Anesthesiology
62:448–456, 1985

Effects of Halothane on the Ventilatory Response to Hypoxia and Hypercapnia in Cats

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The influence of halothane 0.8–1.2% inspired on the peripheral hypoxic chemoreflex was investigated in 13 cats subjected to artificial brain stem perfusion (ABP). This technique allows for an independent control of blood gas tensions and halothane concentration between blood perfusing the brain stem (central) and the systemic circulation (peripheral). In six cats the ventilatory response to isocapnic hypoxia was assessed during overall halothane anesthesia (HO) before and during ABP. Before ABP, systemic and brain stem circulations both were rendered hypoxic. During ABP, hypoxia was induced systemically while the brain stem was maintained hyperoxic. The ventilatory response in non-ABP cats (mean 698 ml·min^{-1} at Pa_{O_2} 6.6 kPa; 50 mmHg) was about half the response in ABP cats (mean 1,194 ml·min^{-1} at Pa_{O_2} 6.5 kPa; 49 mmHg), indicating that in the presence of halothane, central hypoxia depressed ventilation appreciably. Compared with chloralose–urethane anesthesia (CU), halothane reduced the ventilatory response to hypoxia in both perfusion conditions but never abolished it. To assess the influence of halothane on peripheral and central mediation of the CO_2 response during hypoxia, each was assessed during CU anesthesia, during HO, and with halothane applied exclusively peripherally against a background of CU (CUHP). In all drug states, the periphery was kept hypoxic and brain stem hyperoxic. Compared with CU anesthesia, HO and CUHP anesthesia reduced both peripheral (Sp) and central (Sc) CO_2 sensitivity but not the Sp/Sc ratio. Similarly, the extrapolated Pa_{CO_2} at zero ventilation was not detectably different among these three states. This suggests that in this model, the depression of the peripheral chemoreflex response to CO_2 in the presence of hypoxemia by halothane applied peripherally is due to peripheral effects of halothane unrelated to chemoreceptor function. The authors' findings indicate that halothane applied to all structures except the brain stem in an artificially perfused cat model depresses the overall peripheral chemoreflex pathway. A direct effect of halothane on the peripheral chemoreceptors cannot be excluded; with respect to the CO_2 response in the presence of hypoxemia such an effect may be of minor importance in comparison with the depressant effects of halothane on other peripheral structures, *i.e.*, the neuromechanical link between the brain stem and ventilatory movement. Key words: Anesthetics, volatile: halothane. Receptors: chemoreceptors. Ventilation: hypoxic response; hypercapnic response; regulation.

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Received from the Department of Physiology and Physiological Physics, University of Leiden, The Netherlands. Accepted for publication October 9, 1984. Supported in part by the Foundation for Medical Research (FUNGO), which is subsidized by the Netherlands Organization for the Advancement of Pure Research (Z.W.O.).

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IT HAS BEEN REPORTED[1] that the ventilatory response to hypoxia is highly sensitive to halothane. In humans it appears to be abolished[2] in contrast to the response to hypercarbia. The degree of depression of the hypoxic response in dogs is not as severe.[1,3] These findings led to the opinion that, besides effects of halothane on central nervous structures that diminish the hypoxic reflex in proportion to the medullary mediated response to carbon dioxide, halothane has also a potent depressant action on the peripheral chemoreceptors.[4] Support for such an effect came from the observation by Davies *et al.*[5] that in decerebrate cats halothane reduced the impulse activity of the carotid chemoreceptors to hypoxia and hypercapnia, although the concomitant systemic hypotension following halothane administration tended to mask the direct depression of the carotid chemoreceptor discharge responses caused by halothane. The importance of their findings with respect to overall ventilatory control, however, is not clear, as they did not measure ventilation. Moreover, it has been shown that halothane can impair ventilatory responses by actions on the mechanics of the respiratory system.[6–9]

It is not always appreciated that there are at least two opposing effects of hypoxia on ventilation, a stimulatory one, via an action on the peripheral chemoreceptors, and a depressant one, on central nervous structures[10]; both effects could be influenced by halothane. The relative importance of all these effects of halothane on the ventilatory response to hypoxia and hypercarbia is not known. To gain insight into the sites of action of halothane with respect to the peripheral and central chemoreflex loops, central and peripheral effects of hypoxia, hypercarbia and halothane have to be separated. In a previous study[11] we utilized the technique of artificial brain stem perfusion (ABP) in cats to assess some of the sites at which halothane exerts its effects on ventilation during hyperoxia. It is the purpose of this study to determine whether or not halothane abolishes the hypoxic response in a cat model and to investigate the site of action of halothane on the peripheral chemoreflex pathway.

Methods

Experiments were carried out on 13 adult cats of either sex (2–4 kg). Blood from the systemic arterial

circulation was led into a gas exchanger, where it was equilibrated with a gas mixture of CO_2, O_2, and halothane in N_2. The blood subsequently was pumped into a cannulated vertebral artery; the other vertebral artery was clamped. In this way the relevant structures of the central nervous system involved in the regulation of breathing, viz. medulla oblongata and pons, were perfused with blood with a P_{CO_2} (central arterial carbon dioxide tension, $Pa_{CO_2}{}^{c}$) and halothane concentration that could be controlled independently of those of the blood delivered to the peripheral chemoreceptors and to other peripheral structures (peripheral arterial carbon dioxide tension, $Pa_{CO_2}{}^{p}$ and oxygen tension, $Pa_{O_2}{}^{p}$). The latter gas tensions and halothane concentration could be influenced by varying the gas concentrations in the inhaled gas mixture. With the addition of known and adjustable amounts of N_2, saturated at 35° C with halothane vapor, the halothane concentrations in the inspiratory gas mixture and the gas delivered to the gas exchanger were set.

Anesthesia was induced with ketamine hydrochloride (10 $mg \cdot kg^{-1}$ im), followed by inhalation of 1.5% halothane and 30% oxygen in N_2. The trachea was cannulated for continuous measurement of ventilatory flow, end-tidal P_{CO_2} and end-tidal halothane concentration. The inspiratory and expiratory flows were measured by means of a Fleisch no. 0 pneumotachograph; tidal volume was obtained by electronically integrating the flow signal. The volume signal was calibrated with a motor-driven piston pump (stroke volume 40 ml, at frequencies of 15 and 30 min^{-1}). Corrections were made for changes in gas viscosity due to changes in gas composition of the expired gas mixture. Right femoral arterial pressure was measured by a strain gauge. When indicated, nonvolatile anesthetics were infused into the right femoral vein. The left femoral artery and vein were cannulated and connected to an extracorporeal circuit (ECC). The temperature, monitored with a rectal thermistor, was maintained at 36.9–37.7° C by means of a heating pad and an infrared lamp. Two sets of electrodes were inserted in the ECC for the continuous measurement of Pa_{O_2}, Pa_{CO_2}, and pH_a of systemic blood and blood going to the brain stem. Polarizing voltage of the P_{O_2} electrodes was set at 600 mV to avoid errors due to polarographic reduction of halothane,[12] P_{O_2} and P_{CO_2} electrodes were calibrated at 37° C with water equilibrated with gas mixtures delivered by a gas mixing pump (Wösthoff, type M300 A-F). The drift of the P_{CO_2} electrodes (General Electric, type 3128AB) was determined every two hours, and the recorded P_{CO_2} signals were corrected accordingly.[13] After the surgical preparations, the halothane concentration in the inspired gas was lowered to 0.8–1.2%. Measurements first were performed while the brain stem was perfused with systemic blood via the patent vertebral arteries (non-ABP cats). Thereafter, a muscular branch of the vertebral artery was cannulated and the artery itself clamped proximally; the other vertebral artery also was clamped. The ECC was connected to the cannulated vertebral artery, and subsequently blood was pumped into the ponto-medullary region at a flow of 6 ml/min (ABP cats). Tidal volume, respiratory frequency, inspiratory and expiratory CO_2 concentrations, arterial pressure, heart rate, perfusion pressure, temperature, blood gas tensions, and *p*H all were measured continuously, recorded on polygraphs, and processed by a DEC PDP 11/23 minicomputer. Mean tidal volume, and mean inspiratory and expiratory times were determined over 20 breaths; ventilation and respiratory frequency were calculated from these data. More details about surgical procedures and measurements have been described in a previous publication.[14]

Experimental Protocols

In an experiment, three types of anesthetic regimens subsequently were applied:

Halothane Overall (HO) with and without ABP. In non-ABP cats, inspired gas containing 0.8–1.2% halothane. In ABP cats the same concentration also was delivered to the gas exchanger. In this regimen halothane was the only anesthetic used.

Chloralose–Urethane (CU) Anesthesia with ABP. Light chloralose–urethane anesthesia (after induction with halothane) was obtained by intravenous administration of 20 $mg \cdot kg^{-1}$ chloralose and 100 $mg \cdot kg^{-1}$ urethane, stopping the delivery of halothane to the inspired gas and gas exchanger.

Halothane Applied Peripherally during Chloralose–Urethane (CUHP) Anesthesia with ABP. Halothane was applied peripherally by administering gas mixtures containing 0.8–1.2% halothane during chloralose–urethane anesthesia, as in anesthetic regimen CU. Blood delivered to the brain stem was kept free of halothane by purging halothane from the blood in the gas exchanger,[14] in a manner that had been shown previously to be effective in removing more than 95% of blood halothane.

Chloralose–urethane anesthesia without halothane was chosen as a reference condition. The results obtained during halothane anesthesia thus could be compared with those without halothane.

Ventilatory responses to hypoxia and hypercapnia were determined in the different anesthetic regimens. The order in which these regimens were applied was, first, HO, then CU, and CUHP at last. Measurements were made at least 20 min after the surgical procedure was completed or after a change in anesthetic regimen. An overview of the experimental protocols is given in table 1.

TABLE 1. Overview of the Different Protocols to which the Cats Were Subjected

		Anesthetic Regimen		
	Type of Response	HO	CU	CUHP
Non-ABP cats	Hypoxic Response	Overall Hypoxia (1–6)		
ABP cats	Hypoxic response	Peripheral hypoxia (1–3, 5, 6) Central hypoxia (12, 13)	Peripheral hypoxia (1–4, 6)	Peripheral hypoxia (1–4, 6)
	CO_2 response	Peripheral CO_2 (1–4, 6–8) Central CO_2 (1–4, 6–8)	Peripheral CO_2 (1–4, 6–9, 11) Central CO_2 (1–4, 6–9, 11)	Peripheral CO_2 (1–4, 6, 7, 9, 11) Central CO_2 (1–4, 6, 7, 9, 11)
	CO_2 response at two P_{O_2}'s	Peripheral CO_2 (1, 2, 10, 11)		

Cat number in parentheses. HO = halothane anesthesia overall; CU = chloralose–urethane anesthesia; CUHP = chloralose–urethane anesthesia with halothane applied peripherally.

VENTILATORY RESPONSES TO HYPOXIA

The site and magnitude of attenuation of the hypoxic ventilatory response by halothane was studied in six cats. Isocapnic hypoxia was induced by giving the animal five different gas mixtures to inhale. Starting from hyperoxia at a Pa_{O_2} of 50 kPa (375 mmHg) the oxygen tension was lowered every 5 min to 27, 15, 9.5 and 6.5 kPa (203, 113, 71 and 49 mmHg), respectively, and back again to 50 kPa (375 mmHg). By manipulating the CO_2 concentration of the inhaled gas mixture, the Pa_{CO_2}, which was measured continuously, was kept constant. The end-tidal CO_2 signal was used only for monitoring purposes. The inspired P_{CO_2} was elevated somewhat at the beginning of the hypoxic response to be able to control Pa_{CO_2}. Hypoxic ventilatory responses were measured during the following conditions:

1) *HO Anesthesia in Non-ABP Cats.* Arterial Pa_{CO_2} was kept constant in each cat but ranged from 5.5 to 6.1 kPa (41–46 mmHg) between cats.

2) *HO Anesthesia in ABP Cats.* Halothane concentration of inspired gas and of gas delivered to the gas exchanger was the same. In each cat the $Pa_{CO_2}{}^{p}$ was kept constant at the same level as during HO in non-ABP cats. Hypoxia was applied only peripherally. The $Pa_{O_2}{}^{c}$ was about 50 kPa (375 mmHg), the $Pa_{CO_2}{}^{c}$ was constant in each cat but ranged from 3.7 to 5.4 kPa (28 to 40 mmHg) between cats. In two additional cats the effect on ventilation of changes in $Pa_{O_2}{}^{c}$ were measured during peripheral hyperoxia and at constant $Pa_{CO_2}{}^{c}$ and $Pa_{CO_2}{}^{p}$.

3) *CU Anesthesia and* 4) *CUHP Anesthesia in ABP Cats.* Hypoxia was applied only peripherally; central perfusate was hyperoxic as during HO in ABP cats. Blood gas tensions were the same as during HO in ABP cats. Halothane was absent centrally in CU and CUHP.

PERIPHERAL AND CENTRAL CO_2 RESPONSES

The purpose of these experiments was to study the halothane-induced attenuation, if any, on the peripheral CO_2 response under peripherally hypoxic conditions. As we found earlier,[11] that halothane had an effect on the neuromechanical link, the central CO_2 response also was determined and used as a measure of this peripheral effect of halothane. Experiments were performed on nine cats during ABP with centrally hyperoxic blood ($Pa_{O_2}{}^{c}$ 50 kPa; 375 mmHg). At constant $Pa_{CO_2}{}^{c}$ the ventilatory response to changes in $Pa_{CO_2}{}^{p}$ was assessed by administering gas mixtures to which up to 6% CO_2 was added. The steady state ventilation was measured at three or four different $Pa_{CO_2}{}^{p}$ values. The $Pa_{O_2}{}^{p}$ was kept constant at 7 kPa (53 mmHg) by manipulating the O_2 concentration of the inspired gas. These hypoxic peripheral CO_2 response curves were determined at, minimally, three different $Pa_{CO_2}{}^{c}$ values. In this way central and peripheral ventilatory responses to CO_2 were obtained in the three anesthetic regimens.

To study whether the synergistic effect of hypercapnia and hypoxia on ventilation is still present during HO anesthesia, ventilatory responses to changes in peripheral CO_2 tension were determined at two levels of $Pa_{O_2}{}^{p}$ (7 and 50 kPa; 53 and 375 mmHg) in four ABP cats.

ANALYSIS OF DATA

The ventilatory response ($\dot{V}_E$) to changes in the level of $Pa_{CO_2}{}^{p}$ and $Pa_{CO_2}{}^{c}$ could be described satisfactorily by

$$\dot{V}_E = Sp\ Pa_{CO_2}{}^{p} + Sc\ Pa_{CO_2}{}^{c} - K \qquad (1)$$

in which K is a parameter and Sp and Sc are the overall CO_2 sensitivities of the peripheral and central pathways, respectively. These parameters were estimated by using

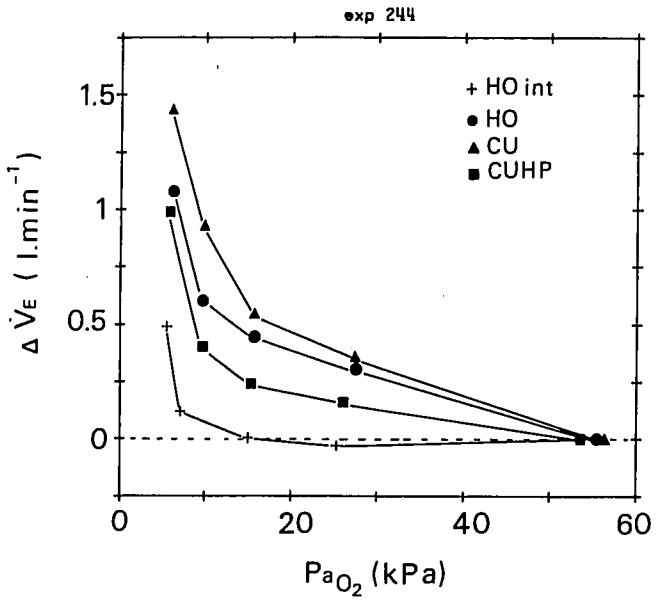

FIG. 1. Ventilatory responses to changes in arterial P_{O_2} of one cat before (int: vertebral arteries intact) and during artificial brain stem perfusion in the presence of halothane overall (HO), chloralose–urethane (CU), and chloralose–urethane with halothane added peripherally (CUHP). Ventilation at hyperoxia was taken as a reference and the changes in ventilation plotted as a function of the overall Pa_{O_2} (HO int) or the $Pa_{O_2}{}^P$ for the ABP cats. In the intact preparation the Pa_{CO_2} was kept constant. During ABP the brain stem was kept hyperoxic and all other blood gas tensions constant with the exception of the arterial $Pa_{O_2}{}^P$.

standard multiple regression analysis. For convenience, we introduce[15] the ratio r = Sp/Sc and the quantity B = K/(Sp + Sc), *i.e.*, the extrapolated Pa_{CO_2} at zero ventilation. The values of r and B obtained in the different anesthetic regimens were compared using two-way analysis of variance with one observation per cell. A level of significance of 0.05 in the F-statistics was chosen. If a significant difference between the anesthetic regimens was found, comparisons between anesthetic regimens were made using Scheffé's test.[16]

Results

Ventilatory Responses to Hypoxia

During overall halothane anesthesia, the increase in ventilation upon lowering the $Pa_{O_2}{}^P$ from 55 to 6.5 kPa (413–449 mmHg) was significantly less in the non-ABP cats compared with the ABP cats ($P < 0.05$, fig. 1). The brain stem was kept hyperoxic in the ABP cats, suggesting that the smaller response to hypoxia in the non-ABP cats during halothane anesthesia was due to brain stem hypoxia. Therefore, the influence on ventilation of lowering the $Pa_{O_2}{}^c$ during halothane anesthesia was investigated in two additional experiments during peripheral hyperoxic conditions. In both cats it was found that tidal volume and ventilation decreased upon lowering the $Pa_{O_2}{}^c$, even though all other blood gas tensions were kept constant (fig. 2). The depressant effect of brain stem hypoxia was most pronounced at a $Pa_{O_2}{}^c$ below 10 kPa (75 mmHg), but even at normoxia ventilation was lower compared with hyperoxia. The level of peripheral chemoreceptor stimulation did not appear to influence the magnitude of the brain stem depression (fig. 3). Relief of brain stem hypoxia resulted in a return of the ventilation to the previous level, showing that the depression was reversible. From these findings it was decided to first study the effects of peripheral hypoxia during peripheral halothane administration at a constant central Pa_{O_2}, for which a hyperoxic condition was chosen.

Of all the anesthetic regimens studied during artificial brain stem perfusion, the increase in ventilation upon lowering the $Pa_{O_2}{}^P$ was most pronounced during chloralose–urethane anesthesia (fig. 1). Administration of halothane peripherally during chloralose–urethane anesthesia resulted in a smaller increase in ventilation at all $Pa_{O_2}{}^P$ levels measured ($P < 0.05$, table 2). Hypoxic depression of the central part of the respiratory control was prevented while the $Pa_{O_2}{}^c$ was hyperoxic; hence the question arose whether the depression of ventilation during halothane anesthesia and peripheral hypoxia should be attributed to a depressed peripheral chemoreceptor responsiveness or to effects of halothane on the mechanical properties of the respiratory system. To distinguish between these possibilities, the ventilatory responses to peripheral and central hypercarbia were determined in the presence of peripheral hypoxia. A similar effect of peripheral halothane on both these responses would suggest an action on reflex elements common to both, whereas a selective effect on the peripheral CO_2 response in the presence of hypoxemia would favor an action on elements unique to the peripheral pathway.

Peripheral and Central CO_2 Responses

The ventilatory responses to changes in $Pa_{CO_2}{}^P$ or $Pa_{CO_2}{}^c$ were measured during peripheral hypoxia ($Pa_{O_2}{}^P$ 7 kPa; 53 mmHg) while the brain stem was kept hyperoxic. In all three anesthetic regimens, ventilation was found to be related linearly to the $Pa_{CO_2}{}^P$ level when measured at one constant $Pa_{CO_2}{}^c$ (fig. 4). The same findings were obtained for ventilation and different $Pa_{CO_2}{}^c$ values determined at a constant $Pa_{CO_2}{}^P$ level. At high $Pa_{CO_2}{}^c$ levels, the response curves tended to become convex; in the analysis only the linear part of the central CO_2 response curves at the lower levels of ventilation was used. Although the Sp and Sc were significantly higher during chloralose–urethane anesthesia compared with CUHP (Scheffé's test, $P < 0.05$), the ratio of the

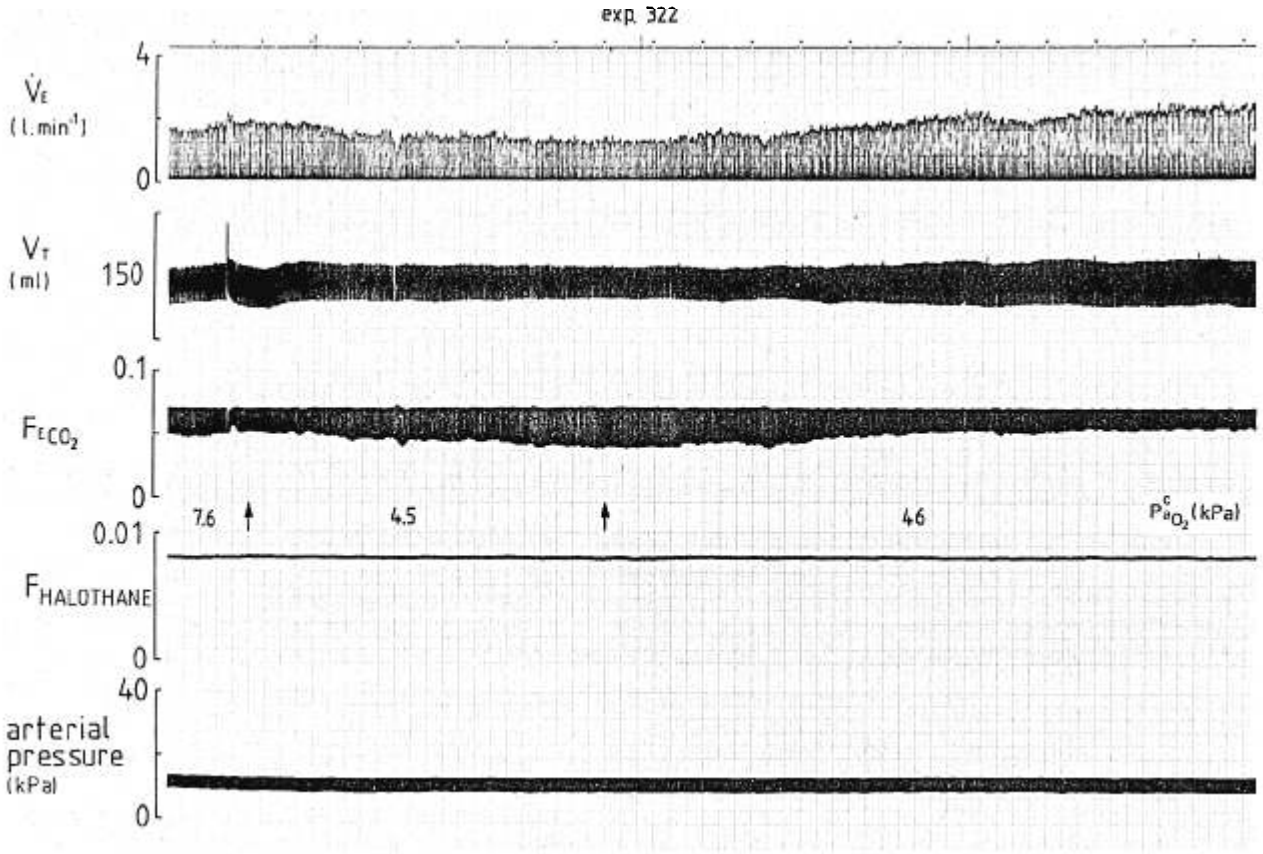

FIG. 2. Polygraphic recording of an experiment in which the central Pa_{O_2} was changed from 7.6 kPa (57 mmHg) to 4.5 kPa (34 mmHg) and subsequently to 46 kPa (345 mmHg) during artificial brain stem perfusion and overall halothane anesthesia in the presence of peripheral hyperoxia. During the central hypoxic depression of ventilation, the Pa_{CO_2} was kept constant by decreasing the carbon dioxide concentration in the inspired gas. $F_{halothane}$ and FE_{CO_2} denote the fraction of halothane and of CO_2 in tracheal gas; uppermost tracing shows time intervals of 1 min.

peripheral and central CO_2 sensitivities and the value obtained for B were not significantly different ($P = 0.07$, table 3). Also, during overall halothane anesthesia the ratios Sp/Sc and the values B were not significantly different from the values obtained during chloralose–urethane anesthesia ($P = 0.70$).

The blood pressure decreased significantly upon administration of halothane peripherally during CU anesthesia ($P < 0.05$); the mean decrease amounted to about 4.2 kPa (32 mmHg).

Peripheral Hypoxic–Hypercapnic Interaction

To investigate whether a multiplicative interaction of hypoxia and hypercarbia at the level of the peripheral chemoreceptors is still present during HO anesthesia,

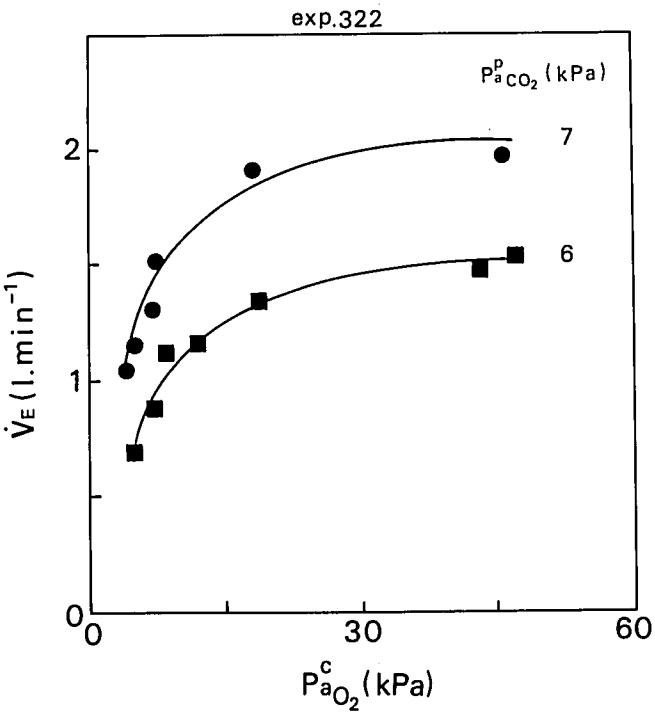

FIG. 3. Ventilatory responses to changes in central Pa_{O_2} at two levels of peripheral Pa_{CO_2} during artificial brain stem perfusion and overall halothane anesthesia in the presence of peripheral hyperoxia. The central Pa_{CO_2} was kept constant at 6.1 kPa (46 mmHg). Solid lines fitted by eye.

TABLE 2. Mean Changes in Ventilation ($\Delta\dot{V}_E$ ml·min^{-1}) at Different Arterial P_{O_2} (kPa) Values of Six Cats (With Standard Errors)

Anesthetic Regimen	Oxygenation Level							
	Pa_{O_2}	$\Delta\dot{V}_E$	Pa_{O_2}	$\Delta\dot{V}_E$	Pa_{O_2}	$\Delta\dot{V}_E$	Pa_{O_2}	$\Delta\dot{V}_E$
HO int	26.2	8	14.6	61	9.4	328	6.6	698
SE	1.1	18	0.7	23	0.4	145	0.2	206
HO	27.1	236	15.8	418	9.6	749	6.5	1,194
SE	0.4	68	0.3	91	0.2	118	0.2	160
CU	26.9	286	15.8	584	9.7	1,080	6.4	1,767
SE	0.3	68	0.6	78	0.3	105	0.2	253
CUHP	25.0	76	14.5	215	9.0	488	6.4	907
SE	0.5	37	0.6	39	0.4	79	0.2	137

Ventilation at hyperoxia (Pa_{O_2} 50 kPa; 375 mmHg) was taken as a reference. Except for HO int, hypoxia was applied only peripherally; central blood being hyperoxic. The $Pa_{CO_2}{}^P$ (or Pa_{CO_2} during HO int) was kept constant in each cat within 0.4 kPa (3 mmHg) but ranged between cats from 5.5 to 6.1 kPa (41 to 46 mmHg). The $Pa_{CO_2}{}^C$ ranged between cats from 3.7 to 5.4 kPa (28 to 41 mmHg) but was constant in each cat within 0.2 kPa (2 mmHg).

HO int = halothane anesthesia in non-ABP cats; HO = halothane anesthesia in ABP cats; same halothane concentration (0.8–1.2%) in inspiratory gas and gas delivered to the gas exchanger. CU = chloralose–urethane anesthesia in ABP cats; CUHP = chloralose–urethane anesthesia with halothane applied peripherally in ABP cats.

the ventilatory response to changes in $Pa_{CO_2}{}^P$ was determined at a $Pa_{O_2}{}^P$ of 50 kPa (375 mmHg) and 7 kPa (53 mmHg) in four cats. During these measurements the central blood gas tensions were kept constant. In all experiments the peripheral CO_2 sensitivity was increased significantly during hypoxia (paired t test, $P < 0.03$); the mean increase amounted to 60% (fig. 5).

Discussion

This study shows that in cats halothane 0.8–1.2% inspired depresses but does not abolish the overall hypoxic stimulation of ventilation. These findings are in agreement with observations in dogs,[1,3] but in contrast to what has been found in humans.[2] A synergistic effect

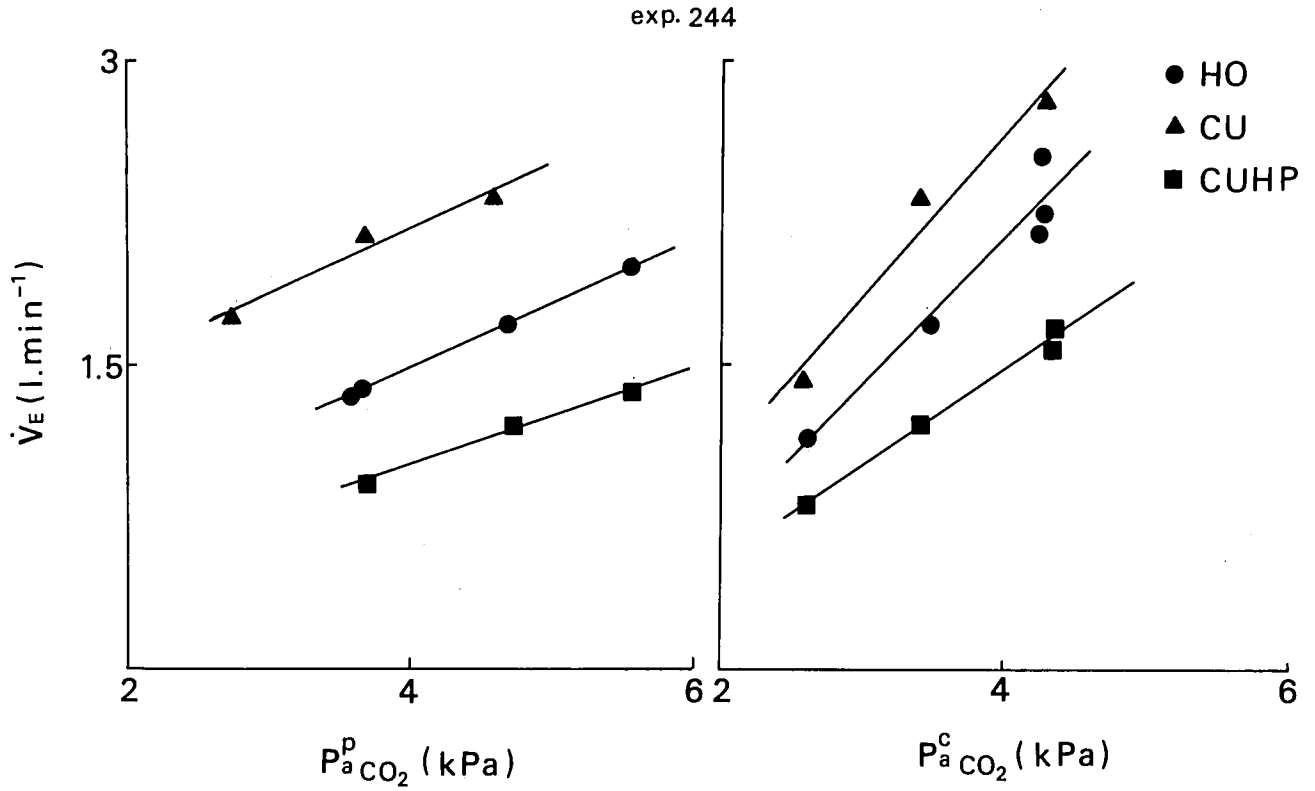

FIG. 4. Ventilatory responses during artificial brain stem perfusion to changes in peripheral Pa_{CO_2} (*left panel*) at constant central Pa_{CO_2} (3.3 kPa; 25 mmHg) and to changes in central Pa_{CO_2} (*right panel*) at constant peripheral Pa_{CO_2} (4.7 kPa; 35 mmHg). The peripheral Pa_{O_2} was kept constant at 7 kPa (53 mmHg), the central Pa_{O_2} at 50 kPa (375 mmHg) during halothane anesthesia overall (HO), chloralose–urethane (CU), and chloralose–urethane anesthesia with halothane added peripherally (CUHP).

TABLE 3. Mean Overall Peripheral (Sp) and Central (Sc) CO_2 Sensitivities ($ml \cdot min^{-1} \cdot kPa^{-1}$), Their Ratios r, and the Values of B (kPa) Together with their Standard Errors (SE) at Different Anesthetic Regimens during Peripheral Hypoxia (7 kPa; 53 mmHg) and Central Hyperoxia (50 kPa; 375 mmHg)

Anesthetic Regimen	Sp	SE	Sc	SE	r	SE	B	SE	n
HO	228	40	500	79	0.45	0.07	1.65	0.50	7
CU	316	51	796	120	0.44	0.09	2.43	0.21	9
CUHP	216	35	536	121	0.48	0.11	2.60	0.27	8

The $Pa_{CO_2}{}^c$ range covered in the experiments was from 2 to 6 kPa (15 to 45 mmHg), the $Pa_{CO_2}{}^p$ range from 2 to 8 kPa (15 to 60 mmHg). n = number of cats; HO = halothane anesthesia overall; CU = chloralose–urethane anesthesia; CUHP = chloralose–urethane anesthesia, with halothane applied peripherally.

of hypoxia and hypercarbia at the level of the peripheral chemoreceptors is still present during halothane anesthesia in our cat model. This is not observed in dogs.[1,3] These findings suggest species differences with respect to peripheral chemoreceptor pharmacology. It is interesting to note that in a recent report Clergue *et al.*[17] showed that during halothane anesthesia in humans administration of oxygen after breathing air resulted in a small but significant transient decrease in ventilation. This indicates that in humans the ventilatory drive due to the peripheral chemoreceptors is also not abolished completely during halothane anesthesia. As suggested by these authors, the absence of a hypoxic ventilatory stimulation in the steady-state[2] might be explained by a balance between peripheral stimulation and central depression by hypoxemia.

To determine whether the ventilatory depression by halothane during hypoxia in cats is due to a depressed peripheral chemoreceptor responsiveness or to effects of halothane on the mechanical properties of the respiratory system, a method has to be used whereby these effects can be distinguished. This was achieved by artificial perfusion of the brain stem with blood in which the gas tensions and halothane concentration can be set to a desired value, independent of the gas tensions in the systemic circulation, because now the central and peripheral chemoreflex can be determined separately. In this system the finding of a depressed peripheral response to hypercarbia during peripheral halothane administration and an unaltered central CO_2 responsiveness would point to a selective depression of the peripheral chemoreceptors.

Therefore, in this study the brain stem was perfused separately from the systemic circulation via a cannulated vertebral artery. To this end blood was drawn from the femoral artery and led through a gas exchanger. The structures perfused are defined as central (*i.e.*, central chemoreceptors, integrating centers), all other structures as peripheral (*i.e.*, respiratory muscles, lung receptors, peripheral chemoreceptors). Recently,[10] this model of artificial perfusion of the brain stem has been used for measuring the responses to hypoxemia. It was found that during chloralose–urethane anesthesia levels of peripheral hypoxemia resulted in a graded increase in peripheral CO_2 sensitivity that did not influence the central CO_2 responsiveness, even in the severely hypocapnic range.[10,18,19] Similarly, central hypoxic depression did not attenuate the central and peripheral CO_2 responsiveness (Sc and Sp), although it resulted in a shift of the B value. Due to the hypoxic stimulation of breathing, lower Pa_{CO_2} levels were observed in this study than during normoxia, as has also been found in humans.[20] However, in contrast to humans,[20] the CO_2 response curves in cats anesthetized with chloralose–urethane are linear down to the apneic threshold, and therefore the CO_2 responsiveness determined in the

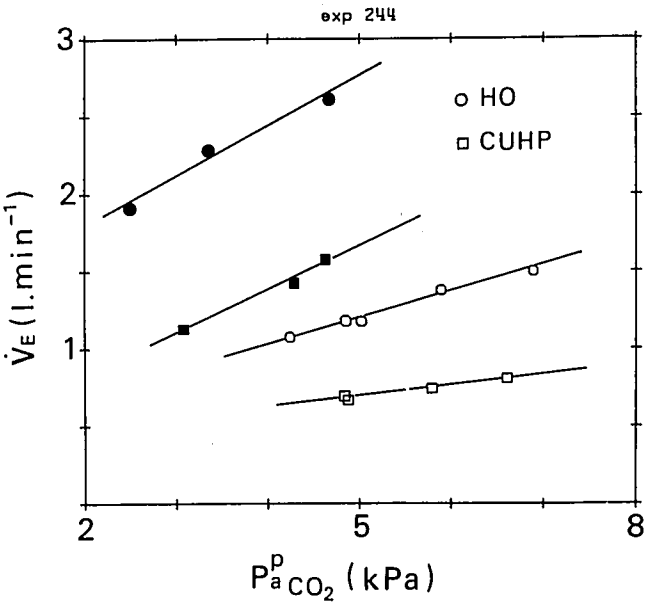

FIG. 5. Ventilatory responses to changes in peripheral Pa_{CO_2} during peripheral hyperoxia (*open symbols*) and peripheral hypoxia (*closed symbols*) illustrated in one cat during halothane overall (HO) and chloralose–urethane anesthesia with halothane added peripherally (CUHP). The central Pa_{CO_2} was kept constant at 4.1 kPa (31 mmHg) and the central Pa_{O_2} at about 50 kPa (375 mmHg).

hypocapnic region above the apneic threshold is also a measure of the CO_2 sensitivity at normal Pa_{CO_2} ranges.[21]

Hypoxia stimulates ventilation via its effect on the peripheral chemoreceptors of the carotid and aortic bodies but at the same time has a depressant effect on central nervous structures. When only the total ventilatory response to overall isocapnic hypoxia is measured, these two antagonistic actions make the interpretation of an effect of halothane on the peripheral chemoreceptors difficult. In this study the ventilatory response to hypoxia during overall halothane anesthesia was significantly lower in non-ABP cats compared with ABP cats. This is probably due to a concomitant change in $Pa_{O_2}{}^c$ in the non-ABP cats and possibly to small differences in halothane concentration in the medullary region between ABP and non-ABP cats. Even at moderate levels of hypoxia (Pa_{O_2} 6.5 kPa; 49 mmHg), the central depressant effect of hypoxia was about half its peripheral stimulating action. Although the extent of central hypoxic depression may be influenced by halothane anesthesia, the occurrence of this effect is not attributable to halothane *per se,* as a similar depression occurred during chloralose–urethane anesthesia.[10] To provide for a constant central reference state it therefore was decided to keep the brain stem hyperoxic.

Although it would be preferable to compare ventilation during halothane anesthesia with the awake state, it was necessary to provide for a background anesthetic during artificial brain stem perfusion, for which chloralose–urethane was chosen. The mean CO_2 responsiveness during peripheral hypoxia under chloralose–urethane in this study is about equal to that in awake cats during hypoxia.[22] The same holds for the ratio of the peripheral to central CO_2 sensitivity, that amounted to 0.36.[22] The hypoxic stimulation of ventilation in the presence of central hyperoxia amounted to 1.7 $l \cdot min^{-1}$ at a Pa_{O_2} of 6.4 kPa (48 mmHg; table 2). After substraction of the central hypoxic depression at this Pa_{O_2} (0.6 $l \cdot min^{-1}$)[10] a stimulation of 1.1 $l \cdot min^{-1}$ remains in the case of overall hypoxemia. This value is close to the values found in awake cats.[23–25] Although our background condition does not appear to affect the CO_2 and O_2 chemoreflexes, the major drawback is that a combination of anesthetics can lead to an interaction, either potentiating or obscuring effects characteristic of one of two regimens. The combination of chloralose–urethane and halothane added peripherally seemed to increase the anesthetic dose in a nonspecific way, as it resulted in a higher reduction of ventilation compared with halothane overall, whereas the ratio Sp/Sc and the B-value remained the same. Halothane, when administered systemically with the exception of the brain stem, against a background of chloralose–urethane anesthesia, depressed the peripheral and central responsiveness to CO_2 equally in the presence of peripheral hypoxia, whereas the synergistic effect of hypoxia and hypercarbia on the peripheral chemoreflex was still present. Moreover, the ratio Sp/Sc and the B-value were similar during overall halothane anesthesia and chloralose–urethane, either with or without halothane added peripherally. These findings suggest that the main depressant effect of peripheral halothane on the overall ventilatory response to CO_2 during peripheral hypoxemia is located in structures common to both the peripheral and central chemoreflex, *i.e.,* the neuromechanical link between brain stem centers and respiratory movements (motorneurons, respiratory muscles, or lung elastance).

Davies *et al.*[5] measured the impulse activity of the carotid body and found that halothane depressed both the CO_2 and O_2 responsiveness; systemic hypotension following halothane administration tended to mask the depression of the peripheral neural CO_2 and O_2 sensitivities. It is known that the aortic chemoreceptor activity of the cat is enhanced by both systemic hypotension and hypoxia.[26] Recently,[27,28] it was shown that a fall in blood pressure at the carotid sinus baroreceptors causes a rapid rise in ventilation independent of the carotid chemoreceptor reflex. In our cat model, a direct depressant effect of halothane on the peripheral chemoreceptors was not manifest in the overall ventilatory response to peripheral and central CO_2 stimulation during peripheral hypoxemia. We therefore cannot confirm the findings by Davies *et al.*[5] However, it may well be that effects of halothane on lung receptors, lung elastance, and indirect effects of blood pressure changes tend to obscure a direct depressant action on the peripheral chemoreceptors.

In summary, halothane 0.8–1.2% inspired reduces the ventilatory response to hypoxia in cats but does not abolish it. Although the results on the ventilatory responses to CO_2 during hypoxemia gave no support for a direct depressant effect of halothane on the peripheral chemoreceptors, such an effect cannot be excluded; if present, however, it appears to be of minor importance when compared with the depressant action of halothane on the neuromechanical link between respiratory centers in the brain stem and ventilatory movements.

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