Anesthesiology
V 41, No 4, Oct 1974



# *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 $Pa_{CO_2}$ (40, 44 and 48 torr). Halothane depressed $\Delta\dot{V}_{40}$ (the increase in ventilation at $Pa_{O_2}$ 40 torr above the normocarbic, hyperoxic ventilation) by 52 per cent at $Pa_{CO_2}$ 40 torr, by 65 per cent at $Pa_{CO_2}$ 44 torr, and by 59 per cent at $Pa_{CO_2}$ 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 47 per cent at $Pa_{O_2}$ 160 torr, by 29 per cent at $Pa_{O_2}$ 74 torr, by 65 per cent at $Pa_{O_2}$ 52 torr, and by 92 per cent at $Pa_{O_2}$ 40 torr, in comparison with the awake responses. The increasing depression of the ventilatory response to carbon dioxide as $Pa_{O_2}$ 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 $Pa_{CO_2}$, 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, and trained to sit or lie quietly, without panting, during these studies. The dogs breathed through cuffed tracheostomy tubes, attached by a nonrebreathing Sierra valve to a closed-circle system. Carbon dioxide within the system was controled by a variable-bypass $CO_2$ absorber placed within the circle. A percutaneous catheter was placed into 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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Received from the Department of Anesthesia and the Cardiovascular Research Institute, University of California, San Francisco, CA. 94122. Accepted for publication February 12, 1974. Supported in part by Program Project Grant HE-06285 from the National Heart and Lung Institute, Career Award 5-K6-HE-19, 412, Anesthesia Program Project Grant 1-PO 1-GM 15571-03, and Training Grant 5-T1-GM00063-13. Presented in part at the national meeting of the American Federation for Clinical Research, 1971.[1].

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 $CO_2$ 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 *p*H 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 $P_{O_2}$ 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 $P_{O_2}$ reading other than zero with halothane vapor in $N_2$ 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 ($\phi_b$) as described by Hulands, Nunn and Paterson.[11] $Pa_{CO_2}$, $Pa_{O_2}$, and *p*H 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 $Pa_{CO_2}$, and no less than 3 minutes following a change in $Pa_{O_2}$. 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 $Pa_{CO_2}$, 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 $Pa_{CO_2}$: 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 = $Pa_{O_2}$. Equation 1 is a linear function; equation 2 is a logarithmic function as applied by Kronenberg *et al.*[12]; equation 3 is

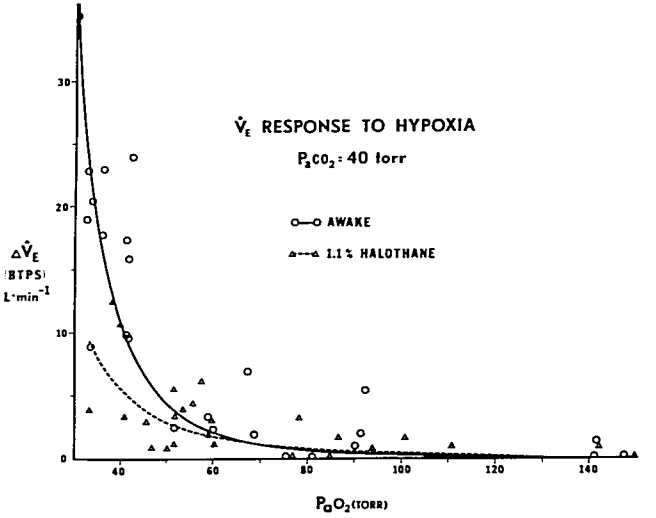


FIG. 1. Effect of 1.1 per cent halothane on the ventilatory response to hypoxia at $Pa_{CO_2}$ 40 torr. See text for description of analysis of data.

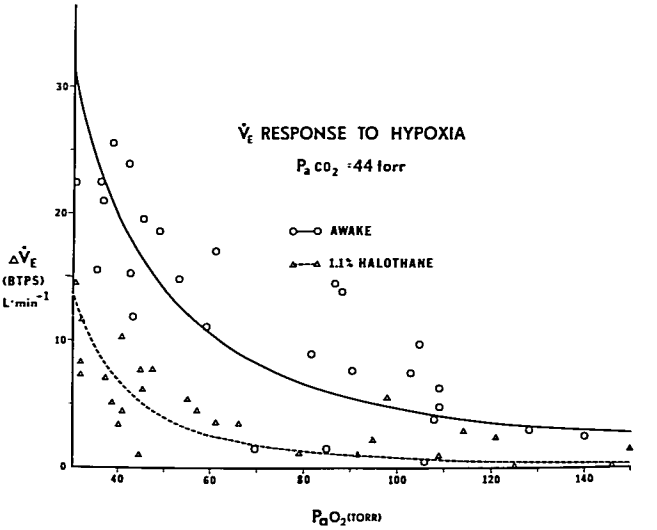


FIG. 2. Effect of 1.1 per cent halothane on the ventilatory response to hypoxia at $Pa_{CO_2}$ 44 torr. See text for description of analysis of data.

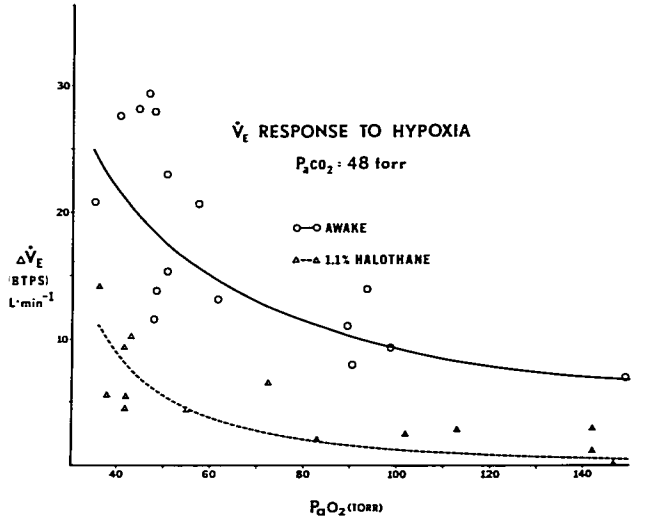


FIG. 3. Effect of 1.1 per cent halothane on the ventilatory response to hypoxia at $Pa_{CO_2}$ 48 torr. See text for description of analysis of data.

a power function; equation 5 is the hyperbolic equation as presented by Lloyd, Jukes and Cunningham[13]; 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 $Pa_{O_2}$ 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 an end-tidal concentration of 1.1 per cent halothane greatly depresses the ventilatory responses to hypoxia at all three levels of $Pa_{CO_2}$ 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 $Pa_{O_2}$ 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 Halothane

| $Pa_{O_2}$ (torr) | Condition of dog | $\Delta\dot{V}_E = Ae^{BX}$ | | | $\Delta\dot{V}_E = AX^B$ | | | $\Delta\dot{V}_E = \frac{A}{X-30} + B$ | | | $\Delta\dot{V}_E = \frac{A}{X-B}$ | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Equation | r | SE | Equation | r | SE | Equation | r | SE | Equation | r | SE |
| 40 | Awake | $\Delta\dot{V}_E = 90.0e^{-\frac{Pa_{O_2}}{18.0}}$ | .75 | 5.63 | $\Delta\dot{V}_E = 43.4 \cdot 10^6 Pa_{O_2}^{-4.12}$ | .76 | 5.47 | $\Delta\dot{V}_E = \frac{52.4}{Pa_{O_2} - 30} + 3.67$ | .73 | 8.64 | $\Delta\dot{V}_E = \frac{1.62}{Pa_{O_2} - 38.3}$ | .58 | 13.0 |
| | 1.1 per cent halothane | $\Delta\dot{V}_E = 18.7e^{-\frac{Pa_{O_2}}{27.1}}$ | .64 | 2.58 | $\Delta\dot{V}_E = 20.4 \cdot 10^4 Pa_{O_2}^{-2.85}$ | .64 | 2.56 | $\Delta\dot{V}_E = \frac{23.2}{Pa_{O_2} - 30} + 1.82$ | .44 | 3.08 | $\Delta\dot{V}_E = \frac{2.33}{Pa_{O_2} - 49.8}$ | .48 | 4.38 |
| 44 | Awake | $\Delta\dot{V}_E = 47.7e^{-\frac{Pa_{O_2}}{44.1}}$ | .72 | 5.81 | $\Delta\dot{V}_E = 64.6 \cdot 10^2 Pa_{O_2}^{-1.57}$ | .73 | 5.75 | $\Delta\dot{V}_E = \frac{113}{Pa_{O_2} - 30} + 6.38$ | .80 | 9.62 | $\Delta\dot{V}_E = \frac{215}{Pa_{O_2} - 26.1}$ | .41 | 8.78 |
| | 1.1 per cent halothane | $\Delta\dot{V}_E = 27.0e^{-\frac{Pa_{O_2}}{29.5}}$ | .73 | 2.32 | $\Delta\dot{V}_E = 40.3 \cdot 10^3 Pa_{O_2}^{-2.35}$ | .69 | 2.40 | $\Delta\dot{V}_E = \frac{8.98}{Pa_{O_2} - 30} + 3.50$ | .72 | 3.69 | $\Delta\dot{V}_E = \frac{2.75}{Pa_{O_2} - 48.2}$ | .51 | 6.65 |
| 48 | Awake | $\Delta\dot{V}_E = 32.6e^{-\frac{Pa_{O_2}}{83.6}}$ | .67 | 6.40 | $\Delta\dot{V}_E = 67.5 \cdot 10^1 Pa_{O_2}^{-0.93}$ | .70 | 6.43 | $\Delta\dot{V}_E = \frac{68.7}{Pa_{O_2} - 30} + 13.1$ | .41 | 8.11 | $\Delta\dot{V}_E = \frac{1054}{Pa_{O_2} - 16.1}$ | .64 | 6.95 |
| | 1.1 per cent halothane | $\Delta\dot{V}_E = 27.7e^{-\frac{Pa_{O_2}}{31.7}}$ | .71 | 2.51 | $\Delta\dot{V}_E = 21.0 \cdot 10^3 Pa_{O_2}^{-2.11}$ | .68 | 2.62 | $\Delta\dot{V}_E = \frac{22.5}{Pa_{O_2} - 30} + 3.70$ | .66 | 4.07 | $\Delta\dot{V}_E = \frac{3.60}{Pa_{O_2} - 50.5}$ | .46 | 7.47 |

TABLE 2. $\Delta\dot{V}_{40}$ Depression by Halothane

| | $\Delta\dot{V}_E = Ae^{BX}$ | | | $\Delta\dot{V}_E = AX^B$ | | | $\Delta\dot{V}_E = \frac{A}{X-30} + B$ | | |
|---|---|---|---|---|---|---|---|---|---|
| | $\Delta\dot{V}_{40}$(l·min$^{-1}$) | | | $\Delta\dot{V}_{40}$(l·min$^{-1}$) | | | $\Delta\dot{V}_{40}$(l·min$^{-1}$) | | |
| $Pa_{CO_2}$ (torr) | 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 ($Pa_{CO_2}$ 40 torr), by 65 per cent when $Pa_{CO_2}$ was 44 torr, and by 59 per cent when $Pa_{CO_2}$ 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 $X = Pa_{CO_2}$. 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 $Pa_{O_2}$. This table also indicates the calculated X intercept—the $Pa_{CO_2}$ at which $\dot{V}_E = 0$, *i.e.*, the theoretical apneic threshold.

TABLE 3. Ventilatory Response to $CO_2$

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

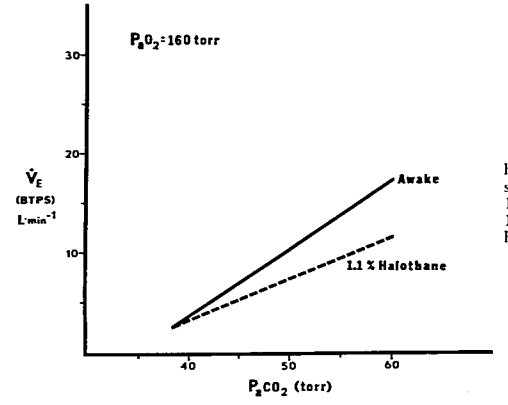


FIG. 4. Effect of 1.1 per cent halothane on the ventilatory response to carbon dioxide at $Pa_{O_2}$ 156.6 ± 6.2 (SE) torr, awake; 167.2 ± 6.1 torr, 1.1 per cent halothane.

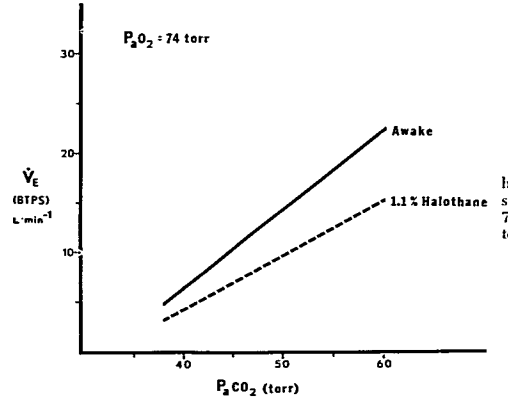


FIG. 5. Effect of 1.1 per cent halothane on the ventilatory response to carbon dioxide at $Pa_{O_2}$ 74.4 ± 2.2 torr, awake; 74.3 ± 2.2 torr, 1.1 per cent halothane.

With the single exception of the $CO_2$ response at $Pa_{O_2}$ = 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 $Pa_{CO_2}$ 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 $Pa_{O_2}$ fell below 74 torr, both in absolute terms and in comparison with the awake state (fig. 8).

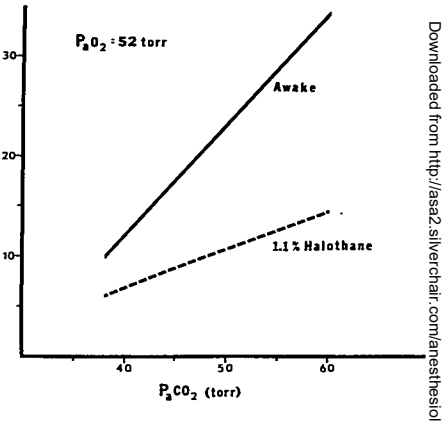


FIG. 6. Effect of 1.1 per cent halothane on the ventilatory response to carbon dioxide at $Pa_{O_2}$ 51.7 ± 1.1 torr, awake; 53.1 ± 1.1 torr, 1.1 per cent halothane.

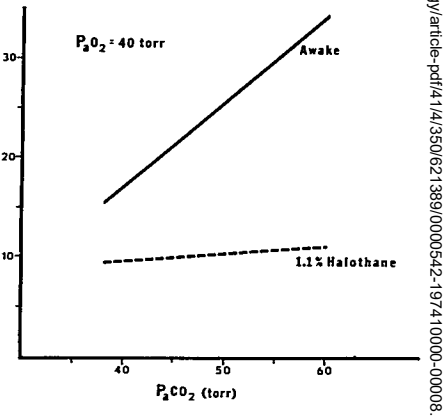


FIG. 7. Effect of 1.1 per cent halothane on the ventilatory response to carbon dioxide at $Pa_{O_2}$ 40.1 ± 0.55 torr, awake; 40.1 ± 0.57 torr, 1.1 per cent halothane.

## Discussion

### HYPOXIC RESPONSE

The ventilatory response to hypoxia is characterized as slight for small reductions in $Pa_{O_2}$ from the normoxic level, then progressively stronger as $Pa_{O_2}$ 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 torr[13] (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

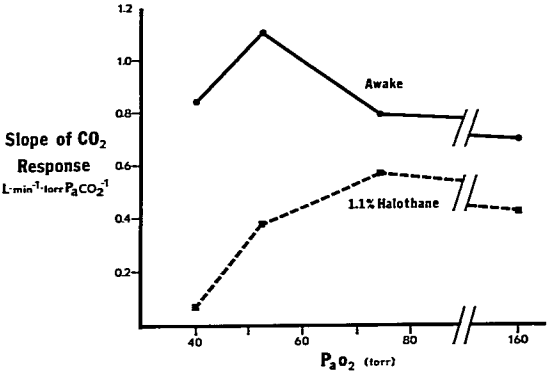


FIG. 8. Effect of 1.1 per cent halothane on the slope of the ventilatory response to carbon dioxide as a function of $Pa_{O_2}$.

well as correlation coefficient of best least-squares fit. It should be noted, however, that the traditional type of hyperbolic analysis[13] (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 investigators[14] (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 Eger[15] 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 $Pa_{CO_2}$ 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 $Pa_{O_2}$ or $Pa_{CO_2}$ compared with the awake response. Figure 9 demonstrates the effect of 1.1 per cent halothane on the effect of $Pa_{O_2}$ on blood pressure at $Pa_{CO_2}$ 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.*

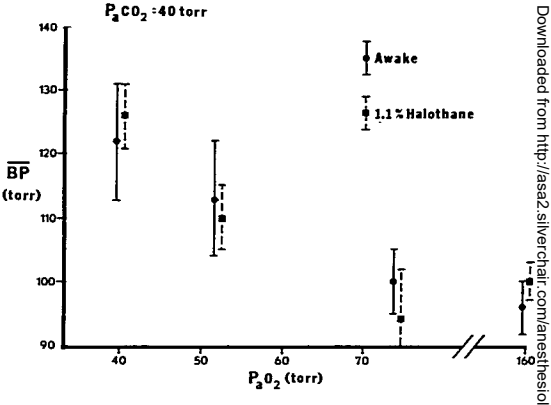


FIG. 9. Effect of 1.1 per cent halothane on the response of mean arterial blood pressure to change in $Pa_{O_2}$, at $Pa_{CO_2}$ 40 torr (mean ± SE).

$Pa_{CO_2}$[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 $Pa_{O_2}$ studied.

## Interaction of Effects of $CO_2$ and Hypoxia on Ventilatory Response

Hypercarbia and hypoxia interact in driving ventilation.[13,22] In the awake animals, a decrease in $Pa_{O_2}$ from 157 to 52 torr resulted in an increase of the slope of the $\dot{V}_E$–$CO_2$ 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 $Pa_{O_2}$ actually decreased the slope of the $\dot{V}_E$–$CO_2$ 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 $CO_2$ 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 $CO_2$.

The authors acknowledge the technical assistance of Merry Nishimura and the computer programming of Mary Ann Wall.

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## Drugs and Their Actions

**HEROIN ADDICTION AND NEONATAL JAUNDICE** The excretory pathway in bilirubin metabolism invplves 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. *(Nathenson, G., and others: The Effect of Maternal Heroin Addiction on Neonatal Jaundice. J Pediatr 81: 899–903, 1973.)*