

## Oxygen Drive to Breathing during Halothane Anesthesia: Effects of Almitrine Bismesilate

F. Clergue, M.D.,\* C. Ecoffey, M.D.,† J. Ph. Derenne, M.D.,‡ P. Viars§

The changes in ventilation and breathing pattern induced by the substitution of pure oxygen for room air were tested in patients during stable halothane anesthesia before and after the administration of almitrine bismesilate, a specific stimulant of the peripheral chemoreceptors. Ventilation was monitored in 25 patients for 15 min while breathing an air-halothane (1.5%) mixture and while breathing then for 10 min an O<sub>2</sub>-halothane (1.5%) mixture. The maneuver was repeated in 11 of these patients after the infusion of 0.5 mg/kg of almitrine bismesilate. Before almitrine administration, O<sub>2</sub> inhalation caused a progressive decrease of minute-ventilation ( $\dot{V}_E$ ) reaching  $94.5 \pm 1.4\%$  (mean  $\pm$  SEM) of the initial value at the tenth minute ( $P < 0.01$ ). This decrease was secondary to a progressive increase of inspiratory and expiratory times. Almitrine bismesilate caused a significant increase in  $\dot{V}_E$  (+11.6%), tidal volume (+14.0%), and mean inspiratory flow (+10.0%) when breathing the air-halothane mixture. Ten minutes after O<sub>2</sub> administration, these variables were not different from those observed before almitrine infusion. This study shows that during halothane anesthesia, hypoxic ventilatory drive is not abolished but is depressed severely. Almitrine bismesilate can restore the hypoxic ventilatory drive. (Key words: Anesthetics, volatile: halothane. Receptors: chemoreceptors. Ventilation: oxygen response; regulation; stimulants.)

GENERAL ANESTHETICS are known to disturb the respiratory control mechanisms, the ventilatory depression depending on the nature of the anesthetic agent and on the level of anesthesia.<sup>1</sup>

Halothane causes a decrease of the ventilatory response to CO<sub>2</sub>.<sup>2,3</sup> In addition, hypoxic ventilatory drive is decreased or abolished with halothane.<sup>3-6</sup> Moreover, Knill and Gelb<sup>3</sup> observed that halothane at 1.1 or 2 MAC nearly always abolished the ventilatory response to isocapnic hypoxia and that hypoxia decreased minute ventilation and the ventilatory response to CO<sub>2</sub>.

The purpose of the present study was to observe the time course of the changes in ventilation and breathing pattern immediately after the substitution of pure oxygen for room air in 25 subjects under stable halothane anesthesia and to determine whether almitrine bismesilate, a specific stimulant of the peripheral chemoreceptors,<sup>7-9</sup> could restore peripheral chemosensitivity.

\* Assistant Professor of Anesthesiology.

† Resident of Anesthesiology.

‡ Professor of Pneumology.

§ Professor of Anesthesiology.

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Address Reprint Requests to Dr. Clergue: G. H. Pitie-Salpetriere, Department of Anesthesiology, 83, Boulevard de L'Hôpital, 75013, Paris, France.

### Materials and Methods

The studies were performed on 25 men undergoing minor urologic operations (vasovasostomy). Mean age ( $\pm$ SEM) was  $35.8 \pm 1.7$  yr (range 23-58), mean body weight  $74.0 \pm 1.5$  kg (range 60-87). None of them had evidence of cardiovascular or respiratory disease. They received no medication on the days preceding the study. Informed consent was obtained from all patients, and the study had the approval of the ethics committee of our institution.

Atropine (0.5 mg) was given intravenously before induction. Anesthesia was induced with iv thiopental (5 mg/kg), and a cuffed endotracheal tube (internal diameter = 8.0 mm) was inserted after iv succinylcholine (1 mg/kg). Controlled ventilation with oxygen was continued until spontaneous respiration was resumed. The patients then were administered a mixture of halothane, nitrous oxide, and oxygen. The surgical procedure lasted  $175 \pm 27$  min. Nitrous oxide was withdrawn 10 min before the end of the operation. The patients lying in the supine position then were administered a mixture of 1.5% halothane in oxygen toward the end of the operative procedure and for an additional 15 min.

At that time, they were connected to the experimental set-up schematically shown in figure 1. The endotracheal tube was connected to a Mauve et Lagarde one-way valve system. They first were given a mixture of halothane in air from a Douglas bag (B). After 15 min, the stopcock C was turned and the inspired gas was changed to a mixture of halothane in oxygen (bag A) for 10 min. The resistance of the inspiratory circuit was  $4.2 \text{ cmH}_2\text{O} \cdot \text{l}^{-1} \cdot \text{s}$ , and that of the expiratory circuit was  $3.6 \text{ cmH}_2\text{O} \cdot \text{l}^{-1} \cdot \text{s}$ , at a flow of 1 l/s. Dead space of the circuit was 75 ml.

The mixture of halothane in air or oxygen was supplied by a continuous-flow Cyprane Mark 3 vaporizer. The dial of the vaporizer was set to 1.5% in both cases. The adequacy of halothane concentration in the bag was checked by an interferometer Carl Zeiss LI 3 when gases of different viscosity and different flow rates entered the vaporizer. Halothane concentration was 1.58% with air and 1.61% with oxygen, for flow rates up to 10 l/min.

The fraction of oxygen in the expired gas was monitored continuously with an O<sub>2</sub> analyzer Rapox Godart 17208 (Gould Godart Bilthoven, the Netherlands), which was calibrated carefully with three standard gases before and after each measurement. It allowed computation of the end-tidal P<sub>O<sub>2</sub></sub>, which was considered to be equal to

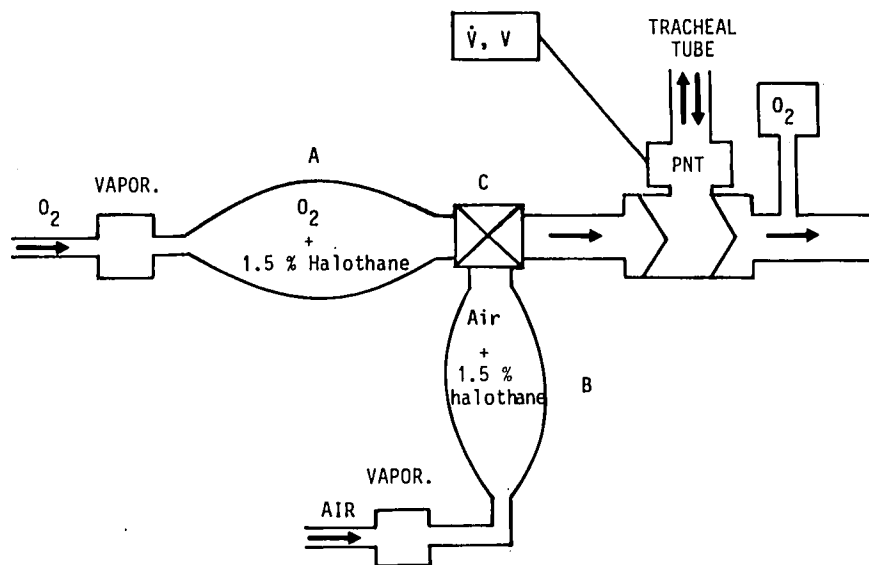


FIG. 1. Diagram of the experimental design.

alveolar  $P_{O_2}$  ( $P_{A_{O_2}}$ ). Volume was measured by electronically integrating the flow signal obtained from a Fleisch n°2 pneumotachograph connected to a Godart 17212 differential pressure transducer. Flow and volume signals were recorded on a Hewlett Packard 3964 A tape recorder and displayed on a Beckman Dynograph R recorder, using a paper speed of 25 mm/s. Arterial blood gases were measured with an I.L. 213 analyzer. The latter was carefully calibrated with three standard gases before and after each measure. The signal obtained from the pneumotachograph was corrected for the different viscosities of  $O_2$  relative to room air.<sup>10</sup>

The fraction of the tidal volume involved in gas exchange is the difference between  $V_T$  and the dead space ( $V_D$ ). As  $V_T$  is decreased under halothane anesthesia and  $V_D$  increased by the dead space of the circuit, the time necessary to obtain pure oxygen at the mouthpiece was checked in a preliminary experiment.  $FI_{O_2}$  changed from 0.21 to 1 within two breaths when a syringe of 300 ml was placed at the mouthpiece and moved with a frequency of 30 cycles/min. In all the patients,  $FI_{O_2}$  was checked to be over 90% within the five breaths following  $O_2$  administration.

Arterial blood was sampled 10 min after the onset of air breathing in 16 patients from an indwelling radial catheter and at the end of the first minute of  $O_2$  administration in seven subjects. The electrocardiogram was

monitored continuously in all subjects. Arterial blood pressure and heart rate were measured during air breathing and every second minute thereafter.

Inspiratory ( $T_I$ ), expiratory ( $T_E$ ), and total breathing cycle durations ( $T_{TOT}$ ) were measured from the flow signal. Tidal volume ( $V_T$ ) was measured by integrating the flow signal. Other ventilatory variables were calculated from these values: respiratory frequency ( $f$ ), minute-ventilation ( $\dot{V}_E$ ), mean inspiratory flow ( $V_T/T_I$ ), and the duty cycle ( $T_I/T_{TOT}$ ). The control values for the ventilatory variables while breathing room air and halothane were means of the 30 individual breaths immediately preceding  $O_2$  administration. From the onset of  $O_2$  inhalation, the ventilatory variables were measured by averaging five individual breaths every 30 s during the first 5 min and every minute thereafter.

In 11 of the 25 subjects, the same protocol was repeated 10 min after the infusion of 0.5 mg/kg of almitrine bis-mesilate given over 5 min: these subjects again initially were administered a mixture of 1.5% halothane in air; after 15 min, the inspired gas was changed to a mixture of 1.5% halothane in oxygen. Ventilation was recorded and analyzed during air breathing and during 10 min following the onset of  $O_2$  breathing.

In an additional series of seven subjects operated for the same reasons, the effects of doxapram on respiration under halothane anesthesia were studied. The subjects

TABLE 1. Results of Ventilatory Variables (mean  $\pm$  SEM) during Air Breathing and 10 Min after  $O_2$  Administration under Stable Halothane Anesthesia ( $n = 25$ )

	$\dot{V}_E$ (l $\cdot$ min <sup>-1</sup> )	$V_T$ (ml)	$f$ (c $\cdot$ min <sup>-1</sup> )	$T_I$ (s)	$T_E$ (s)	$V_T/T_I$ (ml $\cdot$ s <sup>-1</sup> )	$T_I/T_{TOT}$
Air	7.5 $\pm$ 0.3	266 $\pm$ 8	28.4 $\pm$ 1.3	0.99 $\pm$ 0.04	1.23 $\pm$ 0.06	277 $\pm$ 10	0.449 $\pm$ 0.07
10 <sup>th</sup> min $O_2$	7.1 $\pm$ 0.3	279 $\pm$ 11	25.9 $\pm$ 1.2	1.06 $\pm$ 0.05	1.38 $\pm$ 0.07	269 $\pm$ 10	0.437 $\pm$ 0.07
P	<0.001	<0.01	<0.001	<0.001	<0.001	<0.01	<0.01

breathed room air. When minute ventilation was stable, doxapram (1 mg/kg iv followed by 0.6 mg/kg/24 h) was infused. Ventilatory parameters were measured when minute ventilation was stable.

Differences between values obtained after O<sub>2</sub> inhalation and control values were examined using analysis of variance. Differences between the values observed before and after respiratory stimulants were examined using Student's *t* test. Significance was considered present if *P* < 0.05.

### Results

Administration of O<sub>2</sub> did not cause a rapid decrease of  $\dot{V}_E$  (fig. 2). On the contrary, there was a transient insignificant increase in  $\dot{V}_E$  in the first 2 min. During the next 8 min, in all the subjects there was a decrease in  $\dot{V}_E$ , which became significant at the fifth minute.  $\dot{V}_E$  was decreased to  $94.5 \pm 1.5\%$  of the initial value (*P* < 0.001) at the tenth minute.

The time course of the changes in  $V_T$  and *f* during O<sub>2</sub> inhalation are shown in figure 3. Thirty seconds after the onset of O<sub>2</sub> inhalation, *f* decreased ( $-3.2 \pm 1.1\%$ ; *P* < 0.001). Thereafter, *f* continued to decrease, reaching  $8.4 \pm 1.4\%$  (*P* < 0.001) after 10 min. This decrease in *f* was due to an increase in both *T*<sub>I</sub> and *T*<sub>E</sub> (table 1). *T*<sub>I</sub> increased rapidly ( $+4.4 \pm 1.0\%$  after 30 s; *P* < 0.001) and remained stable thereafter, whereas *T*<sub>E</sub> increased

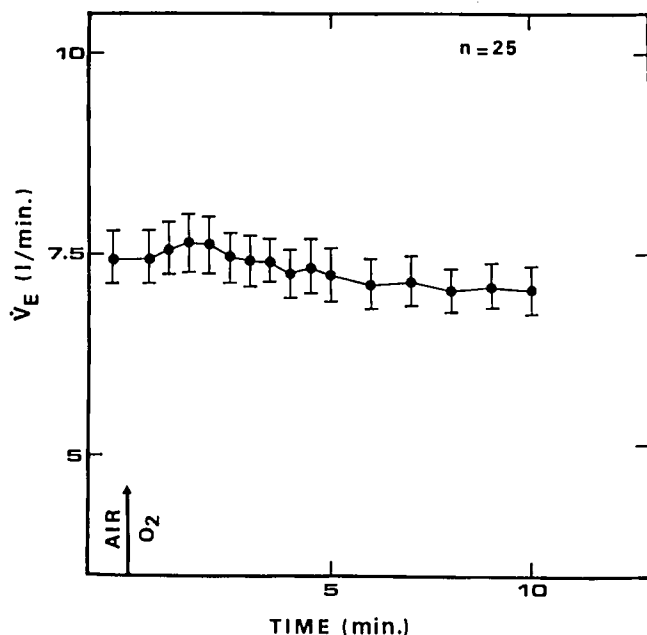


FIG. 2. Time course of changes in minute ventilation ( $\dot{V}_E$ ). The first point is the mean value while breathing the air-halothane mixture; the onset of the inhalation of the O<sub>2</sub>-halothane mixture is indicated by the arrow. Bars indicate 1 SE.

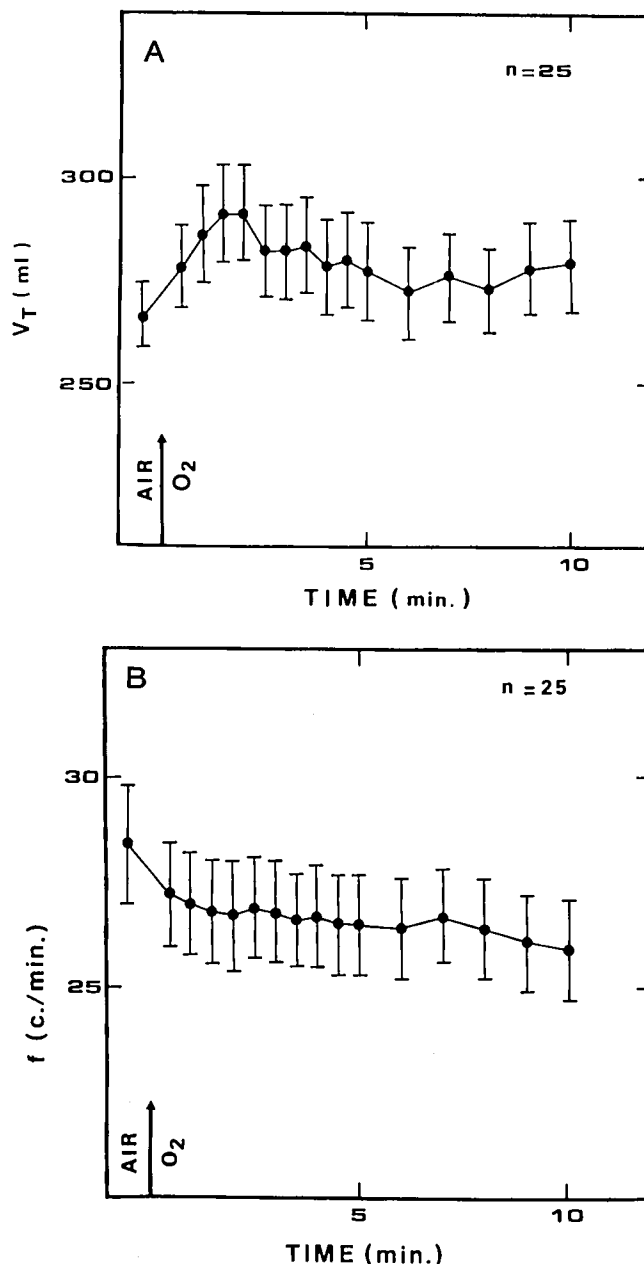


FIG. 3. Time course of changes in tidal volume ( $V_T$ ) (panel A) and respiratory frequency (*f*) (panel B). Symbols are the same as those in figure 2.

continuously from the onset of O<sub>2</sub> administration until the tenth minute (*P* < 0.001). Thirty seconds after the onset of O<sub>2</sub> breathing,  $V_T$  increased significantly (*P* < 0.01) and remained stable thereafter. There was a mild decrease of  $V_T/T_I$ , which was progressive during the course of O<sub>2</sub> inhalation. This decrease was significant at the tenth minute (*P* < 0.01). There was a progressive decrease in  $T_I/T_{TOT}$  (*P* < 0.01 at the tenth minute) due to the progressive changes in *T*<sub>E</sub>.

TABLE 2. Comparison of Ventilatory Variables during Air Breathing and 10 Min after O<sub>2</sub> Administration, before and after Almitrine Infusion, under Stable Halothane Anesthesia (n = 11)

	$\dot{V}_E$ (l·min <sup>-1</sup> )		$V_T$ (ml)		$f$ (c·min <sup>-1</sup> )		$T_I$ (s)		$T_E$ (s)		$V_T/T_I$ (ml·s <sup>-1</sup> )		$T_I/T_{TOT}$	
	Air	10 <sup>th</sup> Min O <sub>2</sub>	Air	10 <sup>th</sup> Min O <sub>2</sub>	Air	10 <sup>th</sup> Min O <sub>2</sub>	Air	10 <sup>th</sup> Min O <sub>2</sub>	Air	10 <sup>th</sup> Min O <sub>2</sub>	Air	10 <sup>th</sup> Min O <sub>2</sub>	Air	10 <sup>th</sup> Min O <sub>2</sub>
Control														
$\bar{m}$	7.8	7.2*	263	266	30.0	27.8†	0.92	0.98†	1.18	1.31†	294	279†	0.441	0.431†
SEM	0.4	0.4	6	10	1.9	1.9	0.06	0.07	0.08	0.09	12	13	0.011	0.011
Almitrine														
$\bar{m}$	8.7	7.2†	299	279‡	29.4	25.4†	0.96	1.08†	1.19	1.32†	326	276‡	0.447	0.436
SEM	0.6	1.2	10	14	2.0	2.1	0.08	0.09	0.10	0.10	21	11	0.009	0.009
P	<0.01	NS	<0.01	NS	NS	<0.02	NS	<0.02	NS	NS	<0.02	NS	NS	NS

Statistical significance between air and O<sub>2</sub> breathing: \*  $P < 0.001$ ; †  $P < 0.01$ ; ‡  $P < 0.05$ .

#### EFFECTS OF INFUSION OF ALMITRINE BISMESILATE

Table 2 shows the values of the ventilatory variables before and after almitrine bismesilate infusion. After almitrine, while breathing air, there was a significant increase in  $\dot{V}_E$ ,  $V_T$ , and  $V_T/T_I$ , without any modification of the respiratory times. When O<sub>2</sub> was administered,  $\dot{V}_E$  decreased rapidly, reaching the values observed under the same conditions without almitrine at the end of the first minute (fig. 4). Thereafter,  $\dot{V}_E$  decreased progressively, reaching a plateau at the end of the fourth minute. These changes in  $\dot{V}_E$  were due to changes in both  $V_T$  and  $f$ .  $V_T$  decreased progressively until the end of the fifth minute, whereas  $f$  followed a pattern similar to that observed without almitrine, although reaching a signif-

icantly lower value at the tenth minute. Both  $T_I$  and  $T_E$  increased continuously from the onset of O<sub>2</sub>-administration.  $T_E$  followed a pattern similar to that observed without almitrine. In contrast,  $T_I$  increased progressively from the onset of O<sub>2</sub> administration up to the tenth minute. The time course of  $V_T/T_I$  and  $T_I/T_{TOT}$  was different from that observed without almitrine:  $V_T/T_I$  reached its nadir at the end of the fifth minute, whereas  $T_I/T_{TOT}$  was not modified (fig. 5).

#### Discussion

Almitrine bismesilate, a piperazine derivative, is a long-acting respiratory drug that stimulates electively the peripheral chemoreceptors. This specific effect of almitrine bismesilate on the peripheral chemoreceptors has been shown in anesthetized dogs<sup>11</sup> and in awake cats.<sup>7</sup> In awake normal human subjects, Guillermin and Radziszewski<sup>12</sup> observed that the oral administration of 5 mg/kg of almitrine bismesilate (S2620) consistently increased tidal volume and respiratory frequency. This increase in ventilation was abolished in less than 1 min when pure oxygen was administered. Flandrois and Guérin<sup>13</sup> found that intravenous infusion of 1 mg/kg of almitrine increased minute ventilation (+12%) in normal subjects and that the administration of pure oxygen suppressed this phenomenon in 20–40 seconds. The time course of the responses observed when pure oxygen was administered in these series<sup>12,13</sup> suggests strongly that the effects of almitrine bismesilate on respiration in normal awake human subjects depends upon peripheral chemoreceptors stimulation. Since halothane suppresses the hypoxic ventilatory stimulation through its effect on the peripheral chemoreceptors, we tested whether almitrine could restore peripheral chemosensitivity.

This study showed that an iv infusion of 0.5 mg/kg almitrine was followed by a marked increase in  $\dot{V}_E$  when breathing the air-halothane mixture. This increase in  $\dot{V}_E$  is the consequence of an increased drive. Mean inspiratory

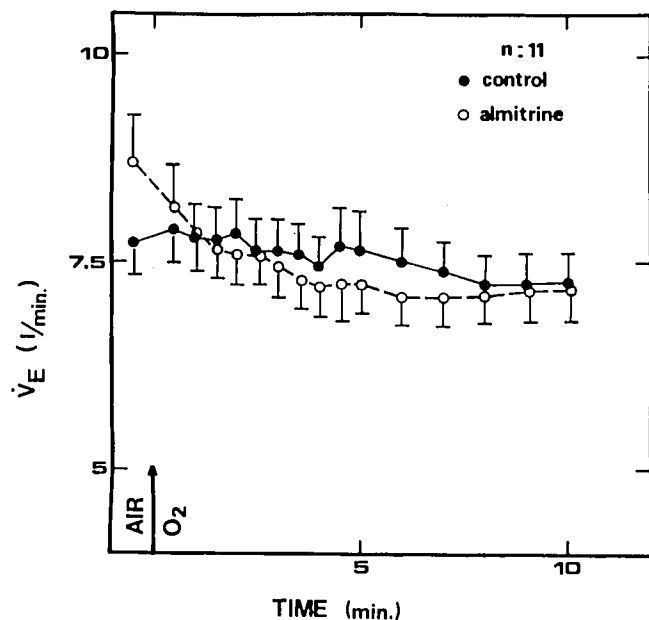


FIG. 4. Time course of changes in minute ventilation in the 11 subjects tested before and after almitrine infusion. Symbols are the same as those in figure 2.

flow and  $V_T$  are increased significantly after almitrine. In contrast, almitrine, in these conditions, has no effect on the timing mechanisms:  $T_I$ ,  $T_E$ ,  $f$ , and  $T_I/T_{TOT}$  are not altered after almitrine.

The administration of  $O_2$  abolishes the analeptic effect of almitrine. One minute after the onset of  $O_2$  breathing,  $\dot{V}_E$  and  $V_T/T_I$  reach the same values with and without almitrine. The effects of  $O_2$  on the timing mechanisms are identical after almitrine, resulting in an increase in  $T_I$  and  $T_E$ .

Therefore, we conclude that almitrine can restore peripheral chemosensitivity in halothane-anesthetized subjects. Accordingly, the therapeutic use of almitrine in the recovery room, after halothane anesthesia, in patients breathing room air, warrants consideration.

The lack of changes in respiratory frequency after almitrine bismesilate administration in our subjects is surprising. Indeed, the stimulation of respiratory activity by pharmacologic or physiologic stimulants usually is associated with an increased respiratory frequency.<sup>7</sup> The response observed in our subjects may be due to a specific effect of almitrine bismesilate or may reflect changes in chemosensitivity under halothane anesthesia.

In anesthetized dogs the increased ventilation observed after administration of 3 mg/kg of almitrine bismesilate is mostly due to an increased respiratory frequency.<sup>11</sup> On the other hand, the increased ventilation observed after the administration of 0.75 mg/kg of the drug in awake cats is due nearly entirely to an increased tidal volume.<sup>7</sup> In awake man the infusion of 5 mg/kg increases  $V_T$  and  $f$ ,<sup>12</sup> whereas at 1 mg/kg, tidal volume increased without major changes in respiratory frequency.<sup>13</sup> Therefore, it is possible that after administration of small doses of almitrine bismesilate (<1 mg/kg), the increased minute ventilation mostly is due to an increased inspiratory flow and tidal volume and that changes in respiratory times are achieved when higher doses are administered.

The lack of changes in respiratory times could depend on changes in chemosensitivity under halothane anesthesia. In order to investigate this possibility, we studied the effects of doxapram in another group of seven normal subjects under halothane anesthesia while they were breathing room air. The results are summarized on table 3. Doxapram is an analeptic drug that stimulates peripheral and central chemoreceptors.<sup>7</sup> Tidal volume increased in all the subjects ( $P < 0.005$ ), whereas respiratory frequency decreased in four subjects and increased in the three others. As a result, minute ventilation increased in a statistically nonsignificant manner. Such small increases in ventilation already have been noticed by Knill and Gelb,<sup>3</sup> who showed that the doxapram-induced ventilatory stimulation was depressed profoundly by halothane. It is therefore possible that halothane modifies the peripheral chemoreceptors response to respiratory stimulants.

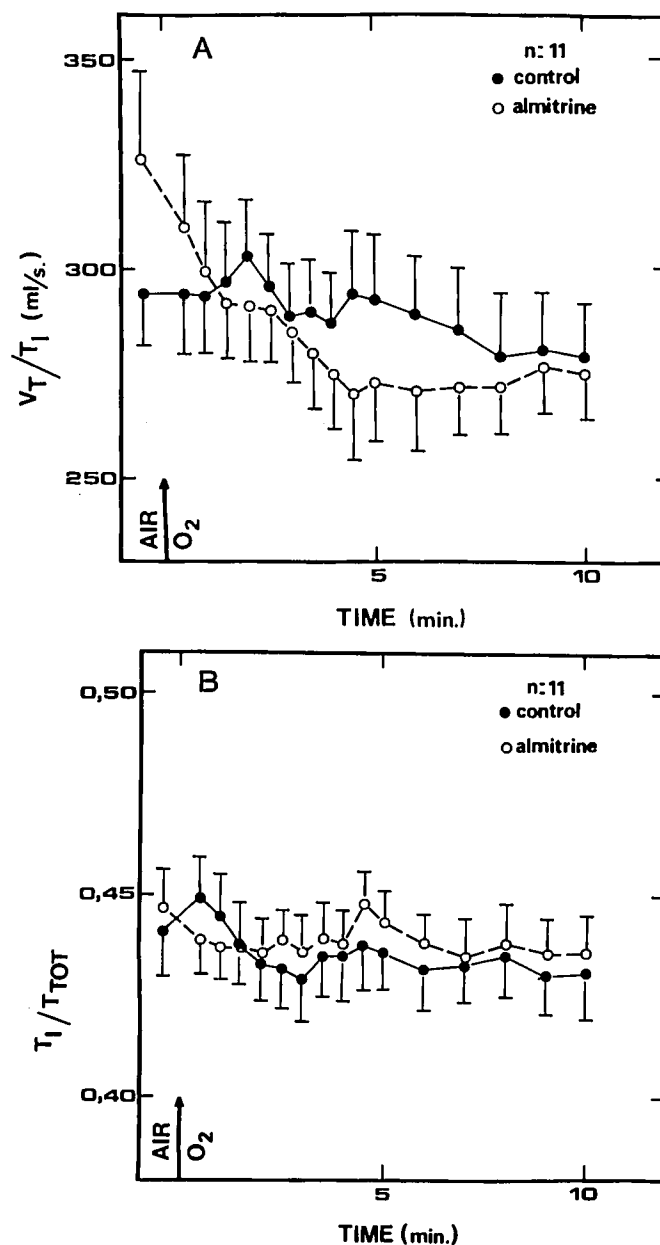


FIG. 5. Time course of changes in mean inspiratory flow ( $V_T/T_I$ ) (panel A) and ratio of inspiratory to total respiratory cycle durations ( $T_I/T_{TOT}$ ) (panel B). Symbols are the same as those in figure 2.

Another interesting finding of this study was the effects of the administration of  $O_2$  on ventilation and breathing pattern. According to Knill and Gelb,<sup>3</sup> halothane abolishes

TABLE 3. Effects of Doxapram on Ventilation on Seven Subjects under Halothane Anesthesia during Air Breathing

	$\dot{V}_E$ (l · min <sup>-1</sup> )	$V_T$ (ml)	$f$ (c · min <sup>-1</sup> )
Control	6.65 ± 0.56	284 ± 23	23.9 ± 2.0
Doxapram	7.06 ± 0.44	307 ± 20	23.2 ± 1.2
P	NS	0.005	NS

hypoxic ventilatory stimulation. However, estimation of the effects of the changes in the level of oxygenation on the respiratory control depends on the method used to test it. It is generally considered that oxygen deficiency influences the respiratory control mechanisms in two ways: hypoxemia stimulates the peripheral chemoreceptors, whereas it depresses the central respiratory control.<sup>14</sup> Hypoxic stimulation is mediated by the peripheral chemoreceptors that respond rapidly.<sup>15</sup> The central effects are slower and need several minutes before reaching a steady state.<sup>16</sup> Therefore, one could assume that different results could be obtained, depending on the time course of the experimental method. Because of their durations, the methods that utilize a progressive decrease in  $FI_{O_2}$ <sup>16,17</sup> to test the hypoxic drive ( $<0.21$ ) or the administration of a constant fraction of inspired oxygen (steady state method) theoretically could be influenced by both effects. Therefore, the study by Knill and Gelb<sup>3</sup> using Weil's method,<sup>17</sup> which lasts for 8–10 min and that did not show any increase in  $\dot{V}_E$  during progressive hypoxia, might have been explained by a balance between these two antagonist effects.

In this study, we used a method derived from the classical test of Dejours *et al.*<sup>18</sup> This method gives an evaluation of the hypoxic drive by measuring the transient decrease in  $\dot{V}_E$  after substitution of  $O_2$  for room air. The decrease in  $\dot{V}_E$  during the first seconds following the onset of  $O_2$  administration represent the influence of the peripheral chemoreceptors on ventilation. The secondary transient increase in  $\dot{V}_E$ , which usually is observed, may reflect, in part, the removal of a central respiratory depression caused by hypoxia.<sup>14,19</sup> The magnitude of the ultimate increase in  $\dot{V}_E$  after the substitution of  $O_2$  for room air in normal awake subjects is 8–10% of the initial  $\dot{V}_E$ .<sup>18</sup>

During halothane anesthesia, our data show that there was no decrease in  $\dot{V}_E$  within the first minute following  $O_2$  inhalation. This is in agreement with the assumption that peripheral hypoxic stimulation is abolished with halothane. However, the absence of change in  $\dot{V}_E$  was the result of opposite effects of  $O_2$  on  $f$  and  $V_T$ . After the third minute,  $\dot{V}_E$  decreased progressively. Part of these changes are consistent with the observations of Knill and Gelb,<sup>3</sup> who reported that during progressive hypoxia, there was an increase in  $f$  with a decrease in  $V_T$ .

The effects of hyperoxia on the respiratory times have not been described previously. The immediate changes observed after  $O_2$  administration were essentially the result of an increase in both  $T_I$  and  $T_E$ . The decrease in  $V_T/T_I$ , an index of the drive to breathing, was moderate after the onset of  $O_2$  inhalation. These immediate changes in the respiratory times can be due to changes in the mechanical properties of the respiratory system or in the timing mechanisms of respiration.

A possible explanation is that the increase in  $T_E$  was related to an increased flow resistance in the respiratory system. We therefore analyzed the expiratory flow–volume curves, according to the method described by Zin *et al.*<sup>20</sup> No change in the expiratory flow–volume curves occurred after  $O_2$  administration. A second possible explanation was that the longer  $T_I$  and  $T_E$  resulted from a change in lung volume. According to the model of the respiratory control system of Clark and Von Euler,<sup>21</sup>  $V_T$  is determined by the relationship between mean inspiratory flow ( $V_T/T_I$ ) and  $T_I \cdot T_I$  is set by central mechanisms until  $V_T$  exceeds a threshold value, above which vagal activity leads to a progressive shortening of  $T_I$ . As it has been reported<sup>22</sup> that hypoxia increases functional residual capacity (FRC), it could be assumed that a decrease in FRC may be induced by  $O_2$  inhalation. Such a change in the pulmonary volume could modify vagal discharge and increase  $T_I$ . This is unlikely, however, since the Hering–Breuer reflex generally is considered to be weak in man.<sup>23</sup> A third possible explanation is that hyperoxia may have a specific action on the timing mechanisms of respiration.

The changes in  $\dot{V}_E$  shown in figure 2 also could have been due to a change in the level of anesthesia. Oxygen breathing can cause ventilation–perfusion mismatch<sup>24</sup> and therefore could modify the arterial concentration of halothane. Furthermore, we observed a mild increase (less than 0.035%) in the inspired fraction of halothane during oxygen breathing. However, the observed changes in  $T_I$  and  $T_E$  cannot be explained by the effects of an increased concentration of halothane. It has been shown in a previous series<sup>25</sup> that an increase in the inspired fraction of halothane is followed by a decrease in  $\dot{V}_E$ ,  $V_T$ ,  $T_I$ , and  $T_E$ . These changes are different from those observed when pure oxygen was administered in our subjects.

After termination of a surgical procedure, there are conditions in which ventilation decreases. In 12 subjects, we measured ventilation 1) during pure oxygen breathing; 2) 10 minutes after administration of room air; and 3) 10 minutes after pure oxygen breathing. Mean values of the ventilatory parameters measured in the last minute of each of the two periods of oxygen breathing were similar ( $V_T = 269 \pm 17$  and  $275 \pm 19$  ml;  $f = 25.9 \pm 2$  and  $25.1 \pm 1.7$ ;  $\dot{V}_E = 6.86 \pm 0.51$  and  $6.77 \pm 0.47$  l/min, respectively). Therefore, we can exclude that changes in respiratory control secondary to the termination of the surgical procedure were responsible for our results.

Another possible explanation for the slow decrease in  $\dot{V}_E$  might be slow changes in blood gases due to impaired gas exchange. The mean  $V_T$  for the 25 subjects was 266 ml. If we take into account the dead space of the circuit (75 ml) and the anatomic dead space (150 ml), only a small fraction of  $V_T$  reaches the alveoli for gas exchange. If gas exchange had been inefficient,  $Pa_{O_2}$  might have

risen progressively, which could have explained the time course of the ventilatory changes that we observed. However, this hypothesis is not confirmed by blood-gas analysis: during air breathing,  $P_{aO_2}$  was  $85 \pm 4$  mmHg ( $n = 16$ ). One minute after  $O_2$  breathing,  $P_{aO_2}$  was  $234 \pm 29$  mmHg (range: 145–344,  $n = 7$ ) and  $340 \pm 16$  mmHg at the fifth minute.

Arterial blood pressure and heart rate remained constant throughout the study without any variation when room air was changed for oxygen breathing. Therefore, the observed respiratory changes cannot be explained by an influence of baroreceptor activity on respiratory control.<sup>26</sup>

In conclusion, during halothane anesthesia, hypoxic ventilatory drive is depressed. Almitrine bismesilate can restore the hypoxic drive. The decrease in  $\dot{V}_E$  that was observed when air was changed for  $O_2$  was due to an increase in respiratory times. These findings cannot be explained by mechanical changes in the respiratory system, by a change in the level of halothane anesthesia, by a slow increase in  $P_{aO_2}$ , or by variations in arterial blood pressure, and will require further investigation.

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## References

1. Pavlin EG: Respiratory pharmacology of inhaled anesthetic agents, *Anesthesia*. Edited by Miller RD. New York, Churchill Livingstone, 1981, pp 349–382
2. Munson ES, Larson CP, Barad AA, Regan MJ, Buechel DR, Eger EI II: The effects of halothane, fluroxene, and cyclopropane on ventilation: A comparative study in man. *ANESTHESIOLOGY* 27:716–728, 1966
3. Knill RL, Gelb AW: Ventilatory responses in hypoxia and hypercapnia during halothane sedation and anesthesia in man. *ANESTHESIOLOGY* 49:244–251, 1978
4. Duffin J, Triscott A, Whitwam JG: The effect of halothane and thiopentone on ventilatory responses mediated by the peripheral chemoreceptors in man. *Br J Anaesth* 48:975–980, 1976
5. Hirshman CA, McCullough RE, Cohen PJ, Weil JV: Depression of hypoxic ventilatory response by halothane, enflurane and isoflurane in dogs. *Br J Anaesth* 49:957–962, 1977
6. Weiskopf RB, Raymond LW, Severinghaus JW: Effects of halothane on canine respiratory responses to hypoxia with and without hypercarbia. *ANESTHESIOLOGY* 41:350–360, 1974
7. Gautier H, Bonora M, Milic-Emili J, Siafakas NM: Ventilatory effects of various respiratory stimulants in awake cats. *Bull Eur Physiopathol Respir* 15(Suppl):183–193, 1979
8. Laubie M, Diot F: Etude pharmacologique de l'action stimulante respiratoire du S 2620. Rôle des chemorecepteurs carotidiens et aortiques. *J Pharmacol* 2:363–374, 1972
9. Bromet N, Aubert Y, Baune A, Courte S, Guillaudeux J: Etude pharmacocinétique de l'almitrine. *Rev Fr Mal Respir* 8:569–576, 1980
10. Radford EP Jr: The physics of gases, *Handbook of Physiology*, section 3, vol. 1, Respiration. Edited by Fenn WO, Rahn FH. Washington D. C., American Physiological Society, 1964, pp 125–152
11. Laubie M, Schmitt H: Long-lasting hyperventilation induced by almitrine: Evidence for a specific effect on carotid and thoracic chemoreceptors. *Europ J Pharmacol* 61:125–136, 1980
12. Guillermin R, Radziszewski E: Effets ventilatoires chez l'homme sain d'un nouvel analeptique respiratoire, le S 2620. *Bull Eur Physiopathol Respir* 10:776–791, 1974
13. Flandrois R, Guerin JC: Action de l'almitrine sur le contrôle chémoréflexe de la ventilation chez l'homme sain et l'insuffisant respiratoire chronique. *Rev Fr Mal Respir* 8:561–567, 1980
14. Gautier H, Bonora M: Effects of carotid body denervation on respiratory pattern of awake cats. *J Appl Physiol* 46:1127–1131, 1979
15. Biscoe TJ, Willshaw P: Stimulus-response relationships of the peripheral arterial chemoreceptors, *Regulation of Breathing*. Edited by Hornbein TF. New York, Marcel Dekker, Inc., 1981, pp 321–345
16. Rebuck AS, Campbell EJM: A clinical method for assessing the ventilatory response to hypoxia. *Am Rev Respir Dis* 119:345–350, 1974
17. Weil JV, Byrne-Quinn E, Sodal EI, Friesen O, Underhill B, Filley GF, Grover RF: Hypoxic ventilatory drive in normal man. *J Clin Invest* 49:1061–1072, 1970
18. Dejours P, Labrousse Y, Raynaud J, Girard F, Teillac A: Stimulus oxygène de la ventilation au repos et au cours de l'exercice musculaire à basse altitude (50 m) chez l'homme. *Rev Franc Et Clin Biol* 3:105–123, 1958
19. Miller MJ, Tenney SM: Hyperoxic hyperventilation in carotid deafferented cats. *Respir Physiol* 23:23–30, 1975
20. Zin WA, Pengelly LD, Milic-Emili J: Single-breath method for measurement of respiratory mechanics in anesthetized animals. *J Appl Physiol* 52:1266–1271, 1982
21. Clark JF, Von Euler C: On the regulation of depth and rate of breathing. *J Physiol (Lond)* 222:267–295, 1972
22. Bouverot P, Fitzgerald RS: Role of the arterial chemoreceptors in controlling lung volume in the dog. *Respir Physiol* 7:203–215, 1969
23. Paskin S, Skovsted P, Smith TC: Failure of the Hering-Breuer reflex to account for tachypnea in anesthetized man. *ANESTHESIOLOGY* 29:550–558, 1968
24. Wagner PD: Recent advances in pulmonary gas exchange. *Int Anesthesiol Clin* 15:81–97, 1977
25. Larson CP, Eger EI II, Muallem M, Buechel DR, Munson ES, Eisele JH: The effects of diethylether and methoxyflurane on ventilation: II. A comparative study in man. *ANESTHESIOLOGY* 30:174–184, 1969
26. Grunstein MM, Derenne JP, Milic-Emili J: Control of depth and frequency of breathing during baroreceptor stimulation in cats. *J Appl Physiol* 39:395–404, 1975