tidal halothane. Only one condition was studied in any one dog on any one day. At least a week elapsed between successive studies of any one animal. Not more than 50 ml of blood were sampled on any one day. In addition to their regular diet, the dogs were given parenteral iron therapy, and their hemocrits were 35–40 per cent.

We did not complete the studies at 1.7 per cent end-tidal halothane because of the almost routine occurrence of severe hypotension.

Results

HYPOXIC RESPONSE

We judged that there were no significant differences among the ventilatory responses of the three dogs to hypoxia, at any level of Pa_{CO₂}, and therefore, the data from all dogs were pooled.

Figures 1–3 illustrate the effects of 1.1 per cent end-tidal halothane on ventilatory responses to hypoxia at three levels of Pa_{CO₂}: 40, 44 and 48 torr.

The data were analyzed by the method of least-squares regression, using six mathematical expressions:

$$Y = A + BX \quad (1)$$

$$Y = Ae^{BX} \quad (2)$$

$$Y = AX^B \quad (3)$$

$$Y = \frac{A}{X - 30} + B \quad (4)$$

$$Y = \frac{A}{X - B} \quad (5)$$

$$Y = \frac{X}{A + BX} \quad (6)$$

where Y = the increase in ventilation above the normocarbic hyperoxic level ($\Delta\dot{V}_E$), and X = Pa_{O₂}. Equation 1 is a linear function; equation 2 is a logarithmic function as applied by Kronenberg *et al.*¹²; equation 3 is

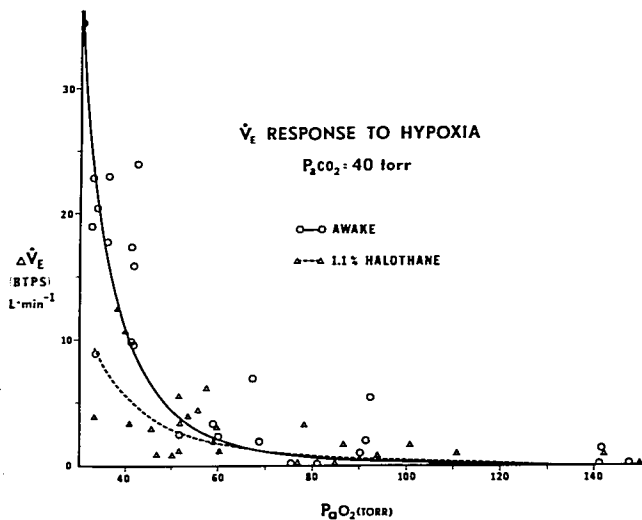


FIG. 1. Effect of 1.1 per cent halothane on the ventilatory response to hypoxia at $P_{a\text{CO}_2}$ 40 torr. See text for description of analysis of data.

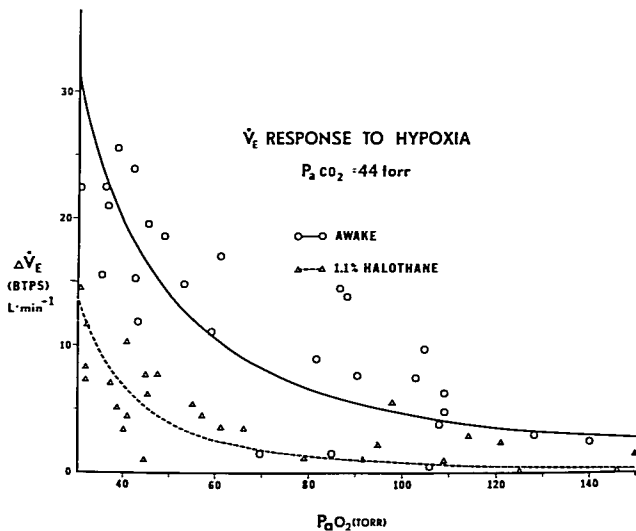


FIG. 2. Effect of 1.1 per cent halothane on the ventilatory response to hypoxia at $P_{a\text{CO}_2}$ 44 torr. See text for description of analysis of data.

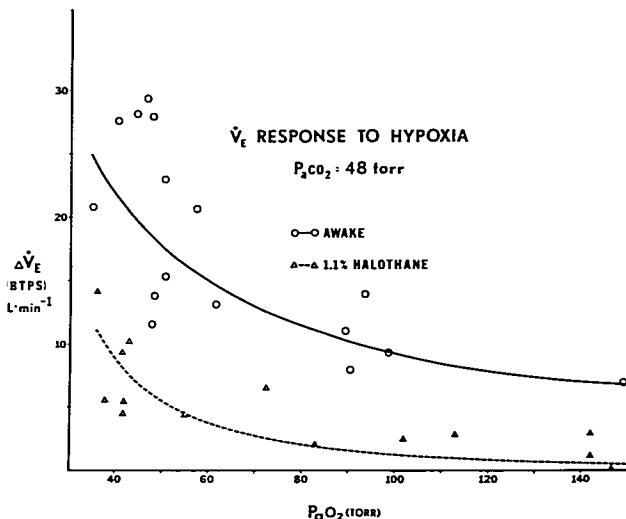


FIG. 3. Effect of 1.1 per cent halothane on the ventilatory response to hypoxia at P_{aCO_2} 48 torr. See text for description of analysis of data.

a power function; equation 5 is the hyperbolic equation as presented by Lloyd, Jukes and Cunningham¹³; equation 4 is the hyperbolic equation with an assumed asymptote of 30 torr, as used by others.¹⁴

General Electric model 225 and UNIVAC model 1106 computers were employed for the above calculations. There was little difference in standard errors and correlation coefficients between equations 2 and 3, whereas the more traditional hyperbolic equation (equation 5) uniformly resulted in lower correlation coefficients and higher standard errors than did the above two. Equation 5 also generally resulted in an unrealistic asymptote (*i.e.*, theoretical P_{aO_2} of maximum ventilation). Equation 4 resulted in mathematical fits of intermediate quality. The computed equations with their correlation coefficients and standard errors are presented in table 1.

Figures 1, 2, and 3 are plots of the computer-calculated power curves (equation

3) of least-squares regression. Inasmuch as there was no difference between the mathematical qualities of fit of the computed logarithmic and power functions (equations 2 and 3) to our data, we chose to present the power curves graphically, since this function seemed to us to best fit the hypoxic data points visually.

It is easily seen from figures 1-3 that at an end-tidal concentration of 1.1 per cent halothane greatly depresses the ventilatory responses to hypoxia at all three levels of P_{aCO_2} studied (40, 44, and 48 torr).

The depression of hypoxic response is quantitated in table 2, which indicates percentage depression of $\Delta\dot{V}_{40}$ ($\Delta\dot{V}_{40}$ is the increase in ventilation at P_{aO_2} 40 torr, above the normocarbic hyperoxic ventilation). The $\Delta\dot{V}_{40}$'s listed in table 2 are those values calculated from the computer-derived equations of logarithmic, power and hyperbolic (with an assumed asymptote of 30 torr) functions (table 1). It can be seen that there

TABLE 1. Ventilatory Responses to Hypoxia, Awake and with 1.1 Per Cent Isoflurane

P _{atm} , (mm)	Condition of dog	$\Delta\dot{V}_E \propto A_{T_{O_2}}$			$\Delta\dot{V}_E \propto A_{T_{O_2}}^{0.75}$			$\Delta\dot{V}_E \propto \frac{A}{X-30} + B$			$\Delta\dot{V}_E \propto \frac{A}{X-1}$		
		Equation	r	SE	Equation	r	SE	Equation	r	SE	Equation	r	SE
-40	Awake	$\Delta\dot{V}_E = 90.0c - \frac{P_{atm}}{18.0}$.75	5.63	$\Delta\dot{V}_E = 43.4 \cdot 10^3 P_{atm}^{-1.12}$.76	5.17	$\Delta\dot{V}_E = \frac{52.4}{P_{atm} - 30} + 3.67$.73	8.64	$\Delta\dot{V}_E = \frac{1.62}{P_{atm} - 38.3}$.58	13.0
	1.1 per cent halothane	$\Delta\dot{V}_E = 18.7c - \frac{P_{atm}}{27.1}$.64	2.58	$\Delta\dot{V}_E = 20.4 \cdot 10^3 P_{atm}^{-2.28}$.64	2.56	$\Delta\dot{V}_E = \frac{23.2}{P_{atm} - 30} + 1.82$.44	3.08	$\Delta\dot{V}_E = \frac{2.33}{P_{atm} - 49.8}$.48	4.38
-44	Awake	$\Delta\dot{V}_E = 47.7c - \frac{P_{atm}}{41.1}$.72	5.81	$\Delta\dot{V}_E = 64.6 \cdot 10^3 P_{atm}^{-1.37}$.73	5.75	$\Delta\dot{V}_E = \frac{113}{P_{atm} - 30} + 6.38$.80	9.62	$\Delta\dot{V}_E = \frac{215}{P_{atm} - 26.1}$.41	8.78
	1.1 per cent halothane	$\Delta\dot{V}_E = 27.0c - \frac{P_{atm}}{29.5}$.73	2.32	$\Delta\dot{V}_E = 40.3 \cdot 10^3 P_{atm}^{-2.28}$.69	2.40	$\Delta\dot{V}_E = \frac{8.98}{P_{atm} - 30} + 3.50$.72	3.69	$\Delta\dot{V}_E = \frac{2.75}{P_{atm} - 48.2}$.51	6.65
-48	Awake	$\Delta\dot{V}_E = 32.6c - \frac{P_{atm}}{35.6}$.67	6.40	$\Delta\dot{V}_E = 67.5 \cdot 10^3 P_{atm}^{-0.92}$.70	6.43	$\Delta\dot{V}_E = \frac{68.7}{P_{atm} - 30} + 13.1$.41	8.11	$\Delta\dot{V}_E = \frac{1054}{P_{atm} - 16.1}$.64	6.95
	1.1 per cent halothane	$\Delta\dot{V}_E = 27.7c - \frac{P_{atm}}{31.7}$.71	2.51	$\Delta\dot{V}_E = 21.0 \cdot 10^3 P_{atm}^{-2.11}$.68	2.62	$\Delta\dot{V}_E = \frac{22.5}{P_{atm} - 30} + 3.70$.66	4.07	$\Delta\dot{V}_E = \frac{3.60}{P_{atm} - 50.5}$.46	7.17

TABLE 2. \dot{V}_{E40} Depression by Halothane

$P_{a_{O_2}}$ (torr)	$\dot{V}_E = Ae^{Bx}$			$\dot{V}_E = AX^B$			$\dot{V}_E = \frac{A}{X-30} + B$		
	$\dot{V}_{E40}(l \cdot \text{min}^{-1})$			$\dot{V}_{E40}(l \cdot \text{min}^{-1})$			$\dot{V}_{E40}(l \cdot \text{min}^{-1})$		
	Awake	Halothane	Per Cent Depression	Awake	Halothane	Per Cent Depression	Awake	Halothane	Per Cent Depression
40	9.75	4.28	56	10.80	5.57	48	8.91	4.14	54
44	19.24	6.96	64	19.78	6.88	65	17.68	4.40	75
48	20.13	8.75	57	21.74	8.79	60	19.97	5.95	70

is little difference in the quantitations of depression as expressed by the three equations. 1.1 per cent end-tidal halothane depressed the ventilatory response to hypoxia by 52 per cent (mean of the values calculated from the exponential and power equations) when the animals were normocarbic ($P_{a_{CO_2}}$ 40 torr), by 65 per cent when $P_{a_{CO_2}}$ was 44 torr, and by 59 per cent when $P_{a_{CO_2}}$ was 48 torr.

It is unfair to examine critically the results of the hypoxic ventilatory response at 1.7 per cent halothane, because of the hypotension which existed at this depth of anesthesia. We did, however, observe a further impressive decrease in the ventilatory response to hypoxia, nearly to the point of complete extinction of the response.

HYPERCARBIC RESPONSE

Analysis of response to carbon dioxide was performed in a fashion similar to that performed for the response to hypoxia, as described above. For this analysis, in the above equations, $Y = \dot{V}_E$ and $X = P_{a_{CO_2}}$. The depression of the ventilatory response to carbon dioxide is illustrated in figures 4-7. The equations, as computed by linear least-squares regression, as well as depression (as calculated from change in slope of the linear regression lines) are shown in table 3. The slope of the ventilatory response to CO_2 is depressed to a variable extent, depending upon $P_{a_{O_2}}$. This table also indicates the calculated X intercept—the $P_{a_{CO_2}}$ at which $\dot{V}_E = 0$, i.e., the theoretical apneic threshold.

TABLE 3. Ventilatory Response to CO_2

$P_{a_{O_2}}$ (torr)	Condition of Dog	$\dot{V}_E = S \cdot P_{a_{CO_2}} - b$		
		Equation	X Intercept	Per Cent Depression of S by Halothane
156.6 ± 6.2 167.2 ± 6.1	Awake 1.1 per cent halothane	$\dot{V}_E = 0.69 P_{a_{CO_2}} - 24.1$ $\dot{V}_E = 0.41 P_{a_{CO_2}} - 13.2$	34.9 32.2	41
74.4 ± 2.2 74.3 ± 2.2	Awake 1.1 per cent halothane	$\dot{V}_E = 0.79 P_{a_{CO_2}} - 25.1$ $\dot{V}_E = 0.56 P_{a_{CO_2}} - 18.2$	31.8 32.5	29
51.7 ± 1.1 53.1 ± 1.1	Awake 1.1 per cent halothane	$\dot{V}_E = 1.10 P_{a_{CO_2}} - 31.8$ $\dot{V}_E = 0.38 P_{a_{CO_2}} - 8.2$	28.9 21.6	65
40.1 ± 0.55 40.1 ± 0.57	Awake 1.1 per cent halothane	$\dot{V}_E = 0.84 P_{a_{CO_2}} - 16.7$ $\dot{V}_E = 0.066 P_{a_{CO_2}} + 7.0$	19.9 -106	92

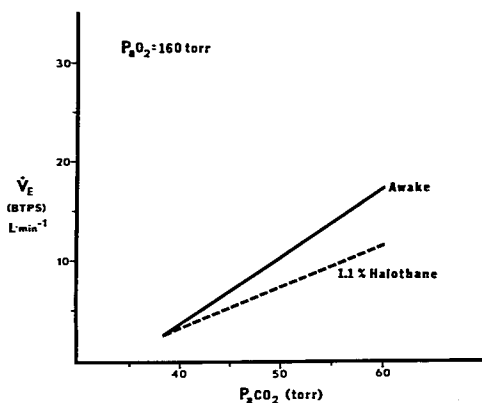


FIG. 4. Effect of 1.1 per cent halothane on the ventilatory response to carbon dioxide at P_{aO_2} 156.6 ± 6.2 (SE) torr, awake; 167.2 ± 6.1 torr, 1.1 per cent halothane.

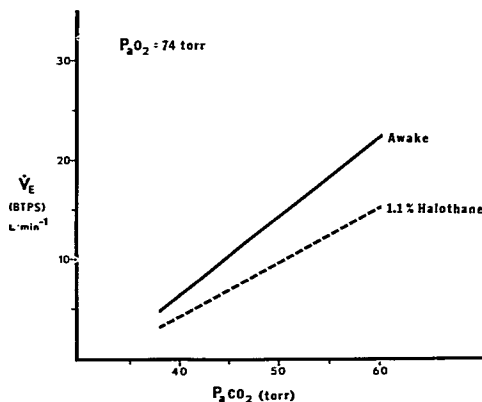


FIG. 5. Effect of 1.1 per cent halothane on the ventilatory response to carbon dioxide at P_{aO_2} 74.4 ± 2.2 torr, awake; 74.3 ± 2.2 torr, 1.1 per cent halothane.

With the single exception of the CO_2 response at $P_{aO_2} = 40$, 1.1 per cent end-tidal halothane did not have a large effect on the X intercept.

INTERACTION OF HYPOXIC AND HYPERCARBIC RESPONSES

The slopes of CO_2 response as a function of P_{aCO_2} for awake and anesthetized animals are

shown in figure 8. The classic interaction of the effects of CO_2 and hypoxia on ventilatory response as demonstrated in the awake state was greatly altered by 1.1 per cent end-tidal halothane. Halothane increasingly depressed the slope of the CO_2 response as P_{aO_2} fell below 74 torr, both in absolute terms and in comparison with the awake state (fig. 8).

FIG. 6. Effect of 1.1 per cent halothane on the ventilatory response to carbon dioxide at P_{aO_2} 51.7 ± 1.1 torr, awake; 53.1 ± 1.1 torr, 1.1 per cent halothane.

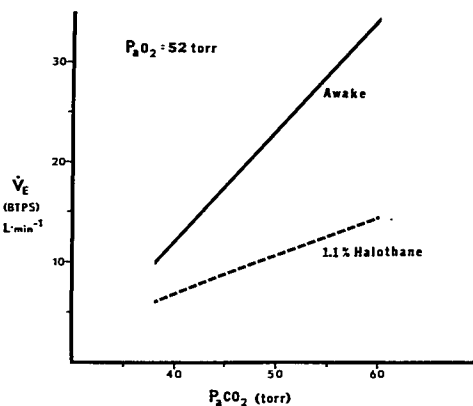
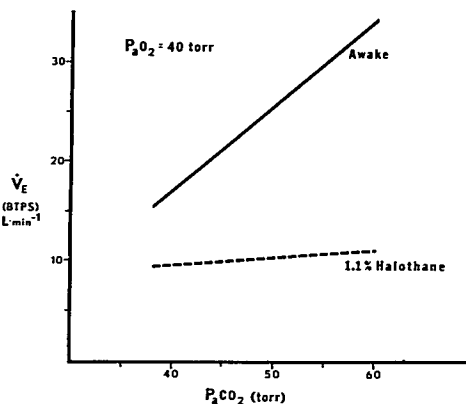


FIG. 7. Effect of 1.1 per cent halothane on the ventilatory response to carbon dioxide at P_{aO_2} 40.1 ± 0.55 torr, awake; 40.1 ± 0.57 torr, 1.1 per cent halothane.



Discussion

HYPOXIC RESPONSE

The ventilatory response to hypoxia is characterized as slight for small reductions in P_{aO_2} from the normoxic level, then progressively stronger as P_{aO_2} falls into the range of 30–40 torr. This has usually been described

as a hyperbolic response as P_{O_2} approaches an asymptotic value in the region of 30 torr¹³ (term "B" of equation 5). Kronenberg *et al.*¹² showed a good fit of their data to an exponential equation of the form of equation 2 above.

In the analysis of our data, logarithmic and power functions (equations 2 and 3) yielded approximately equally good results in terms of standard error of the computed curve, as

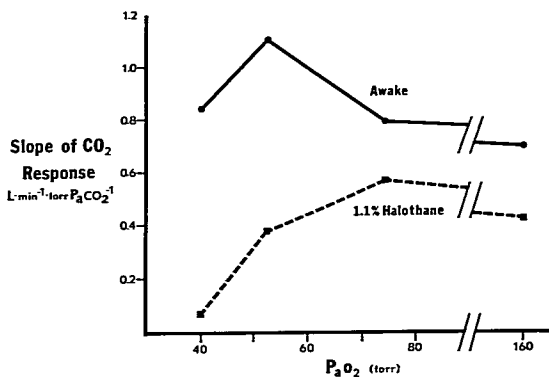


FIG. 8. Effect of 1.1 per cent halothane on the slope of the ventilatory response to carbon dioxide as a function of P_{aO_2} .

well as correlation coefficient of best least-squares fit. It should be noted, however, that the traditional type of hyperbolic analysis¹³ (equation 5) resulted in uniformly lower correlation coefficients and higher standard errors than did the above three mathematical expressions. Modification of this expression to include an assumed asymptote (of 30 torr), as is practiced by some investigators¹⁴ (equation 4), resulted in correlation coefficients and standard errors of intermediate values.

Likewise, the power and logarithmic equations resulted in approximately equal expressions of the depression by halothane of the ventilatory response to hypoxia, when compared with the awake control values of the same dogs (tables 1 and 2). Despite the poorer fit to the data by equation 4, the depression as expressed by that function was in fairly close agreement with the depression expressed by the logarithmic and power terms.

Cullen and Eger¹⁵ examined the ventilatory response to hypoxia in halothane-anesthetized dogs; however, they did not test the animals in the awake state, nor did they maintain P_{aCO_2} constant while testing the hypoxic response.

Changes in blood pressure may change ventilation by at least two mechanisms. A decrease in blood pressure might cause a decrease in carotid body perfusion and, thus,

cause relative carotid-body tissue hypoxia, with resultant increased carotid-body firing.^{16,17,18} Alternatively, an increase in blood pressure reflexly, via the baroreceptors, may cause a decrease in ventilation.^{16,19,20} It is, therefore, appropriate to examine the courses of the animals' blood pressures during these studies. In these studies 1.1 per cent end-tidal halothane failed to cause a significant change in mean blood pressure at any P_{aO_2} or P_{aCO_2} compared with the awake response. Figure 9 demonstrates the effect of 1.1 per cent halothane on the effect of P_{aO_2} on blood pressure at P_{aCO_2} 40 torr.

There has been no direct evidence gathered by others in support of, or contrary to, our data. Biscoe and Millar,²⁰ using pentobarbital-anesthetized cats, demonstrated decreased carotid-body chemoreceptor discharge during normoxia and hyperoxia, but not during hypoxia when halothane was added to the barbiturate anesthesia. Chemoreceptor response in that study was complicated by arterial hypotension, with possible decreased carotid-body blood flow.

HYPERCARBIC RESPONSE

Depressant drugs, and all general anesthetics, decrease the slope of the plot of \dot{V}_E vs.

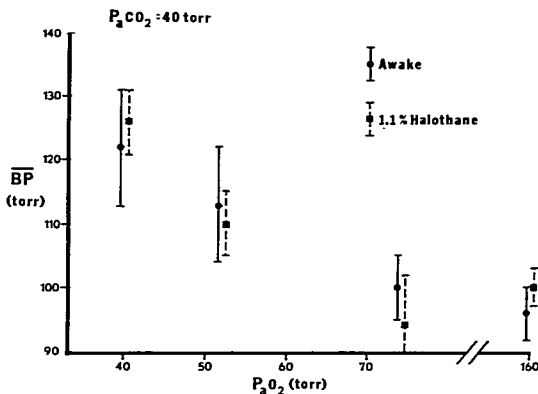


FIG. 9. Effect of 1.1 per cent halothane on the response of mean arterial blood pressure to change in P_{aO_2} , at P_{aCO_2} 40 torr (mean \pm SE).

$P_{aCO_2}^{2,3,4,5}$, i.e., the ventilatory response to carbon dioxide is depressed. In the course of our investigations into the effect of halothane on the ventilatory response to hypoxia we have gathered ample data to reconfirm the depression of the ventilatory response to carbon dioxide by halothane at all levels of P_{aO_2} studied.

INTERACTION OF EFFECTS OF CO₂ AND HYPOXIA ON VENTILATORY RESPONSE

Hypercarbia and hypoxia interact in driving ventilation.^{13,22} In the awake animals, a decrease in P_{aO_2} from 157 to 52 torr resulted in an increase of the slope of the \dot{V}_E -CO₂ response curve by 59 per cent, as shown in figure 8 and table 3. In the anesthetized state (1.1 per cent halothane), a similar reduction of P_{aO_2} actually decreased the slope of the \dot{V}_E -CO₂ response curve by 7 per cent.

We know that following denervation or extirpation of their carotid chemoreceptors human subjects show respiratory depression with hypoxia,^{23,24} presumably caused by medullary depression. However, these subjects do not manifest depression of the CO₂ response when hypoxia is added. We, therefore, conclude that the effect of halothane is more depressant than complete chemoreceptor removal. Thus, whereas the depression of

hypoxic ventilatory response by halothane may in part include a mechanism involving the carotid body, at least one other site of action must be also involved.

CLINICAL IMPORTANCE

These findings of marked depression of the ventilatory response to hypoxia by halothane may not apply in man, but lacking evidence, the anesthesiologist may well assume that hypoxia may not stimulate ventilation during halothane anesthesia, and may depress it, and in addition block the usual response to CO₂.

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Drugs and Their Actions

HEROIN ADDICTION AND NEONATAL JAUNDICE The excretory pathway in bilirubin metabolism involves conjugation of bilirubin to the glucuronide by the action of hepatic glucuronyl transferase. Certain drugs, notably phenobarbital, enhance glucuronyl transferase activity and thereby lessen the severity of jaundice. Absence of significant jaundice among infants of heroin-addicted mothers suggests a possible modifying effect of heroin on bilirubin accumulation in the newborn infant. A group of addicted newborn infants, undergoing narcotic withdrawal, demonstrated a significantly lower level of serum bilirubin than control infants in the first three days of life. Laboratory experimentation suggests that opiate drugs may increase bilirubin excretion by enhancement of glucuronyl transferase activity, and suggests that infants of heroin-addicted mothers may possess a mechanism for increased turnover of other biologic substances whether through glucuronidation or enzyme induction. (*Nathanson, G., and others: The Effect of Maternal Heroin Addiction on Neonatal Jaundice. J Pediatr* 81: 899-903, 1973.)