

## Site of Selective Action of Halothane on the Peripheral Chemoreflex Pathway in Humans

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Halothane in humans depresses the ventilatory response to hypoxemia in a manner that suggests a selective action on one or more components of the peripheral chemoreflex arc. To test the hypothesis that this action is at the carotid bodies themselves, the authors studied the ventilatory response to subanesthetic concentrations of halothane (0.15–0.30% inspired) in six fit volunteers maintained in a steady state of isocapnic hypoxemia ( $PE_{O_2}$  50 mmHg). Upon exposure to halothane, hypoxemia-driven ventilation decreased promptly and progressively (from  $7.5 \pm 1.2 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$  in the control state to  $5.9 \pm 0.9$  and  $4.8 \pm 0.7 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$  at 30 s and 60 s of inhalation respectively, means  $\pm$  SEM). The relationship of hypoxemia-driven ventilation to end-tidal halothane tensions at 30 and 60 s of halothane wash-in ( $PE_{Hal}$  0.4 and 0.6 mmHg, respectively) approached the relationship observed in near steady states of halothane inhalation. The results are interpreted as indicating that the site of selective action is at a tissue that accumulates halothane very rapidly during the first minute of inhalation. To make possible such pharmacokinetics, that tissue would require 1) a location having a brief circulatory transit time from the lungs, and 2) an extremely high rate of perfusion in relation to its capacity for uptake of halothane. The only tissue of the peripheral chemoreflex pathway that can satisfy these requirements is that of the carotid bodies. (Key words: Anesthetics, volatile: halothane. Receptors: carotid body; chemoreceptors. Ventilation: hypoxic response.)

HALOTHANE in humans severely impairs the normal ventilatory responses to hypoxemia and to a low dose of doxapram,<sup>1,2</sup> reflex responses that are mediated by peripheral chemoreceptors. The depression of these responses is out of proportion to the reductions of resting ventilation and of the ventilatory response to added  $CO_2$  produced by halothane. Indeed, sedating or subanesthetic doses of halothane reduce the peripheral chemoreflex responses selectively.

These observations suggest a potent action of halothane on one or more components of the peripheral chemoreflex pathway not involved in regulating resting ventilation or mediating the medullary mediated response to  $CO_2$ . Such components could be the peripheral chemoreceptors themselves, local elements that modulate their sensing function,<sup>3</sup> immediate central neural connections of the peripheral chemoreceptors,<sup>4</sup> and/or cen-

tral neural circuits that modulate peripheral chemoreceptor input.<sup>5</sup> These components are located in the carotid bodies of humans<sup>6</sup> or in the brain.

Davies *et al.* observed that halothane 0.5–1.0% inspired in decerebrate cats reduced the carotid sinus nerve discharge responses to several peripheral chemoreceptor stimuli, effects that implied a potent desensitizing action of halothane at the carotid bodies.<sup>7</sup> However, certain characteristics of their preparation precluded an accurate assessment of these effects with respect to ventilatory control and the possibility of species specificity<sup>3,8</sup> does not permit extrapolation of their observations to humans. We wished to test the hypothesis that the selective effect of halothane on peripheral chemoreflexes in humans is due to an action at the carotid bodies.

Pharmacokinetic models of inhaled anesthetic uptake,<sup>9,10</sup> together with known circulatory characteristics of the carotid bodies and the brain, suggested that during an exposure to halothane, the increase of halothane tension in the carotid bodies would begin earlier and be much faster than in the brain (see "Discussion"). Accordingly, an effect related to halothane tension in the carotid bodies would develop much more quickly than an effect related to halothane tension in the brain. To discriminate between carotid body and brain sites of action, therefore, we studied the time course of the selective effect of halothane on the ventilatory response to hypoxemia. We examined this response in relation to end-tidal halothane tension during two phases of exposure to subanesthetic halothane: 1) a near steady state as achieved after 20 min of a constant end-tidal tension when, according to predicted halothane pharmacokinetics, both carotid body and brain tensions would have approached and equilibrated with end-tidal tension; and 2) the first minute of wash-in of halothane when carotid body tension would approach end-tidal tension but brain tension would be relatively low. We reasoned that a similar ventilatory response in each of these phases would support the hypothesis of an action on the carotid bodies rather than an action in the brain.

### Methods

This study was approved by the Human Research Committee of the University of Western Ontario.

There were six subjects, five males and one female, all of whom were healthy and experienced in studies of

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ventilatory control. Ages, weights, and heights of subjects were, respectively,  $28 \pm 4$  yr,  $75 \pm 11$  kg, and  $170 \pm 19$  cm (means  $\pm$  SD).

Studies were conducted in a darkened room. The subject sat in a comfortable chair with his nose occluded by a clip and breathed through a mouthpiece from a non-rebreathing circuit incorporating a Rudolph #1400 non-rebreathing valve. Air, nitrogen, and carbon dioxide were delivered to the inspiratory limb of this circuit, and sub-anesthetic concentrations of halothane were produced by diverting a variable portion of these gases through a Flutec Mark II® (Cyprane, Keighley, West Yorkshire, England) vaporizer.

Resting ventilation was measured with the subject quietly breathing air and with end-tidal oxygen and carbon dioxide tensions nearly steady (range  $\pm 2$  mmHg). Hypoxemia-driven ventilation was measured with the  $P_{E_{O_2}}$  close to 50 mmHg and with the  $P_{E_{CO_2}}$  close to resting, *i.e.*, isocapnia. This level of hypoxemia was chosen as one that could be induced and maintained constant with relative ease through all phases of the proposed study. Isocapnic hypoxemia was induced over a 4–5-min period by gradually replacing inhaled air with a mixture of air, nitrogen, and, if necessary, carbon dioxide. Measurements of hypoxemia-driven ventilation were made when subjects had been nearly steady with respect to  $P_{E_{CO_2}}$  (range  $\pm 2$  mmHg) throughout induction of hypoxemia and with respect to  $P_{E_{O_2}}$  (range  $\pm 2$  mmHg) for at least 2 min.

To assess the time course of the selective effect of halothane on the response to hypoxemia, we measured hypoxemia-driven ventilation in two phases of subanesthetic halothane uptake: 1) near steady-states, with end-tidal halothane tensions of approximately 0.4 and 0.7 mmHg, and 2) during the first minute of wash-in of halothane 0.15–0.30% inspired (approximately 1.1–2.2 mmHg inspired, respectively). For comparative purposes, the end-tidal halothane tensions of the near steady states had been selected to approximate the end-tidal tensions expected at 30 and 60 s of wash-in. We also measured resting ventilation during the same periods of uptake.

The sequence of tests was varied among subjects. All wash-in tests were separated from previous tests by at least 24 h.

To achieve near steady states of halothane uptake, we induced each selected end-tidal tension and maintained it constant for 20 min, with appropriate inspired concentrations of halothane. At each end-tidal tension, we recorded resting and hypoxemia-driven ventilation, as well as end-tidal tensions of halothane, oxygen, and carbon dioxide.

To study the first minute of halothane wash-in, we first ensured that the subject was nearly steady with respect to the end-tidal gas tensions of his resting or hypoxemia state. Then, without warning to the subject, we introduced halothane 0.15–0.30% into the inhaled gas. (The subject could not detect halothane by smell or other means at

this time). Through the subsequent minute, end-tidal gas tensions were monitored closely and inspired oxygen and carbon dioxide concentrations adjusted if necessary to keep end-tidal oxygen and carbon dioxide tensions within close limits (range  $\pm 2$  mmHg). Since the hyperpnea associated with hypoxemia increased the initial rate of rise of end-tidal halothane tension, it was necessary to reduce and adjust inspired halothane concentrations during hypoxemia tests in order to match the end-tidal halothane tensions of these tests with the end-tidal tensions observed or expected in tests with subjects resting. Values of ventilation and end-tidal tensions were determined at 30 and 60 s of wash-in, timed from the appearance of halothane in end-tidal gas.

Inspired ventilation was measured by pneumotachography using a Fleisch #3 flow transducer incorporated into the inspiratory limb of the nonrebreathing circuit. Volume was calibrated regularly with an air calibration syringe and correction factors, previously determined by calibrating with air, nitrogen, and carbon dioxide, were applied for the various gas mixtures inhaled. Values of near steady state ventilation were determined from 1-min recordings. Value of instantaneous ventilation at 30 and 60 s of wash-in were calculated from the averaged volumes and respiratory cycle lengths of three consecutive breaths about the 30 and 60 s points in time. All ventilatory values were corrected for body surface area and expressed at BTPS.

During tests, inhaled gas was sampled intermittently and exhaled gas was sampled continuously at all other times. Each was withdrawn from a port close to the non-rebreathing valve and analyzed for its oxygen, carbon dioxide, and halothane vapor concentrations by a Perkin-Elmer #1100 mass spectrometer. Oxygen and carbon dioxide signals were calibrated each testing day with Canadian Liquid Air Specialty gases. The halothane signal regularly was checked against calculated vapor concentrations of measured amounts of halothane injected into a closed chamber of known volume, pressure, and temperature. End-tidal plateau concentrations were converted to tensions, using the measured barometric pressure of the day of testing.

All ventilation, gas and vapor data were inscribed continuously on a Hewlett-Packard® #77585B multi channel polygraph recorder.

We assessed possible differences amongst ventilation data in the various conditions studied with an analysis of variance for repeated measurements, using the MANOVA procedure of the SPSS computer software package and the least significant difference test for multiple comparisons. We tested for possible trend components within the analysis of variance, using the MANOVA procedure. Possible correlations between ventilation and end-tidal halothane tensions were assessed by the least-squares linear regression technique. *P* values of 0.01 or less were accepted as indicative of significance.

TABLE 1. Ventilatory Effects of Subanesthetic Halothane

	Resting				Hypoxemia			
	$P_{ET_{H_2O}}$ (mmHg)	$P_{ET_{CO_2}}$ (mmHg)	$P_{ET_{O_2}}$ (mmHg)	$\dot{V}_I$ ( $l \cdot \min^{-1} \cdot m^{-2}$ )	$P_{ET_{H_2O}}$ (mmHg)	$P_{ET_{CO_2}}$ (mmHg)	$P_{ET_{O_2}}$ (mmHg)	$\dot{V}_I$ ( $l \cdot \min^{-1} \cdot m^{-2}$ )
Awake	—	$41 \pm 1$	$97 \pm 2$	$3.4 \pm 0.3$	—	$41 \pm 1$	$50 \pm 1$	$7.5 \pm 1.2^*$
Halothane steady states	$0.4 \pm 0.01$	$41 \pm 1$	$97 \pm 1$	$3.1 \pm 0.2$	$0.4 \pm 0.01$	$41 \pm 1$	$50 \pm 2$	$4.8 \pm 0.3^{*\dagger}$
	$0.7 \pm 0.01$	$40 \pm 1$	$98 \pm 2$	$3.4 \pm 0.1$	$0.7 \pm 0.03$	$41 \pm 1$	$51 \pm 1$	$3.8 \pm 0.2^{*\dagger}$
Halothane wash-in								
0 s	—	$41 \pm 1$	$97 \pm 2$	$3.4 \pm 0.3$	—	$41 \pm 1$	$50 \pm 1$	$7.5 \pm 1.2^*$
30 s	$0.4 \pm 0.02$	$40 \pm 1$	$97 \pm 2$	$3.4 \pm 0.3$	$0.4 \pm 0.01$	$41 \pm 1$	$50 \pm 1$	$5.9 \pm 0.9^{*\dagger}$
60 s	$0.6 \pm 0.01$	$40 \pm 1$	$97 \pm 3$	$3.5 \pm 0.3$	$0.6 \pm 0.03$	$40 \pm 2$	$50 \pm 1$	$4.8 \pm 0.7^{*\dagger}$

n = 6.

All values means  $\pm$  SEM.

\* Different from resting ventilation, same state ( $P < 0.01$ ).

† Different from hypoxemia ventilation, awake ( $P < 0.01$ ).

## Results

There were no untoward effects of these studies. During near steady state exposures to subanesthetic halothane, subjects became somewhat drowsy, but were coherent and had full recall of the experiment afterwards. During the first minute of halothane wash-in, subjects were unaware of a sedative effect. During the first minute of wash-in, while they were hypoxemic, however, subjects sensed a reduction in their urge to breathe.

Values of ventilation and end-tidal oxygen and carbon dioxide tensions at rest were all within normal limits (table 1). Neither the near steady states of subanesthetic halothane nor the first minute of wash-in had a detectable effect on these variables.

Isocapnic hypoxemia increased ventilation as expected (table 1). Near steady states of subanesthetic halothane-reduced hypoxemia-driven ventilation in a manner that related linearly to end-tidal tension (fig. 1,  $r = 0.68$ ,  $P < 0.01$ ; linear trend,  $P < 0.001$ ).

The first minute of halothane wash-in increased end-tidal halothane tension as expected and reduced hypoxemia-driven ventilation promptly and progressively with time (table 1). The onset of ventilatory depression was evident at  $12 \pm 1.6$  s (mean  $\pm$  SEM). The decreasing ventilation at 30 and 60 s of wash-in related linearly to the increasing end-tidal halothane tensions observed at the same times (linear trend,  $P < 0.001$ ). The relationship between ventilation and end-tidal halothane observed in the first minute of wash-in approached the relationship observed in the near steady states (fig. 1).

## Discussion

Near steady states of subanesthetic halothane reduced the ventilatory response to isocapnic hypoxemia markedly, without detectable effect on resting ventilation and  $P_{ET_{CO_2}}$  (table 1). When studied previously, similar states of subanesthetic halothane reduced the ventilatory responses to isocapnic hypoxemia and to a peripheral chemoreceptor stimulating dose of doxapram, without effect on ventilation and the response to added  $CO_2$ .<sup>1,2</sup> To-

gether, these observations indicate that halothane has a selective effect on peripheral chemoreceptor-mediated responses and, accordingly, they suggest a potent action of halothane on components of the peripheral chemoreflex pathway distinct from other components of ventilatory control.

The important new observation of the present study was the rapidity with which this selective effect on the response to hypoxemia developed. When subjects were exposed to subanesthetic halothane while hypoxemic, their ventilatory response to hypoxemia decreased

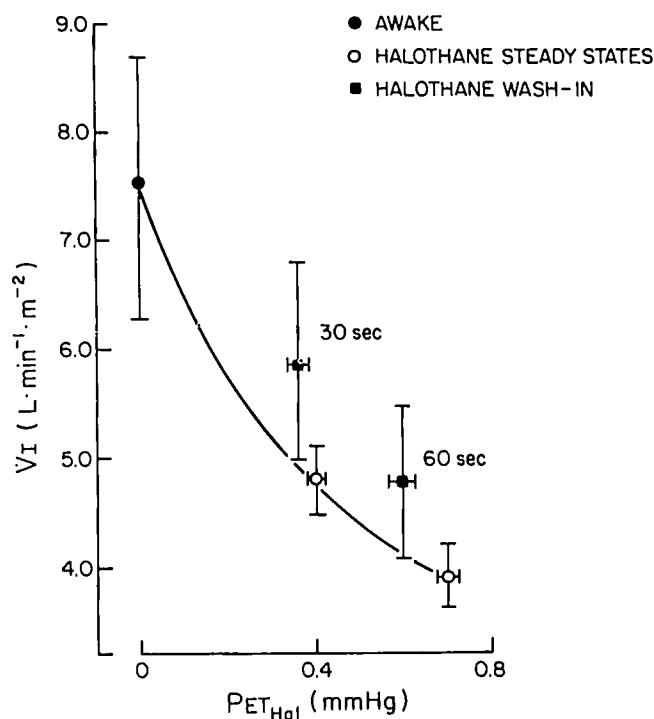


FIG. 1. Relationship between hypoxemia-driven ventilation and end-tidal halothane tensions in near steady states and during the first minute of wash-in (means  $\pm$  SEM). Line between steady state data points was hand drawn. Wash-in values were those observed at 30 and 60 s. The relationship between these variables during the first minute of wash-in approached the relationship in the near steady state.

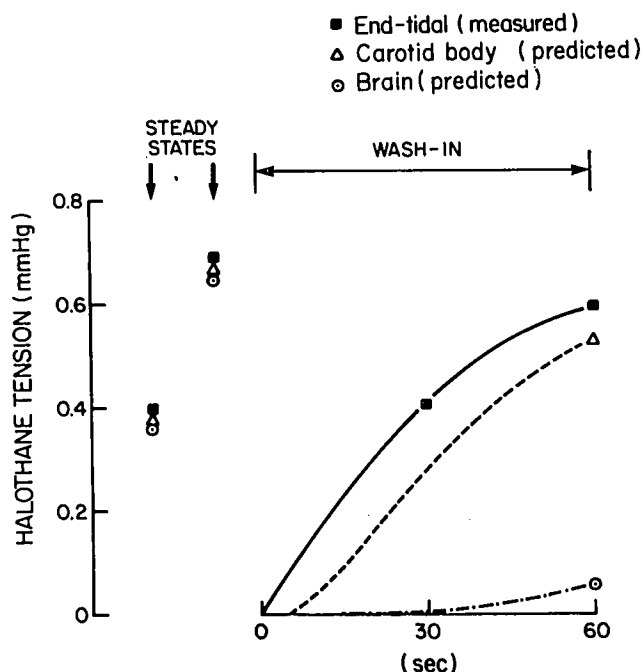


FIG. 2. Pharmacokinetic predictions of carotid body and brain tensions of halothane in relation to measured end-tidal tensions, during steady states of subanesthetic halothane and during the first minute of wash-in. Points of end-tidal tension represent the mean values observed in our subjects (table 1); the curve between points was hand drawn. Carotid body and brain tensions were computed from circulatory transit times and tissue uptake time constants (table 2), using an iterative technique. In steady states, carotid body and brain tensions have equilibrated with end-tidal tension and are similar to each other. During the first minute of wash-in, carotid body tensions increase rapidly to approach end-tidal, while brain tensions lag considerably behind.

promptly and progressively as end-tidal halothane tension increased (table 1). The effect on hypoxemia-driven ventilation at 30 and 60 s of wash-in, when related to end-tidal halothane tension, approached the effect observed in near steady and equilibrated states (fig. 1). In other

TABLE 2. Values Used to Predict Tissue Halothane Tensions in Relation to End-tidal Halothane Tensions

	Carotid Bodies	Brain
(a) Alveolar to tissue circulatory transit time (s)	5	14
(b) Equilibrium tissue/blood partition coefficient	2.6	2.6
(c) Tissue blood flow ml · 100 g <sup>-1</sup> · min <sup>-1</sup> ml · ml <sup>-1</sup> · s <sup>-1</sup> *	2,000 0.35	50 0.01
(d) Tissue uptake time constant [(b)/(c)] s	7	260

For sources of values, see text.

\* Assumed tissue density, 1.05 g · ml<sup>-1</sup>.

words, the full effect of end-tidal halothane developed extremely rapidly, almost within the first minute of inhalation.

We were unable to follow the time course of effect immediately beyond 1 min of wash-in as it became increasingly difficult to keep end-tidal oxygen and carbon dioxide tensions within close limits ( $\pm 2$  mmHg). This was no doubt due to the accumulating effects of ventilatory depression and the associated unsteady respiratory state.

We interpret the time course of effect we observed as support for our hypothesis of a potent action of halothane on the carotid bodies. This interpretation depends upon the unique compatibility of our findings with predicted pharmacokinetics of halothane at the carotid body site.

In near steady states of halothane inhalation, the effect on hypoxemia-driven ventilation relates to halothane tension in end-tidal gas<sup>2</sup> (fig. 1). We assume that in all conditions of inhalation, the effect depends upon halothane tension at the site of action. Thus, to make possible the time course of effect we observed would require that the site of action tension increase early and rapidly to approach its steady state relationship with end-tidal tension during the first minute of inhalation.

To see if either carotid body or brain tension follows the required time course, each was predicted in relation to measured end-tidal halothane tensions, using a model of halothane uptake from the lungs based upon standard pharmacokinetic principles.<sup>9-12</sup> The model assumes that end-tidal and arterial halothane tensions are equal, that delivery of anesthetic from the alveoli to each tissue is delayed by circulatory transit<sup>11</sup> and, that uptake in each tissue follows first order, perfusion limited kinetics.<sup>9,10</sup> A model of this nature has been tested in dogs and was found to represent measured tissue-related tensions of halothane reasonably accurately through several minutes of uptake.<sup>12</sup>

To predict carotid body and brain tension time curves, we calculated each tissue tension in relation to end-tidal tensions at each half-second of wash-in. The end-tidal tension time curve was based upon the end-tidal values we had observed (fig. 2). Carotid body and brain halothane tensions were computed for each half second of time, on the basis of the end-tidal tension that preceded that point in time by the alveolar to tissue circulatory transit time, the time constant for halothane uptake at that tissue, and the immediately preceding tissue tension (table 2). Tension time curves then were drawn through the computed points (fig. 2). The sources of the circulatory transit times and tissue uptake time constants used in these calculations were as follows.

The alveolar to carotid body circulatory transit time was the difference between a measured antecubital vein to carotid artery circulatory time<sup>13</sup> and an estimated antecubital vein to alveolar time.<sup>11</sup> The alveolar to brain transit time was the sum of this alveolar to carotid artery

time and a measured carotid artery to jugular bulb time.<sup>14</sup> These circulatory transit times are consistent with the time lags observed from change of end-tidal CO<sub>2</sub> concentration to the onset of carotid body and medullary mediated CO<sub>2</sub> effects.<sup>15</sup> The time constant of tissue uptake, representing the ratio of the tissue capacity for halothane in relation to its rate of delivery, was the ratio of the equilibrium tissue/blood partition coefficient to the tissue blood flow expressed per unit tissue volume. The carotid body/blood partition coefficient was assumed equal to that of the brain.<sup>16</sup> The value for carotid body blood flow per unit tissue volume was the value determined in cats.<sup>17</sup> Carotid body blood flow in humans can be inferred to be of the same order of magnitude from the extraordinarily rapid time course of carotid body mediated CO<sub>2</sub> and O<sub>2</sub> effects in humans.<sup>15,18</sup> The brain blood flow was the conventional value reported for the human brain as a whole. The flow rate to the brain stem, the region most likely concerned with the peripheral chemoreflex pathway, is similar to overall cerebral blood flow in anesthetized cats.<sup>19</sup> We are aware of no information on the flow rates to the particular regions of the brain and brain-stem concerned with the peripheral chemoreflex pathway.<sup>3,4</sup> However, our predictions of brain tensions of halothane in the first minute of inhalation and in the near steady state are not particularly sensitive to the value chosen for brain blood flow (see below).

In steady states, the carotid body and brain tensions are predicted to be similar to each other and to end-tidal tensions (fig. 2). During the first minute of wash-in, however, the tissue time curves differ markedly. The rate of increase of tension in the carotid bodies far exceeds that in the brain, such that carotid body tension approaches end-tidal while brain tension remains quite low. This greater increase of tension in the carotid bodies during early wash-in is due to two factors: first, the closer location of the carotid bodies to the lungs in the circulatory system and, second, the much greater blood supply of the carotid bodies.

The nature of these predictions for the first minute of wash-in and near steady-states is rather insensitive to the specific values chosen to make them. For example, increasing or reducing carotid body or brain blood flow values by 50% does not affect the similarity of tissue tensions in the near steady states and alters only slightly the marked differences during early wash-in.

The predicted time courses of carotid body and brain halothane tensions were compared with the observed time course of hypoxemia-driven ventilation. At 12 s of wash-in, with no halothane tension in the brain and carotid body tension just developing, the onset of ventilatory depression was observed. At 30 s of wash-in, with very little tension predicted for the brain but carotid body tension about 70% of end-tidal, the mean reduction of hypoxemia-driven ventilation was 60% of the full or near

steady state effect of the same end-tidal tension. At 60 s of wash-in, with brain tension predicted to be about 10% of end-tidal and carotid body tension 90%, the mean reduction of the response was 80% of the full effect of that end-tidal tension. If one assumes that the end-tidal tension–effect curve of the near steady states represents the site of action tension–effect relationship, these mean reductions of hypoxemia-driven ventilation during early wash-in were only slightly less than expected on the basis of carotid body tensions. The small differences between expected and observed could be accounted for on the basis of an alveolar to arterial gradient for halothane,<sup>20</sup> a diffusion time for halothane in tissues, and/or a time delay for halothane pharmacodynamics. They also could be due to experimental or prediction error. In any case, the time course of effect is clearly incompatible with predicted brain tensions alone and remarkably consistent with the tension–time curve predicted for the carotid bodies. We conclude that the evidence favors the carotid bodies as the major site of desensitization of the peripheral chemoreflex pathway by subanesthetic halothane.

If an action at a brain site were to account for the effect we observed, this site would require a location within a brief circulatory transit time from the lungs and an enormous rate of perfusion—at least 20 times the average rate of cerebral blood flow. We cannot exclude the possibility that the region of the brain concerned with peripheral chemoreceptor input has these characteristics. However, this seems unlikely. The site of the brain-stem that mediates ventilatory responses to CO<sub>2</sub> is affected by a change of end-tidal CO<sub>2</sub> after a lag time of 20 s.<sup>15</sup> The lag time to the onset of the halothane effect we observed was just 12 s. A region of the brain-stem having the required rate of blood flow or the required vascularity, to our knowledge, has not been described.

Our interpretation is corroborated by other observations. During wash-in of halothane, our subjects noted that their urge to breathe decreased well before any perception of sedation. This is consistent with an action at a site that accumulates halothane more rapidly than the brain. In the decerebrate cats studied by Davies *et al.*,<sup>7</sup> subanesthetic halothane reduced discharges of the carotid sinus nerve in a temporal pattern consistent with our predicted pharmacokinetics at the carotid bodies of humans and with the effects on hypoxemia-driven ventilation we observed.

Subanesthetic doses of halothane markedly impair not only the response to hypoxemia but also the peripheral chemoreceptor mediated response to a low dose of doxapram.<sup>1</sup> Recent evidence suggests that subanesthetic halothane also depresses the peripheral chemoreceptor mediated response to acute metabolic acidemia.<sup>†</sup> All peripheral chemoreceptor-mediated responses utilize the same reflex pathway. Since the effect of subanesthetic halothane on the hypoxemia response appears not to be

due to an action on the brain components of this pathway, it is unlikely that its effect on the other responses is due to an action on the brain components. In other words, subanesthetic halothane may impair several peripheral chemoreflexes by an action at the carotid bodies.

Although a carotid body action apparently accounts for the marked impairment of peripheral chemoreflex responses by subanesthetic halothane in humans, it may not account for the additional impairment of these responses produced by anesthetic doses.<sup>1,†</sup> The depressive effects of halothane anesthesia on peripheral chemoreflexes are not clearly selective, since anesthesia also reduces resting ventilation and the ventilatory response to other stimuli. Accordingly, anesthetic doses—unlike subanesthetic—must act on components of the ventilatory control system apart from those which function exclusively in the peripheral chemoreflex pathway, *i.e.*, on the central ventilatory controller and/or on the series of neural, neuromuscular, and muscular processes between the controller and the ventilatory pump. These additional actions could account for the additional depressive effects on peripheral chemoreflexes. Thus, although the effects of subanesthetic doses of halothane indicate a potent carotid body action and effects of anesthetic doses mimic carotid body ablation in several ways,<sup>1</sup> we cannot necessarily infer that the entire depressive action of anesthetic doses occurs at the carotid bodies.

The carotid bodies, when stimulated by hypoxemia, evoke several important physiologic defenses against hypoxemia—including hyperpnea, hypertension, a favorable redistribution of cardiac output<sup>21</sup> and, in the unanesthetized state, central nervous system arousal.<sup>22</sup> These various responses all depend upon the same carotid body sensing function and input to the brain.<sup>21,22</sup> To the extent that halothane acts to desensitize the carotid bodies, it would be expected to impair them all.

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