

## Sites of Action of Halothane on Respiratory Pattern and Ventilatory Response to CO<sub>2</sub> in Cats

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To assess the major sites of action of halothane on the control of breathing, the ventilatory response to CO<sub>2</sub> was studied in 11 cats and partitioned into tidal volume and frequency response. In these cats artificial perfusion of the ponto-medullary region was applied. In essence, this technique allows one to deliver to the brainstem blood-gas tensions and anesthetic concentrations at predetermined levels which are independent from those in the systemic circulation; thus the central and peripheral effects of halothane and CO<sub>2</sub> can be determined separately.

In cats exposed both centrally and peripherally to halothane (1.0–1.6%) tachypnea was observed which disappeared when the blood perfusing the brainstem was purged of halothane. From these results it follows that the tachypnea is exclusively due to an action of halothane on structures in the brainstem. In these cats the extrapolated Pa<sub>CO<sub>2</sub></sub> at zero ventilation was significantly lower during general halothane anesthesia than during light chloralose-urethane anesthesia ( $P < 0.05$ ). In cats lightly anesthetized with chloralose-urethane, halothane (0.5–1.5%) was either administered centrally or peripherally. In these experiments the “overall” ventilatory CO<sub>2</sub> sensitivity of both the peripheral and central chemoreflex pathways decreased significantly ( $P < 0.01$ ). However, the ratio between these two sensitivities remained the same ( $P > 0.5$ ). The extrapolated Pa<sub>CO<sub>2</sub></sub> at zero ventilation was not affected by halothane provided its concentration was below 1% ( $P > 0.7$ ). From these results we conclude that the depressant effect of halothane on ventilation originates centrally as well as peripherally. Furthermore, from the findings that the ratio of the CO<sub>2</sub> sensitivities and the extrapolated Pa<sub>CO<sub>2</sub></sub> at zero ventilation remained constant, the authors argue that halothane acts on the processing part of the neural respiratory drive (integrating centers) rather than on the neural activity of the peripheral and central chemoreceptors *per se*. The peripheral effect is mainly on the neuromechanical link between integrating centers and respiratory movements. (Key words: Anesthetics, volatile: halothane. Ventilation: carbon dioxide response; regulation; tachypnea. Receptors: chemoreceptors.)

GENERAL ANESTHETICS affect the respiratory control system. However, detailed knowledge of these effects is not available. For halothane for example, central as well as peripheral effects have been demonstrated to play a role<sup>1–3</sup> in the depressant effect on ventilation, but in spite of much experimental work, the relative importance of the central and peripheral components is

not known. This is also true for the tachypnea observed during halothane anesthesia<sup>4</sup>: originally it was thought to be caused by a peripheral action of halothane mediated vagally<sup>1,5–9</sup>; more recent investigations<sup>10–12</sup> point, however, to an action on the bulbo-pontine pacemaker. A satisfactory answer to these questions has in part been hampered by a lack of suitable experimental methods. The technique of artificial brainstem perfusion (ABP) is very well suited to address these questions; it was developed originally to separate the central and peripheral effects of chemical stimulation on ventilation.<sup>13</sup> With this technique predetermined blood-gas tensions and halothane concentrations can be delivered to the brainstem independent of the systemic blood-gas tensions. It thus becomes possible to differentiate between peripheral and central effects of halothane on the respiratory control system.

We therefore applied this technique to study whether tachypnea originates from a central or a peripheral action of halothane. Furthermore, we studied the major sites at which halothane exerts a depressant effect on the ventilatory response to peripheral and central CO<sub>2</sub> stimulation. We have previously extensively investigated and quantified the contribution of the central and peripheral chemoreceptors to ventilation during hyperoxia.<sup>14–17</sup> We therefore limited ourselves in this study to the effect of halothane during hyperoxia; the action of halothane during hypoxia will be investigated separately.

### Methods

Experiments were performed on cats using the ABP technique. With this technique, the ponto-medullary region is perfused artificially with the cat's own blood. To that end blood from a femoral artery is fed into a gas exchanger. After establishing the desired blood-gas tensions and halothane concentration in this gas exchanger, the blood is pumped into the medulla oblongata and pons via a cannulated vertebral artery (fig. 1). In this way, the central chemosensitive structures and respiratory integrating centers are perfused artificially with blood of which the P<sub>CO<sub>2</sub></sub> (hence called central arterial carbon dioxide tension, Pa<sub>CO<sub>2</sub></sub>) and halothane concentration can be controlled experimentally at any level by equilibration with gas mixtures administered to the gas exchanger. The peripheral chemoreceptors (aortic and carotid bodies) are supplied with blood by

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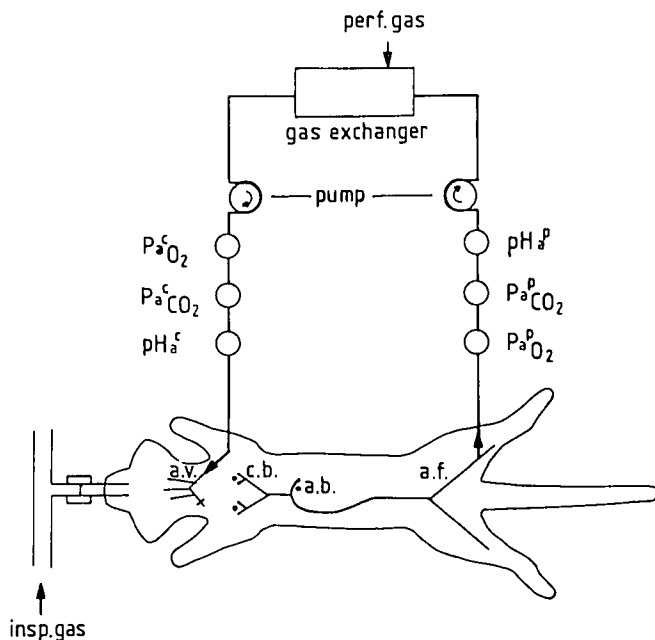


FIG. 1. Diagram of the experimental model. Blood from a femoral artery (a.f.) is pumped into a gas exchanger where it is equilibrated with a gas mixture (perf. gas) of adjustable composition. This blood is then pumped into the brainstem via a vertebral artery (a.v.). The carotid (c.b.) and aortic (a.b.) bodies are perfused via the systemic circulation, and their blood-gas tensions are influenced by the inspiratory gas mixture (insp. gas).

the systemic circulation. The  $P_{CO_2}$  of this blood (referred to as peripheral arterial carbon dioxide tension,  $Pa_{CO_2}^p$ ) and its halothane concentration can be varied by varying the  $CO_2$  and halothane concentration of the inspire.

All experiments, performed on 11 adult cats of either sex with a body weight from 2.6 to 3.8 kg, proceeded as follows. Anesthesia was induced with 10 mg/kg ketamine hydrochloride intramuscularly, followed by inhalation of a gas mixture containing 1.3% halothane and 30%  $O_2$  in  $N_2$ . Thereafter, the right femoral vein was cannulated for the administration of nonvolatile anesthetics during the experiment when needed. The trachea was cannulated for the measurement of inspiratory and expiratory flow by means of a Fleisch no. 0 pneumotachograph; tidal volume was obtained by integrating the flow signal. Temperature was monitored by a rectal thermistor and maintained at  $36.9$ – $37.7^\circ C$  by means of a heating lamp. Femoral arterial pressure was measured by means of a strain gauge. These signals were processed by a DEC PDP 11/10 minicomputer. Mean tidal volume and mean inspiratory and expiratory time were determined over 20 breaths; ventilation and respiratory frequency were calculated from these data.

An extracorporeal circuit (ECC) was connected between the left femoral artery and the left femoral vein.

Electrodes were inserted for the continuous measurement of  $Pa_{O_2}$ ,  $Pa_{CO_2}$  and  $pH_a$ . The left vertebral artery or a branch to a muscle was exposed in the neck. Measurements were first performed while the brainstem was perfused with systemic blood via the patent vertebral arteries. Thereafter, one vertebral artery was cannulated and the ECC disconnected from the femoral vein and connected to the cannulated vertebral artery. Blood was subsequently pumped into the ponto-medullary region at a constant flow of 6 ml/min; the other vertebral artery was clamped. The surgical procedures (which usually lasted six hours) as well as the measurements of the inspiratory and expiratory duration, ventilation, blood-gas tensions, etc., have been described in detail in a previous publication<sup>13</sup> which also contains information about the effectiveness of the extracorporeal circuit in removing halothane from blood used to perfuse the brainstem.

All experiments were performed during hyperoxia ( $Pa_{O_2} > 375$  mmHg). During artificial perfusion of the brainstem with a constant  $Pa_{CO_2}^c$ , the ventilatory response to changes in  $Pa_{CO_2}^p$  was assessed by giving the cat gas mixtures to inhale which contained 60%  $O_2$  in  $N_2$  and to which  $CO_2$  was added in concentrations up to 6%. Usually, the steady-state ventilation ( $\dot{V}_E$ ) was measured at three different peripheral  $Pa_{CO_2}$  values. Such a peripheral ventilatory response was determined at two or three different central  $Pa_{CO_2}$  values. In this manner the ventilatory responses to changes in both peripheral and central  $P_{CO_2}$  were assessed.

## EXPERIMENTAL PROTOCOLS

In order to elucidate the site of action of halothane this anesthetic was administered exclusively peripherally (*i.e.*, to the non-artificially perfused part of the animal via the systemic circulation) or centrally (*i.e.*, to the artificially perfused brainstem). To have a reference state without halothane the animal was kept under anesthesia with another anesthetic, for which chloralose-urethane was chosen. This, however, made it necessary to examine the effects of peripherally and centrally administered halothane with and without chloralose-urethane.

### Protocol 1

The main purpose of this group of experiments was to study the effects of removal of halothane from the perfused brainstem on tidal volume, respiratory frequency, and the ventilatory response to  $CO_2$ . Furthermore, we measured the same variables during light chloralose-urethane anesthesia, which we used as a reference state. Because of the complexity and the duration of the experiments, further measurements after the administration of halothane (centrally or peripherally) were not

always possible. Therefore, not all desired anesthetic regimens could be studied in one and the same cat. As a compromise, we performed a separate series of experiments as outlined in the second protocol.

According to protocol 1, the animals (six cats) were kept under general halothane anesthesia (HO = halothane overall). Before commencing artificial perfusion of the ponto-medullary region, the ventilatory response to CO<sub>2</sub> was assessed. To this end, up to 4% CO<sub>2</sub> was added to the inspire which consisted of 60% O<sub>2</sub> in N<sub>2</sub>. Ventilation and PaCO<sub>2</sub> were measured during near steady-state conditions. The perfusion was then started with blood that was free of halothane (HP = halothane peripherally), and the ventilatory response to changes in central and peripheral PaCO<sub>2</sub> were assessed. Thereafter, the anesthetic regimen was altered in all six cats. In five cats, 10–15 mg/kg chloralose and 50–75 mg/kg urethane were slowly infused intravenously while the halothane concentration in the inspiratory gas mixture was decreased to zero. In the one remaining cat, 20 mg/kg pentobarbital was given instead of chloralose-urethane. After approximately half an hour, when near ventilatory and circulatory steady states had been achieved, the ventilatory responses to changes in PaCO<sub>2</sub><sup>p</sup> and PaCO<sub>2</sub><sup>c</sup> were determined again. In four of the five cats anesthetized with chloralose-urethane, halothane was added either to the gas mixture in the gas exchanger and thus to the blood perfusing the brainstem (CUHC = chloralose-urethane with halothane centrally), or to the inspiratory gas mixture and thus to the systemic circulation with the exception of the ponto-medullary region (CUHP = chloralose-urethane with halothane peripherally). Again, the ventilatory response to changes in peripheral as well as central P<sub>CO<sub>2</sub></sub> were assessed during hyperoxia.

#### Protocol 2

The purpose of these experiments was to study the peripheral and central effects of halothane on tidal volume, respiratory frequency, and the ventilatory response to CO<sub>2</sub> with a background anesthesia of chloralose-urethane. Five cats were under general chloralose-urethane (CU) anesthesia (20 mg/kg chloralose and 100 mg/kg urethane intravenously). We first assessed the ventilatory responses to changes in peripheral as well as central PaCO<sub>2</sub>. This was repeated when halothane was subsequently administered peripherally and/or centrally. All experiments were performed during hyperoxia.

#### Evaluation of Data

Using standard multiple regression analysis, we found that ventilation ( $\dot{V}_E$ ) could be satisfactorily described by:

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

where K is a constant. The overall CO<sub>2</sub> sensitivity of the peripheral pathway (Sp) as well as the overall CO<sub>2</sub> sensitivity of the central pathway (Sc) were independent of the central arterial P<sub>CO<sub>2</sub></sub> and peripheral arterial P<sub>CO<sub>2</sub></sub>. In discussing the effects of anesthetics on ventilation, it is convenient, as shown in a previous publication,<sup>14</sup> to introduce the ratio  $r = Sp/Sc$  and a quantity  $B = K/(Sp + Sc)$ .

For non-artificially perfused cats  $Pa_{CO_2}^p = Pa_{CO_2}^c = Pa_{CO_2}$ , and equation (1) reduces to the familiar description of the ventilatory CO<sub>2</sub> response curve:

$$\dot{V}_E = S(Pa_{CO_2} - B) \quad (2)$$

where S is equal to (Sp + Sc), and B is the extrapolated PaCO<sub>2</sub> at zero ventilation.

Results of the experiments were subjected to statistical analysis by Student's *t* test for paired samples.

## Results

### PATTERN OF BREATHING

We restricted ourselves to the question whether tachypnea as caused by halothane originates centrally or peripherally. We only studied the breakdown of ventilation into tidal volume ( $V_T$ ) and respiratory frequency. This partitioning of  $\dot{V}_E$  into  $V_T$  and frequency has been shown by Hey *et al.*<sup>18</sup> to be independent of the type of respiratory stimuli O<sub>2</sub> and CO<sub>2</sub>, *i.e.*, peripheral or central chemoreceptor stimulation. We found that this is also true for CO<sub>2</sub> stimulation of the peripheral and central chemoreceptors in our cats. The relation between  $\dot{V}_E$  and  $V_T$  was shown by Hey *et al.*<sup>18</sup> to be adequately described by:

$$\dot{V}_E = m(V_T - k) \quad (3)$$

where *m*, the slope of the  $\dot{V}_E - V_T$  relationship, is a frequency parameter, and *k* is the intercept on the  $V_T$ -axis.

### Halothane Overall vs. Halothane Peripherally

In cats anesthetized with halothane, the respiratory frequency decreased significantly when the halothane in the blood perfusing the brainstem was blown off in the gas exchanger. This is exemplified in figure 2. Changes in  $\dot{V}_E$  and  $V_T$  were brought about by altering the CO<sub>2</sub> tensions. During general halothane anesthesia, the frequency parameter *m* is much larger than when the ponto-medullary region is kept free of halothane (fig. 2). The lines converge more or less to the origin, indicating that changes in ventilation are predominantly

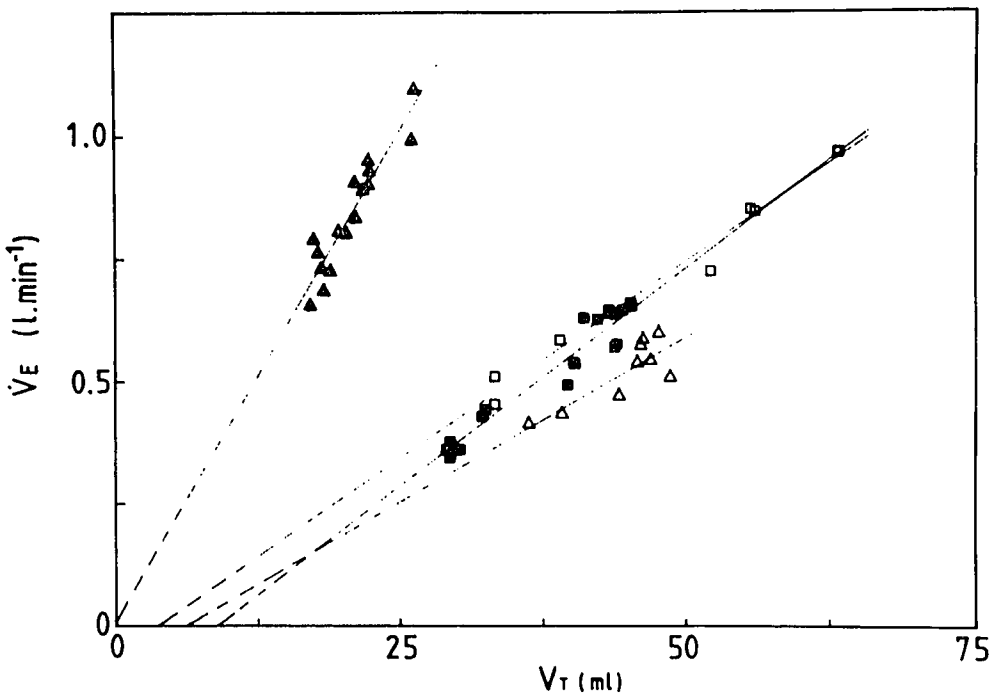


FIG. 2. Ventilation as a function of tidal volume during general halothane (1.4%) anesthesia ( $\blacktriangle$ ), halothane only peripherally ( $\blacksquare$ ), combination of chloralose-urethane anesthesia and 0.8% halothane peripherally ( $\triangle$ ), and during chloralose-urethane anesthesia ( $\square$ ). Data of experiment 812.

caused by changes in tidal volume, the respiratory frequency changing only slightly.

In figure 3, ventilation, inspiratory, and expiratory duration of a typical experiment during general halothane anesthesia are shown starting at the onset of artificial brainstem perfusion. Prior to the artificial perfusion, the  $P_{aCO_2}$  was 48 mmHg and the respiratory

frequency 55/min. The latter value is brought about by an inspiratory and expiratory duration of roughly 0.5 s each. The artificial perfusion of the brainstem with blood which was free of halothane was started with a  $P_{CO_2}$  of 37 mmHg. The blood flow was augmented in steps of 1 ml/min up to about 6 ml/min, a value sufficient to perfuse at least the pons and medulla oblongata.<sup>13</sup> In this particular case it led to a decrease in ventilation due to the combined effect of the perfusion with a lower  $P_{CO_2}$  and the central removal of halothane. A decrease in ventilation of this size usually gives only a slight decrease in respiratory frequency. However, the frequency fell to about a normal level (25/min) here; both the inspiratory and expiratory time increased. When the artificial perfusion was stopped and brainstem subsequently perfused with blood from the systemic circulation which still contained halothane, the reverse was observed. These results show that the effect of halothane on the pattern of breathing with respect to tachypnea is predominantly mediated centrally. This is also demonstrated by table 1 which shows that the mean of

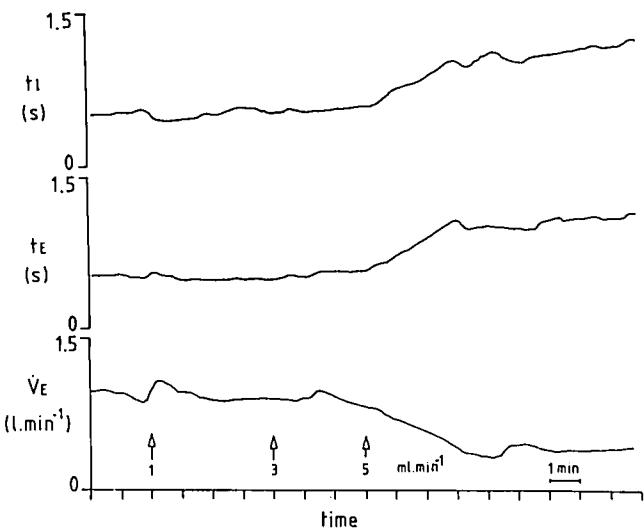


FIG. 3. Ventilation, inspiratory and expiratory duration before ( $P_{aCO_2}$  = 48 mmHg) and during artificial medullary perfusion ( $P_{aCO_2}$  = 37 mmHg) with blood flows augmented in steps of 1 ml/min (some values indicated by arrows). General anesthesia with 1.4% halothane. Before perfusion the breathing frequency was high (55/min). When the blood was purged of halothane, breathing frequency decreased to near normal values (25/min).

TABLE 1. Frequency Parameter  $m$  and Intercept  $k$  of the  $\dot{V}_E - V_T$  Plot Described as  $\dot{V}_E = m(V_T - k)$  during General Overall Halothane Anesthesia (HO) and when Only the Ponto-medullary Region Was Kept Free from Halothane (HP)

Parameter	HO	HP
$m$ ( $\text{min}^{-1}$ )	$38.8 \pm 2.3$	$24.6 \pm 3.0$
$k$ (ml)	$-1.7 \pm 3.2$	$4.9 \pm 0.8$

Values are means  $\pm$  SE of six cats. Values are significantly different for  $m$  ( $P < 0.01$ ) but not for  $k$  ( $P > 0.05$ ).

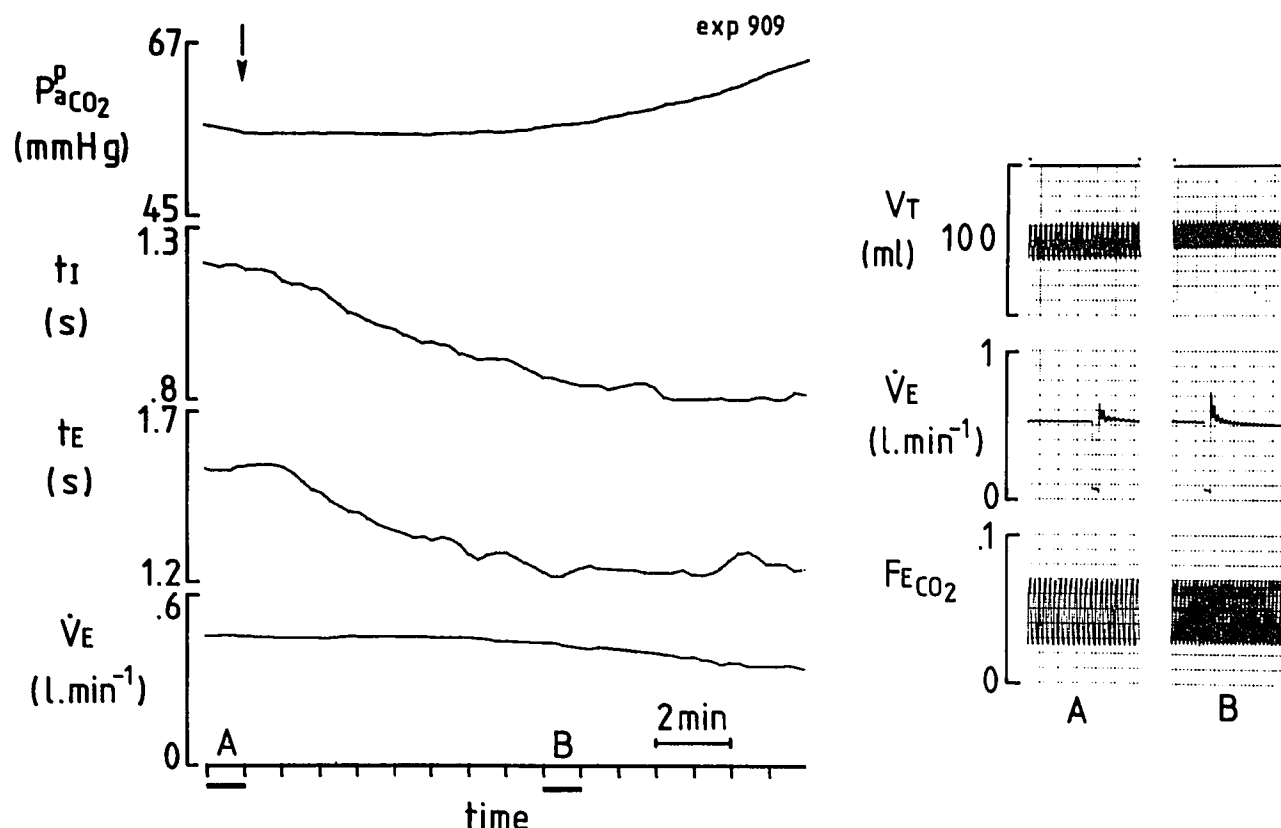


FIG. 4. Time course of ventilation, inspiratory and expiratory duration, and peripheral  $P_{aCO_2}$  after administration of 1% halothane centrally (arrow). The polygraphic recording of tidal volume, ventilation, and inspiratory and expiratory  $CO_2$  concentration at time A and B is also shown.

the respiratory frequency parameter  $m$  decreased significantly ( $P < 0.01$ ; mean difference  $14.2/\text{min}$ , SE  $3.4$ ) when the halothane was removed from the ponto-medullary region. This implies, as the intercept on the  $V_T$ -axis did not change significantly, that at all levels of  $\dot{V}_E$  the respiratory frequency is highest when halothane has been administered centrally.

#### Halothane Centrally or Peripherally with a Background of Chloralose-urethane

Additional information about the effect of centrally administered halothane, was derived from five cats lightly anesthetized with chloralose-urethane. Figure 4 shows the effect of a step-like addition of 1% halothane to the gas in the gas exchanger in one experiment. It shows that the ventilation remained constant for about nine minutes. Meanwhile, however, the inspiratory and expiratory duration decreased considerably. Thereafter, the ventilation also diminished. The same phenomena were observed in the other four cats. At near steady states, however, there was no significant difference between the parameters  $m$  and  $k$  compared with the values estimated without centrally administered halothane (table 2).

In five cats we administered halothane peripherally with a background of chloralose-urethane anesthesia. An example of the results of such an experiment can be seen in figure 2. The results of all experiments (table 3) show that the  $\dot{V}_E - V_T$  plots were not significantly different from those obtained without halothane in the same animal.

#### RESPIRATORY MINUTE VOLUME

##### Halothane Centrally or Peripherally with a Background of Chloralose-urethane

During general chloralose-urethane anesthesia, we administered halothane centrally as well as peripherally.

TABLE 2. Respiratory Frequency Parameter  $m$  and the Intercept  $k$  of the  $\dot{V}_E - V_T$  Plot during General Chloralose-urethane Anesthesia (CU) and with Additional Halothane Administered Only Centrally (CUHC)

Parameter	CU	CUHC
$m$ ( $\text{min}^{-1}$ )	$27.4 \pm 3.0$	$30.2 \pm 5.3$
$k$ (ml)	$4.5 \pm 2.0$	$7.2 \pm 3.2$

Values are means  $\pm$  SE of five cats. Differences are not significantly different for  $m$  ( $P > 0.4$ ) or  $k$  ( $P > 0.1$ ).

TABLE 3. Respiratory Frequency Parameter  $m$  and the Intercept  $k$  of the  $\dot{V}_E - V_T$  Plot during General Chloralose-urethane Anesthesia (CU) and when Additional Halothane Was Administered Peripherally (CUHP)

Parameter	CU	CUHP
$m$ ( $\text{min}^{-1}$ )	$27.7 \pm 1.2$	$25.5 \pm 0.9$
$k$ (ml)	$4.0 \pm 2.1$	$4.5 \pm 1.5$

Values are means  $\pm$  SE of five cats. Differences are not significant for  $m$  ( $P > 0.1$ ) or  $k$  ( $P > 0.8$ ).

The data of all the experiments are collected in table 4. An example of a CUHC experiment during artificial perfusion of the brainstem is depicted in figure 5. It shows the ventilatory response to changes in  $\text{PaCO}_2^p$  at a constant  $\text{PaCO}_2^c$  as well as the ventilatory response to

changes in  $\text{PaCO}_2^c$  at constant  $\text{PaCO}_2^p$  in the same cat. Figure 5 illustrates the general finding that upon application of halothane exclusively to the ponto-medullary region, the central (Sc) as well as the peripheral (Sp)  $\text{CO}_2$  sensitivities diminish significantly (five cats,  $P < 0.01$  for both Sp and Sc). The ratio  $r = \text{Sp}/\text{Sc}$ , however, did not change significantly ( $P > 0.5$ ). This implies that the relative depression of the central and peripheral  $\text{CO}_2$  sensitivities is the same. Also the B-value did not change significantly ( $P > 0.7$ ).

When halothane was administered peripherally (CUHP) only, at concentrations up to 1%, Sp as well as Sc decreased significantly (five cats,  $P < 0.02$  for both Sp and Sc) but not their ratio  $r$  ( $P > 0.6$ ). The parameter B showed a tendency to decrease, but this did not achieve a level of significance ( $P > 0.08$ ). In one exper-

TABLE 4. Variables of the Ventilatory Response to  $\text{CO}_2$  with Different Anesthetic Regimens

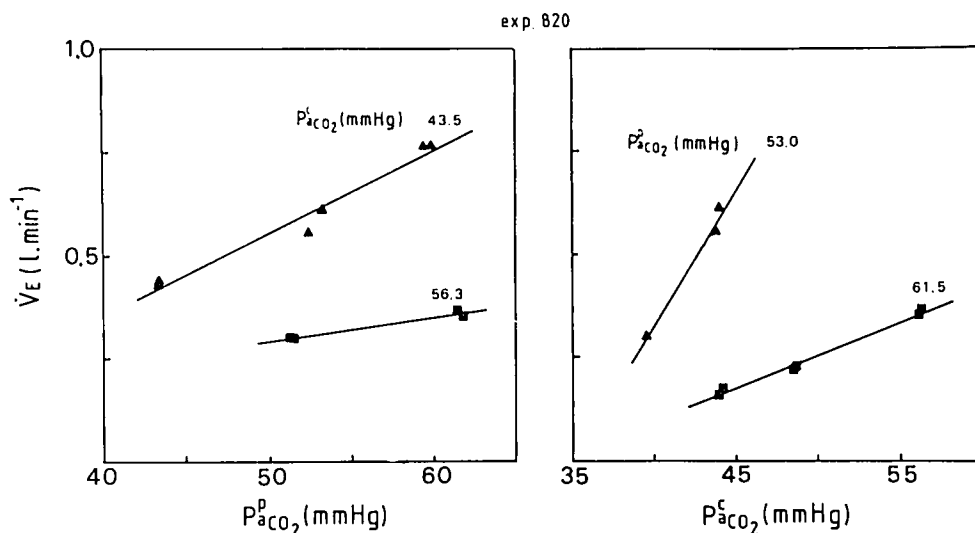
Experiment Number	Anesthesia	Halothane (%)	S $\text{ml} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$	Sp $\text{ml} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$	Sc $\text{ml} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$	r	B mmHg
904	CU			26.0	73.1	0.36	25.0
	CUHP	0.5		25.2	52.8	0.48	27.3
	CUHP	1.0		10.1	30.8	0.33	24.2
850	CU			14.4	63.5	0.23	29.2
	CUHP	0.8		8.8	32.5	0.27	24.4
820	CU			19.9	74.7	0.27	39.5
	CUHC	1.0		4.3	15.5	0.28	39.3
812	HO	1.4	23.7				2.3
	HP	1.4		8.1	53.6*	0.15	35.6
	CU			18.3	106.3	0.17	35.0
808	HO	1.4	30.4				10.6
	CUHP	1.0		14.8	74.1	0.20	37.4
	CUHP	1.5		17.7	25.9	0.69	39.9
909	HO	1.2	21.3				22.9
	CU			10.8	95.2	0.11	40.1
	CUHP	0.8		5.6	45.2	0.12	37.4
	CUHC	0.5		2.13	12.8	0.17	33.1
906	HO	1.0	34.3				34.4
	HP	1.0		12.4	59.6	0.21	30.0
	Pentob.			18.8	54.5	0.34	29.9
127	HO	1.4	24.2				18.2
	CU			15.4	75.5	0.20	38.4
	CUHC	1.0		9.0	28.8	0.31	40.3
128	HO	1.6	24.5				2.9
	HP	1.6		47.4	134.2*	0.35	31.3
	CU			53.3	172.6	0.31	20.7
	CUHC	0.5		31.0	129.4	0.24	24.8
129	CU			38.1	89.8	0.42	30.8
	CUHP	1.0		19.3	56.7	0.34	31.4
	CUHC	1.0		17.4	42.9	0.40	28.7
848	CU			23.9	152.2	0.16	33.2
	CUHP	1.0		14.7	44.1	0.33	28.1

Slopes S, Sp, and Sc are due to changes in overall arterial, peripheral arterial, and central arterial  $\text{CO}_2$  tension; the B value is the arterial  $\text{CO}_2$  tension at zero ventilation. HO = overall halothane; CU = overall chloralose-urethane; HP = halothane peripherally, i.e., the brainstem excluded; CUHP = overall chloralose-urethane with additional halo-

thane peripherally; CUHC = overall chloralose-urethane with additional halothane centrally; Pentob. = overall pentobarbital.

\* Only the approximately linear part at lower levels of ventilation was used.

FIG. 5. (left). Ventilation as a function of the peripheral  $P_{CO_2}$  at constant central  $P_{CO_2}$  as indicated. (right). Central  $CO_2$  response curves at constant peripheral  $P_{CO_2}$ . Chloralose-urethane anesthesia with (■) and without (▲) additional halothane administered centrally.



iment in which the halothane concentration was further increased to 1.5%,  $Sp$  in contrast to  $Sc$  did not decrease any further.

#### *Halothane Overall, Halothane Peripherally, Chloralose-urethane*

In six cats the "overall" ventilatory response to  $CO_2$  was assessed under general halothane anesthesia (HO) at concentrations of 1–1.6% before the commencement of artificial medullary perfusion. In five of these cats the extrapolated  $P_{aCO_2}$  at zero ventilation could be compared with the B value obtained in the same cat during artificial perfusion of the ponto-medullary region when no halothane had been applied. We found that the B values were significantly less ( $P < 0.05$ ) during overall halothane anesthesia.

In three cats the ventilatory response to changes in peripheral and central  $P_{aCO_2}$  were determined when the animals were only under peripheral halothane anesthesia (see table 4). In two of these cats the slope of the central  $CO_2$  response curve diminished with increasing  $P_{aCO_2}$  (fig. 6). In these two cases the approximately linear part of the curve at lower levels of ventilation was used. Upon visual inspection it can be seen (table 4, exp. 812 and 128) that the ratio  $r$  and the B value are about the same when compared with the values during chloralose-urethane or pentobarbital anesthesia.

#### Discussion

In the cat, the main structures involved in the autonomic central regulation of breathing, *i.e.*, the pons and medulla oblongata, are supplied with blood by the vertebral arteries. There is very little overlap between the areas perfused by the carotid and vertebral arteries.<sup>19</sup> With dye studies we have shown earlier<sup>13</sup> that

using the brainstem perfusion technique, the artificially perfused area extended to pons, medulla oblongata, and cerebellum, and we found no appreciable admixture of blood from the systemic circulation to these areas at any level of  $P_{aCO_2}$  during hyperoxia. The local regulation of cerebral blood flow is not disturbed by the artificial brainstem perfusion because the vertebral arteries communicate with the circle of Willis via the basilar artery, and the surplus of blood pumped into the vertebral artery can drain off to the cerebrum. This means that halothane administered to the blood via the gas exchanger not only reaches the ponto-medullary area and the

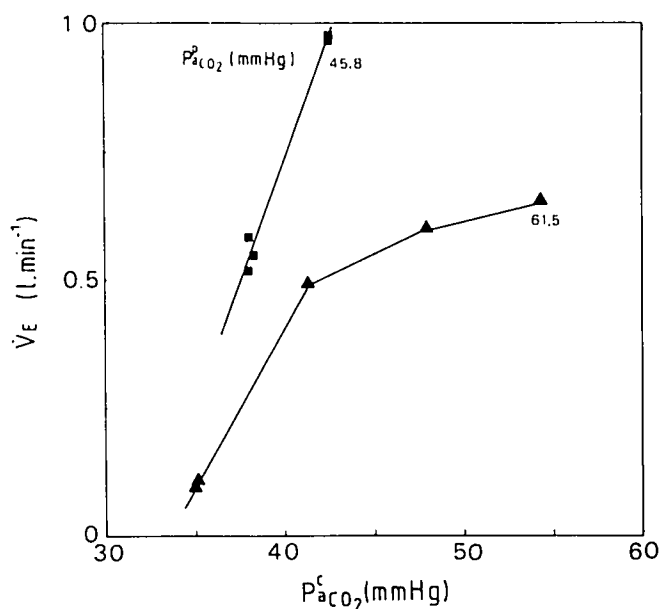


FIG. 6. Ventilatory response to changes in central  $P_{CO_2}$  at constant peripheral  $P_{CO_2}$  during peripheral halothane anesthesia (▲) and chloralose-urethane anesthesia (■) in the same cat.

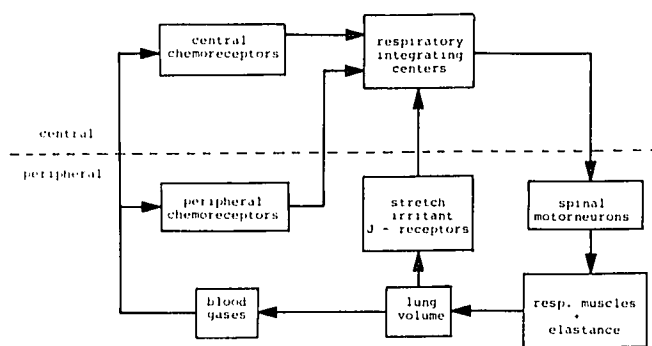


FIG. 7. Schematic diagram of the ventilatory control system.

cerebellum, but also the cerebrum in small amounts due to overflow into the circle of Willis. Due to this overflow, which is a prerequisite to ensure that at least the central chemosensitive structures and the respiratory integrating centers are perfused exclusively with blood from the gas exchanger, the anatomic sites affected by halothane may therefore extend somewhat beyond the brainstem *per se*.

When halothane is administered to the inspire, at least 97% of the anesthetic is removed from the blood in the gas exchanger<sup>13</sup> and thus from the blood perfusing the ponto-medullary region. As the maximum concentration used in the inspire was 1.6%, the ponto-medullary region may have been perfused with blood having a maximum concentration equivalent to an inspired concentration of 0.05%. It is unlikely that such low concentrations have an appreciable effect on the central regulation of breathing.

#### PATTERN OF BREATHING

Most volatile anesthetics, including halothane, produce tachypnea, *i.e.*, rapid and shallow breathing. The explanation of this phenomenon is rather complex. It has been well-documented that halothane stimulates stretch and J-receptors in the lungs<sup>6,7</sup>; the lung irritant receptors are probably inhibited by halothane.<sup>20</sup> In rabbits, it is plausible that tachypnea induced by halothane originates predominantly from these lung receptors as it is abolished by vagotomy.<sup>8,9</sup> Furthermore, results from experiments where anodal blocks were applied to the vagi suggest that the tachypnea was due to stimulation of J-receptors.<sup>8</sup> The state of affairs in humans and cats is much less clear. Dundee and Dripps<sup>21</sup> suggested that sensitization of the stretch receptors could explain the tachypnea induced by inhalation anesthetics. This point of view was challenged by Paskin *et al.*<sup>10</sup> as they found no evidence in humans that the tachypnea was mediated by the Hering-Breuer reflex. The sensitization of pulmonary stretch receptors cannot be the sole

cause in anesthetized cats either, because tachypnea is still present after bilateral vagotomy.<sup>1,11</sup>

Our findings show that the tachypnea induced by halothane in concentrations of 1.0–1.6% originates centrally; it is most probably an effect on structures in the pons and medulla oblongata, although effects on other parts of the brain cannot be ruled out entirely. This is in agreement with the conclusions of Mazzarelli *et al.*,<sup>11</sup> who found that the timing of the occluded breath which was taken as an index of the bulbopontine respiratory rhythm, was not significantly altered after vagotomy in cats anesthetized with halothane. Recently, Marsh *et al.*<sup>12</sup> concluded from experiments in dogs that halothane acts on the bulbopontine pacemaker.

When halothane is administered centrally, the increase in breathing frequency precedes the depression of ventilation by several minutes (see fig. 4), suggesting that the site of action of halothane with respect to tachypnea is anatomically distinct from that part of the brainstem where the afferent neural signals of the carotid bodies and the central chemoreceptors are processed. It is interesting to note that with a background of chloralose-urethane anesthesia this effect of halothane on the pattern of breathing in the near steady state seems to disappear (see table 2): the respiratory frequency remained at a high level in only two of five cats. This may serve as an indication that the presence of a light background anesthesia can profoundly mask a characteristic action of a test anesthetic. Therefore, our finding that halothane applied peripherally with a background of chloralose-urethane did not change the pattern of breathing significantly cannot serve as evidence that the effect of halothane on lung receptors, as reflected in the pattern of breathing, is negligible. However, from a comparison of the parameters of the  $\dot{V}_E - V_T$  plot, it may be concluded that any effect on lung receptors must be small (see tables 1, 2, and 3).

#### RESPIRATORY MINUTE VOLUME

To facilitate the discussion on the action of halothane on the ventilatory response to  $\text{CO}_2$ , we propose a model of the ventilatory control system schematically depicted in figure 7. The central part comprises the central chemoreceptors and the respiratory integrating centers in which the neural signals from central and peripheral chemoreceptors are processed and where rhythmic signals are produced. All structures located in the area perfused by the vertebral artery are defined as central, and all other structures as peripheral. Thus, the peripheral part of the control system contains, among other things, spinal motor neurons, respiratory muscles, and lung receptors.

There is a general consensus that halothane causes a dose-dependent depression of the ventilatory response



to inhaled  $\text{CO}_2$ . Usually it is attributed to depression of central respiratory neurons.<sup>1</sup> It was, however, suggested by Tusiewicz *et al.*<sup>3</sup> that a decrease of ventilation could also result from mechanical dysfunction of the respiratory pump (in our model spinal motor neurons, respiratory muscles, and elastance), that is a peripheral effect. Subsequent experiments led them to the conclusion that a major component of the ventilatory depression resulted from depression of intercostal muscle function with relative sparing of diaphragmatic activity. Our results also support both a central and peripheral action of halothane on ventilation. A central effect originating in the ponto-medullary region is demonstrated by administration of halothane exclusively to this area. The finding that upon administration of halothane exclusively centrally Sp and Sc are depressed, is evidence that one of the central effects of halothane on ventilation resides in the integrating centers, provided the peripheral  $\text{CO}_2$  sensitivity does not depend on the integrity of the central chemoreceptors. An action of halothane on the central chemoreceptors is unlikely as discussed at the end of this section. The central  $\text{CO}_2$  sensitivity (Sc) apparently is depressed when halothane is present only peripherally. This effect is dose-dependent and is most pronounced at higher levels of ventilation and at halothane concentrations larger than 1%, where it leads to a limitation of the central ventilatory response to  $\text{CO}_2$  (see fig. 6). In non-artificially perfused cats during anesthesia with inspired halothane concentrations greater than 1%, the B values were significantly smaller than the values found under chloralose-urethane anesthesia (table 4). It has been shown<sup>16</sup> that the B value obtained by extrapolation to zero ventilation is the actual apneic threshold for rhythmic ventilation in cats anesthetized with chloralose-urethane. Hickey *et al.*,<sup>22</sup> using volatile anesthetics in humans, found when using ether, halothane, and isoflurane that the B value obtained by extrapolation was less than the actual apneic threshold determined by hyperventilating the subjects to apnea. Their findings and ours may have to do with the curvilinear nature of the response curve during halothane anesthesia (fig. 6). In our non-artificially perfused cats, the measured  $\dot{V}_E$  and  $\text{Pa}_{\text{CO}_2}$  values probably belong to the upper part of the  $\text{CO}_2$  response curve, where it can still be described satisfactorily by a linear function. However, extrapolation leads to a  $\text{Pa}_{\text{CO}_2}$  which is lower than the actual apneic threshold.

It has been reported<sup>23</sup> that methoxyflurane increases the effective elastance for the total respiratory system. Here elastance is defined as the ratio of peak mouth occlusion pressure to the tidal volume of an unobstructed breath at the same chemical drive. This elastance is increased further when the  $\text{CO}_2$  level is raised.<sup>23</sup> It has the dual effect of reducing the ventilatory re-

sponse to  $\text{CO}_2$  and displacing the intercept to lower levels of  $\text{P}_{\text{CO}_2}$ . Derenne *et al.*<sup>23</sup> suggested that halothane has a similar effect on the elastance. Indeed, such an effect can be deduced from the results reported by Mazzarelli *et al.*<sup>11</sup>; they found in cats inhaling 3% halothane that the mouth occlusion pressure, although depressed, still increased upon increasing the  $\text{P}_{\text{CO}_2}$ , while minute ventilation remained constant or even decreased. Besides this peripheral effect of halothane on the effective elastance, other peripheral factors such as depression of intercostal muscle function and inhibition of spinal motor neurons as suggested by Tusiewicz,<sup>3</sup> should also be considered. Our perfusing technique does not allow us to discriminate between those several possibilities. All these effects on the neuromechanical link between integrating centers and respiratory movements will lead to a depression of both Sp and Sc, and are in all probability responsible for the curvilinear nature of the  $\text{CO}_2$  response curve at halothane concentrations above 1%. An additional effect of halothane on the peripheral chemoreceptors may also be present, but seems to be of minor importance as argued below.

To discuss possible effects of halothane on the central and peripheral chemoreceptors, we return to the schematic presentation of the respiratory control system above (fig. 7).

In this model, the ventilation is the output of the box "lung volume." It is supposed that the lung receptors only modulate the breakdown of  $\dot{V}_E$  into  $\dot{V}_T$  and respiratory frequency. Experimentally it was found that  $\dot{V}_E$  as a function of the inputs  $\text{Pa}_{\text{CO}_2}^p$  and  $\text{Pa}_{\text{CO}_2}^c$  to the peripheral and central chemoreceptors, could be described by equation (1). Substituting  $K = (\text{Sp} + \text{Sc})B$  and rearranging we find:

$$\dot{V}_E = \text{Sp}(\text{Pa}_{\text{CO}_2}^p - B) + \text{Sc}(\text{Pa}_{\text{CO}_2}^c - B)$$

After carotid body denervation, the first term on the right hand side of this equation drops out, so that it is reasonable to take the second term as the contribution of the central chemoreceptors to the ventilation, and consequently the first term as the contribution of the peripheral chemoreceptors.<sup>17</sup> The parameters, Sp, Sc, and B depend not only on the characteristics of the peripheral and central chemoreceptors, but also on the boxes "integrating centers," "spinal motor neurons," and "respiratory muscles and elastance."

It was found that at halothane concentrations below 1% B was not influenced by halothane. Also the ratio Sp/Sc remained constant upon administration of halothane exclusively centrally or peripherally. Taken together, this suggests that the main action of halothane is on that part of the pathways to ventilation common to both the peripheral and central chemoreceptors. In other words, the action of halothane mainly resides in

the integrating centers, the spinal motor neurons, respiratory muscles, and elastance rather than in the peripheral and central chemoreceptors as such. However, small effects on these receptors cannot be excluded with the present experimental accuracy, especially at halothane concentrations greater than 1%. For the peripheral chemoreceptors such an effect has been reported by Biscoe *et al.*<sup>24</sup>

In summary, halothane induces tachypnea by a central action on the rhythm generator. Besides a central depressant effect on ventilation, halothane also depresses the respiratory pump, *i.e.*, spinal motor neurons, respiratory muscles, and elastance. An effect on the peripheral and central chemoreceptors during hyperoxia seems to be of minor importance.

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