

## Mechanism of Halothane-induced Tachypnea in Cats

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The aim of the present investigation was to analyze the mechanism of the tachypnea induced in cats by increasing the halothane concentration from 1.2 to 3 per cent: in particular, the authors tried to quantify the afferent vagal and the central component. Two variables were measured: 1) the breathing frequency following occlusion of the airways at end-expiratory volume, and 2) the rate of change of pressure developed in the airways during the inspiratory effort following occlusion of the airways. The former was taken as an index of the central timing of breathing, and the latter as an index of the respiratory output. Increasing halothane concentration under isocapnic conditions ( $P_{A_{CO_2}} \approx 45$  torr) caused an increase in frequency of occluded breaths from 25 to 35 cps (mainly achieved through a shortening of the inspiratory phase) and a decrease in the rate of change of occlusion pressure from  $-18$  to  $-10$  cm  $H_2O$ /sec. At either halothane concentration vagotomy or complete cold vagal block did not significantly modify the two respiratory variables considered. The results of these experiments suggest that the excitatory effect of increasing halothane concentration on respiratory timing, and the inhibitory effect on respiratory output, were centrally and not vagally mediated. (Key words: Anesthetics, volatile: halothane. Carbon dioxide: ventilatory response. Lung: function. Parasympathetic nervous system: vagus. Ventilation: tachypnea.)

RECENTLY, Miserocchi *et al.*<sup>1</sup> studied the mechanism of rapid shallow breathing following injection of phenyl-diguanide (a stimulant of vagal J-receptors) and exposure to histamine aerosol (a stimulant of vagal irritant receptors). In both instances it was found that there was a marked leftward displacement of the tidal volume-*vs.*-inspiratory time relationship curve (Hering-Breuer threshold curve),<sup>2</sup> corresponding to a marked shortening of the duration of inspiration during occlusion of the airways at end-expiratory volume. The timing of occluded breaths was taken as an index of the bulbopontine respiratory rhythm<sup>3</sup> in the absence of phasic lung-volume-related vagal information. It was concluded that stimulated J- and irritant receptors act by increasing the frequency of discharge of the bulbopontine respiratory pacemaker and by lowering the volume threshold for inhibition of inspiratory activity.

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In view of these results, the aim of the present investigation was to analyze the mechanism of the tachypnea induced by halothane. Halothane is known to cause rapid shallow breathing and  $CO_2$  retention in both animals and man.<sup>4</sup> These changes are dose related: the greater the dose of halothane, the more profound the changes. We tried to quantify the vagal and the central component in the genesis of the observed pattern of breathing.

### Materials and Methods

Experiments were carried out in 13 male, adult cats (2-3 kg). Anesthesia was administered via a halothane vaporizer (Fluotec Mark 2®) through which a flow of oxygen and nitrogen, 50 per cent each, was passed. Anesthesia was induced by placing the animal in a plastic box into which halothane was delivered through a side opening, at a concentration of 3 per cent and a total flow of 6 l/min. After 5 min the cats were sufficiently anesthetized for the surgical procedure to be started. This consisted of tracheal cannulation and insertion of a catheter into a femoral artery. Halothane was then delivered to the cat by means of a T-piece system applied to the tracheal cannula, which did not cause any appreciable change in tracheal pressure. The flow of halothane was kept as high as three to four times the estimated minute ventilation of the animal. The cat lay supine throughout the experiment and its temperature was kept at normal values by aid of a heating pad. Tidal volume was measured through a volume-displacement body plethysmograph whose frequency response was flat up to 7 cycles/sec. Tracheal pressure was measured through a side-arm of the tracheal cannula by a Sanborn 267B® pressure transducer.

Studies were made at two halothane concentrations, 1.2 and 3 per cent inspired. The response to steady-state inhalation of  $CO_2$  mixtures in oxygen, 50 per cent (balanced nitrogen) was studied by passing them directly through the halothane vaporizer. End-tidal  $CO_2$  concentration was measured with a Beckman LB-2® analyzer. We determined the effects that these concentrations of halothane had on the  $CO_2$  meter and made the appropriate corrections. In three cats arterial blood-gas values were analyzed with a Radiometer MB5 3ML2® blood microsystem.

Although the uptake of halothane by the brain is a slow process,<sup>5</sup> we observed that the respiratory and

cardiovascular variables were essentially steady after 20 min. Accordingly, we started our measurements in O<sub>2</sub>, 50 per cent, and with the different CO<sub>2</sub> mixtures after that time. To offset the problem of the continuous uptake of halothane, we used two different protocols. In Group A (four cats), studies were made at a halothane concentration of 1.2 per cent, then at 3 per cent; following bilateral vagotomy studies were repeated at 3 and then at 1.2 per cent. In Group B (four cats), studies were made at 3, then at 1.2 per cent. Following bilateral vagotomy they were repeated at halothane doses of 1.2 and then 3 per cent. In this way the effects of vagotomy at both 1.2 and 3 per cent could be compared when presumably only small changes in the brain concentration of halothane had occurred from the time before to after vagotomy. Post-vagotomy measurements were started at least 5 min after sectioning of the nerves.

In eight cats we used a rapid cooling technique to block afferent fibers in the vagus nerves. This allowed us to compare the breathing patterns before and after functional vagotomy in a very short space of time, which was not the case after surgical vagotomy. The nerves were isolated from the surrounding tissues and placed into the grooves of stainless steel thermodes through which a refrigerated solution was passed. Nerves were cooled to a temperature of 0–1 C, which should have ensured complete block of all afferent traffic. In some animals vagotomy was performed while the vagus nerves were cooled.

For each condition of steady-state breathing we estimated the durations of inspiration (T<sub>I</sub>) and of expiration (T<sub>E</sub>) from the spirometric tracing. We also performed occlusions of the airways at end-expiratory volume by clamping a short rubber tube inserted between the tracheal cannula on one side and the T piece on the other. The timing of occluded breaths allowed us to exclude the phasic vagal input from pulmonary stretch receptors, leaving only the tonic afferent discharge of vagus nerves at the end-expiratory volume. The occluded inspiratory and expiratory times (T<sub>I</sub><sup>o</sup> and T<sub>E</sub><sup>o</sup>) were taken from the record of tracheal pressure from the onset of the inspiratory effort to peak negative pressure and from this moment to the onset of a next inspiration, respectively. Comparison of the timing of occluded breaths with that occurring after vagotomy or complete block of the afferent traffic in the vagus allowed an estimate of the central effect of the anesthetic. As an index of the output of the respiratory centers we measured 1) the pressure developed in the lungs 0.5 sec after the onset of an inspiratory effort against closed airways (P 0.5), and 2) the mean inspiratory flow rate

(V<sub>I</sub>/T<sub>I</sub>). Occlusion pressures are reported as positive values. We also measured the volume attained on the spirometric tracing 0.5 sec after the onset of an inspiration. Data were collected with paper running at 25 mm/sec.

At halothane, 1.2 per cent, the response curves for each of these variables to increasing P<sub>A</sub>CO<sub>2</sub> were estimated by fitting a regression line through the three experimental points for each cat. At halothane, 3 per cent, as only two values of P<sub>A</sub>CO<sub>2</sub> were considered, the slope of the response curves was evaluated by joining the two experimental points with a straight line. The positions of all the response curves were estimated for P<sub>A</sub>CO<sub>2</sub> 47.5 torr, a value that was close to actual experimental values in individual cats.

### Results

Prior to vagotomy, minute and tidal ventilation decreased and respiratory frequency and P<sub>A</sub>CO<sub>2</sub> values increased (fig. 1, A, B, and C) as halothane concentration was increased from 1.2 (*open circles*) to 3 per cent (*open triangles*).<sup>¶</sup> The increase in respiratory frequency was due to decreases in the durations of both inspiration (fig. 2, C) and expiration (fig. 2, D). In addition, there was an increase in frequency of the occluded breaths (f<sup>o</sup> in fig. 1, D<sup>¶</sup>): this was also due to shortening of both the inspiratory and the expiratory phases (fig. 2, A and B<sup>¶</sup>). An increase in halothane concentration from 1.2 to 3 per cent also caused decreases of the pressure developed in the airways 0.5 sec after the onset of an occluded breath (fig. 3, A) and of the mean inspiratory flow rate (fig. 3, B).

The response curves to increasing CO<sub>2</sub> for minute and tidal ventilation (fig. 1, A and B), occlusion pressure (fig. 2, A) and mean inspiratory flow rate (fig. 2, B) were significantly decreased by an increase in halothane concentration.<sup>¶</sup> Conversely, the response curves for the frequencies of unoccluded and occluded breaths were significantly increased (fig. 1, C and D<sup>¶</sup>): correspondingly, the CO<sub>2</sub> response curves for inspiratory and expiratory durations for unoccluded and occluded breaths (fig. 2, A and B) were reset to shorter values. This effect was particularly marked for the occluded inspiratory time (fig. 2, A). The changes in timing of unoccluded breaths induced by an increase in halothane concentration were smaller than those occurring for occluded breaths. The changes in breathing frequency (for occluded and unoccluded breaths) due to increases in depth of anesthesia or P<sub>A</sub>CO<sub>2</sub> were mainly achieved through changes of the inspiratory time, the expiratory time being less modulated.

<sup>¶</sup> Tabulated data are available from the author.

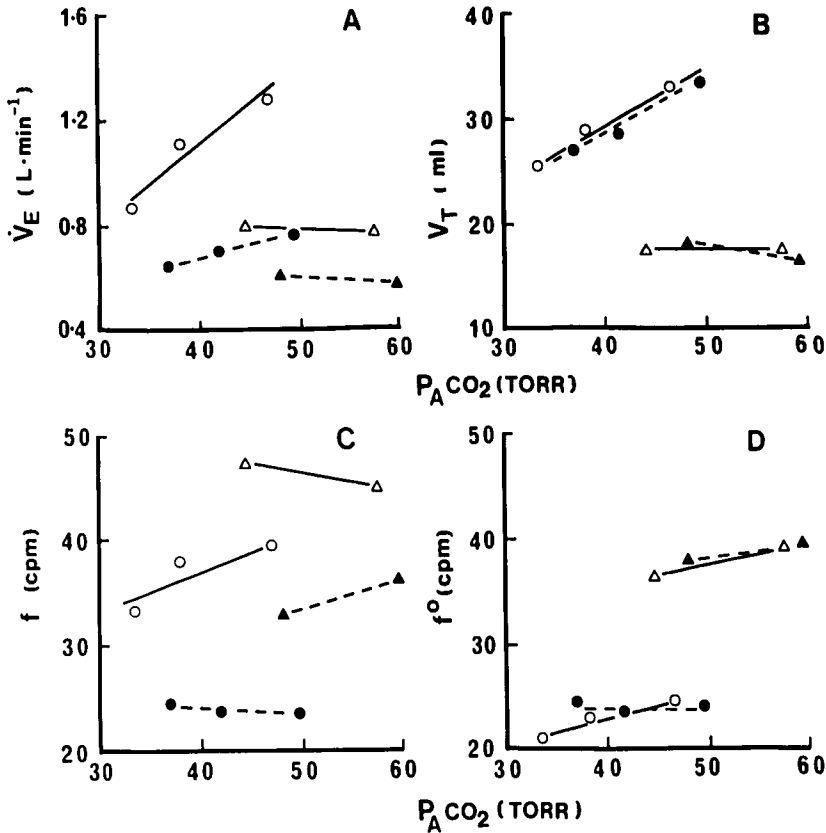


FIG. 1. *A*, ventilatory responses to hypercapnia at halothane concentrations of 1.2 (circles) and 3 per cent (triangles), before vagotomy (open symbols) and after vagotomy (closed symbols). *B*, tidal volume responses to hypercapnia under the same conditions as in *A*. *C*, frequency responses to hypercapnia under the same conditions as in *A*. *D*, frequency responses of occluded breaths under the same conditions as in *A*. Values shown are the means for all the animals. Lines drawn through prevagotomy and post-vagotomy points at 1.2 per cent halothane are mean regression lines. At 3 per cent halothane, prevagotomy and postvagotomy points were joined by straight lines.

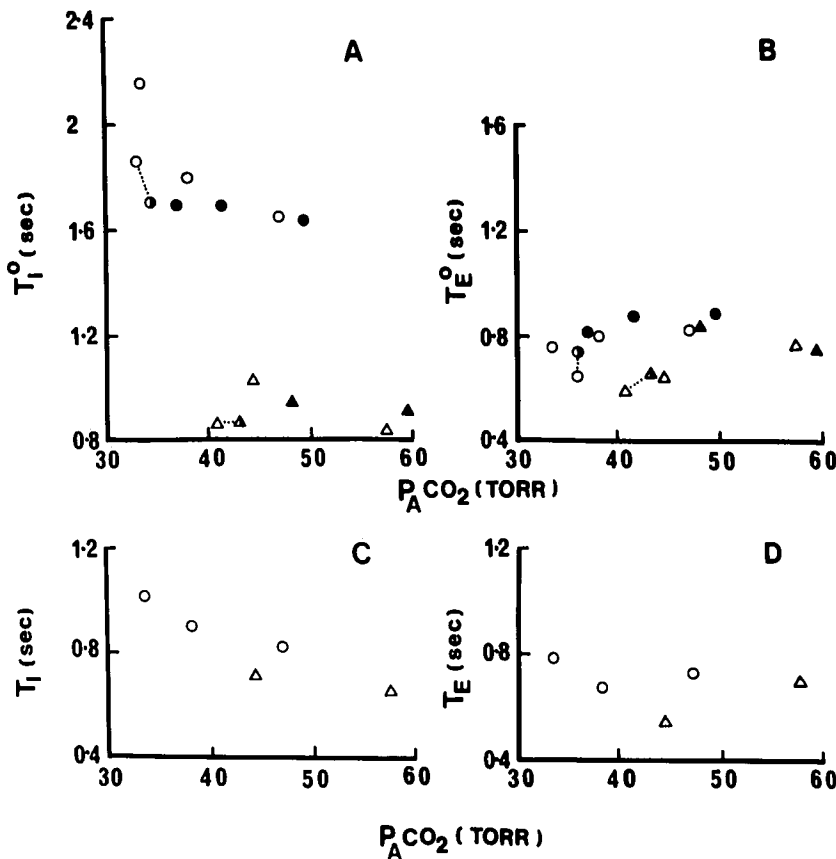
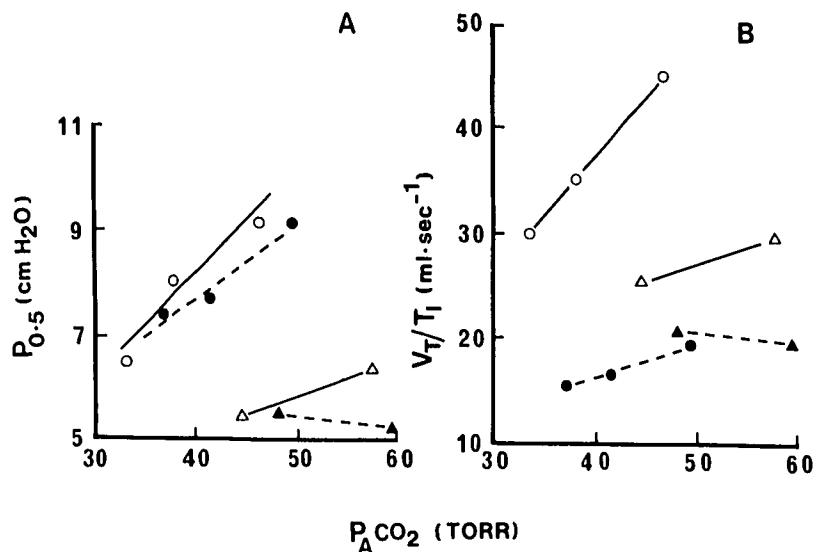


FIG. 2. Mean values for all the animals at  $T_I^0$  (*A*) and  $T_E^0$  (*B*) before (open symbols) and after vagotomy (closed symbols) at 1.2 (circles) and 3 per cent halothane (triangles), plotted vs.  $P_A CO_2$ . Points joined by dotted lines refer to cats in which vagal cooling was done; at each halothane concentration open symbols refer to vagi intact; half-filled symbols to vagi cooled to 1 C. *C* and *D* show the  $T_I$  and  $T_E$  values plotted vs.  $P_A CO_2$ .

FIG. 3. Same conditions and symbols as in figure 1: halothane concentrations of 1.2 (circles) and 3 per cent (triangles), before vagotomy (open symbols) and after vagotomy (closed symbols). A, pressure developed 0.5 sec after the onset of an inspiratory effort following occlusion of the airways at the end-expiratory volume plotted vs.  $P_{A_{CO_2}}$ . Pressures were reported with changed signs, i.e., as positive values. B, mean inspiratory flow rate, as a ratio of tidal volume to inspiratory time duration during unoccluded breaths, plotted vs.  $P_{A_{CO_2}}$ . Means for all animals are shown. Lines drawn through prevagotomy and post-vagotomy points at 1.2 per cent halothane are mean regression lines. At 3 per cent halothane, prevagotomy and postvagotomy points were joined by straight lines.



At both halothane concentrations vagotomy caused decreases in minute ventilation (fig. 1, A), frequency of unoccluded breaths (fig. 1, C) and mean inspiratory flow rate (fig. 2, B) response curves to CO<sub>2</sub> in both groups of cats.¶ No significant difference was found when comparing the postvagotomy frequencies of occluded breaths with the prevagotomy values at the

same halothane concentrations.¶ In addition, the post-vagotomy values of inspiratory and expiratory durations were similar to those found before vagotomy (fig. 3A and B).

At both halothane concentrations complete vagal block (fig. 2A and B) did not cause significant changes in the duration of the occluded inspiratory and

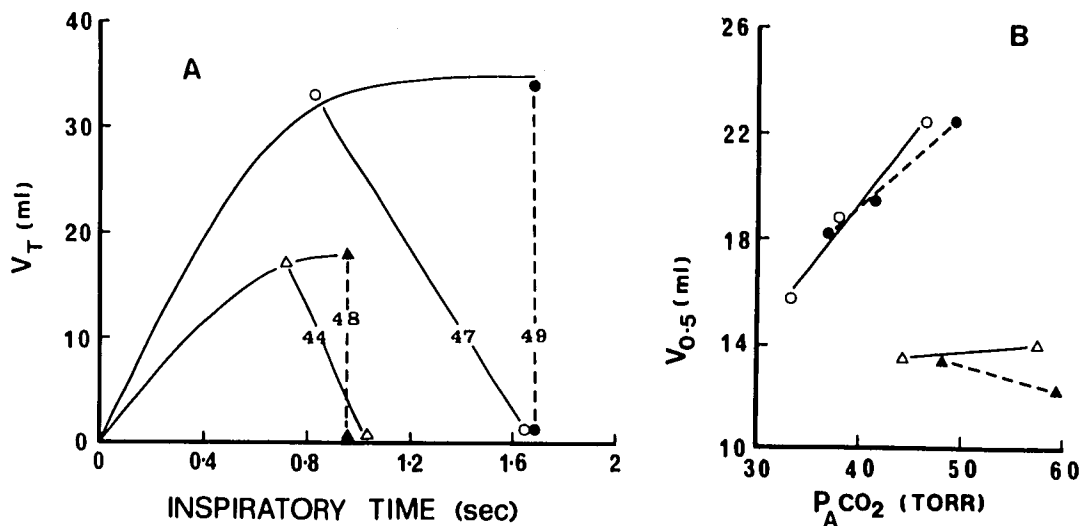


FIG. 4. Symbols as in figure 1: halothane concentrations of 1.2 (circles) and 3 per cent (triangles), before vagotomy (open symbols) and after vagotomy (closed symbols). A, tidal volume vs. inspiratory time relationships for almost isocapnic conditions ( $\approx 47$  torr) at the two halothane concentrations used before and after vagotomy. These relationships were approximately drawn by joining the coordinates of the unoccluded to those of the occluded breaths in each condition. Lung volume quantifies the afferent phasic vagal input from pulmonary stretch receptors. The relationships have a negative slope, meaning that progressively less afferent input from pulmonary stretch receptors is needed to cut short inspiratory activity as time progresses. Numbers indicate  $P_{A_{CO_2}}$  values. The inspiratory volume profiles were also drawn. Notice that at each halothane concentration: 1) vagotomy abolished the negative slope of the tidal volume vs. inspiratory time relationship owing to the suppression of phasic vagal afferents from pulmonary stretch receptors; 2) the postvagotomy duration of inspiration was essentially equal to the prevagotomy duration of inspiration during occluded breaths; 3) vagotomy did not cause any increase in tidal volume owing to the plateauing of the inspiratory volume profile, particularly at the low halothane concentration.

B, volume attained 0.5 sec after the onset of inspiration during unoccluded breaths plotted vs.  $P_{A_{CO_2}}$ . Means for all animals are shown. Lines drawn through prevagotomy and postvagotomy points at 1.2 per cent halothane are mean regression lines. At 3 per cent halothane, prevagotomy and postvagotomy points were joined by straight lines.

expiratory times compared with the control values with an unblocked vagus. Vagotomy in three cats at 1.2 and in two cats at 3 per cent halothane while the vagus nerves were kept cooled did not significantly change the occluded inspiratory and expiratory durations.

We studied the tidal volume *vs.* inspiratory time relationships at the two halothane concentrations before and after vagotomy (fig. 4, *A*). These relationships, representing the volume threshold for inhibition of inspiratory activity,<sup>2</sup> were approximated by joining with a straight line the coordinates of the unoccluded to those of the occluded breaths<sup>8</sup>; they were labelled with numbers referring to the  $P_{\text{ACO}_2}$  values at which they were obtained. According to this model,<sup>2</sup> inspiratory activity is cut off when the inspiratory volume profiles (continuous lines starting from the origin) cross the corresponding volume-threshold curve. Increasing halothane concentration before vagotomy resulted in a leftward displacement of the tidal volume *vs.* inspiratory time relationship curve and a decrease in the inspiratory volume profile (fig. 4, *A*). Accordingly, inspiration was interrupted at a smaller tidal volume and at a shorter inspiratory time. After vagotomy, owing to the suppression of the vagal phasic modulation, the tidal volume *vs.* inspiratory time relationship curve became vertical. Moreover, for each halothane concentration the postvagotomy inspiration time duration was equal to the prevagotomy occluded inspiratory time. In addition, vagotomy did not affect the rising phase of the inspiratory volume profile. Indeed, the volumes attained 0.5 sec after the onset of inspiration *vs.*  $P_{\text{ACO}_2}$  were similar before and after vagotomy at the same halothane concentration.

In three animals breathing  $\text{O}_2$ , 50 per cent, and halothane, 1.2 per cent,  $P_{\text{aCO}_2}$  and *pH* were  $35 \pm 3$  (SE) torr and  $7.3 \pm 0.01$ , respectively. At halothane, 3 per cent, the corresponding values were  $43 \pm 5$  torr and  $7.23 \pm 0.05$ , respectively. The  $P_{\text{ACO}_2}$  values in these animals at halothane 1.2 and 3 per cent were  $34 \pm 1$  and  $44 \pm 5$  torr, respectively, and compared well with the  $P_{\text{aCO}_2}$  values.

Before vagotomy at halothane, 1.2 per cent, mean blood pressure was  $101 \pm 2$  (SE) torr, and it decreased to  $74 \pm 1$  torr at halothane, 3 per cent. Postvagotomy values at the same concentrations were  $110 \pm 4$  and  $85 \pm 2$  torr.

### Discussion

Increasing the halothane concentration from 1.2 to 3 per cent in our cats caused breathing to become more rapid and shallow, with a decrease in total ventilation and an increase in end-tidal  $P_{\text{CO}_2}$ . These results are comparable to those found in unpre-

medicated man.<sup>4,6</sup> Deepening halothane anesthesia also resulted in a great decrease in the ventilatory response to hypercapnia (fig. 1), confirming previously published data in both animal and man.<sup>4,7</sup> At halothane, 3 per cent, cats were essentially unable to increase tidal volume and respiratory frequency with increasing  $P_{\text{ACO}_2}$ . The increase in frequency of breathing occurring when going from halothane, 1.2 per cent to 3 per cent reflected an increase in the central respiratory rhythm, which occurred mainly through a shortening of the occluded inspiratory time. This resulted in a leftward displacement of the tidal volume *vs.* inspiratory time relationship curve. Such respiratory effects were described as a result of an increase in  $P_{\text{ACO}_2}$  in cats anesthetized with pentobarbital.<sup>8</sup> However, this mechanism cannot explain the effect observed with deepening the halothane anesthesia since, under iso- $P_{\text{CO}_2}$  conditions, the occluded inspiratory time was much shorter at halothane, 3 per cent, than at 1.2 per cent (fig. 2, *A*). Another mechanism through which an increase in central respiratory rhythm may occur is an increase in the amount of afferent input from the vagus at the end-expiratory volume. This was described to occur in case of massive stimulation of vagal irritant and J-receptor endings within the lungs.<sup>1</sup>

Results of our study showed that at both halothane concentrations vagotomy (or vagal block) did not affect the timing of occluded breaths: this finding excluded a role played by vagal afferents and proved that the tachypnea resulting from increasing the halothane concentration to 3 per cent was of central origin. It should be mentioned that a stimulating action of halothane on J receptors was found at concentrations above 5 per cent.<sup>9,12</sup> Vagotomy, at both halothane concentrations, did not affect the output of the respiratory centers when measured in terms of occlusion pressure, proving that this variable was set through a purely central mechanism. An excitatory effect on respiratory timing with little modulation of the expiratory time and an inhibitory effect on respiratory output was also observed in the case of tachypnea following stimulation of vagal irritant and J-receptor endings.<sup>1</sup> This suggests that vagal afferents from these receptors as well as the higher halothane concentration may activate the same central mechanism. Halothane-induced tachypnea was found by Ngai *et al.*<sup>13</sup> in midcollicular-decerebrated cats, indicating that the mechanism responsible for the tachypneic effect should involve pontine or medullary structures.

Vagotomy, at both halothane concentrations, greatly depressed the ventilatory response to  $\text{CO}_2$ . Indeed, suppression of the phasic vagal input from pulmonary stretch receptors caused a lengthening of inspiratory

and expiratory durations, and in addition, tidal volume did not substantially increase, owing to a plateauing of the inspiratory volume profile (fig. 4, *A*). On the other hand, as noted before, vagotomy did not affect the output of the respiratory centers, nor the initial part of the inspiratory volume profile (fig. 4, *B*). Thus, the occurrence of a plateauing phase of the inspiratory profile represents an example where different conclusions may be drawn concerning the respiratory output when the latter is estimated in terms of occlusion pressure<sup>14</sup> on one side and total pulmonary ventilation or mean inspiratory flow rate<sup>2</sup> on the other.

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