Influence of 0.2 minimum alveolar concentration of enflurane on the ventilatory response to sustained hypoxia in humans

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Summary

To determine the influence of 0.2 minimum alveolar concentration (MAC) of enflurane on the time course of ventilation during sustained hypoxia, we studied 10 healthy adult volunteers with and without enflurane. The following design was used: end-tidal $P_{O_2}$ was maintained at 13.3 kPa for 8 min, at 6.7 kPa for 20 min and at 13.3 kPa for 8 min. End-tidal $P_{CO_2}$ was held constant throughout at 0.67 kPa above the subject's natural value. Control experiments were conducted with no hypoxia imposed. During the experiment subjects breathed via a mouthpiece from an automated gas mixing system which controlled end-tidal values. Enflurane reduced baseline (euoxic) ventilation from 20.9 (SEM 2.0) litre min$^{-1}$ to 11.7 (2.4) litre min$^{-1}$ (ANOVA, $P<0.001$). Enflurane reduced the acute ventilatory response to hypoxia (AHVR) from 20.1 (3.3) litre min$^{-1}$ to 1.8 (0.5) litre min$^{-1}$ (ANOVA, $P<0.001$), and the ventilatory off-response at cessation of hypoxia from 11.7 (2.4) litre min$^{-1}$ to 1.8 (0.5) litre min$^{-1}$ (ANOVA, $P<0.001$). There was no significant difference in hypoxic ventilatory decline (HVD) without and with enflurane (8.9 (2.4) litre min$^{-1}$ vs 5.5 (1.1) litre min$^{-1}$; ANOVA, ns). These results confirm that 0.2 MAC of enflurane suppressed the acute ventilatory response to hypoxia, but had no significant effect on the subsequent ventilatory decline during sustained hypoxia. (Br. J. Anaesth. 1997; 78: 707–713).

Key words


In humans the time course of ventilation during a period of sustained hypoxia lasting approximately 30 min is characterized by a rapid increase in ventilation over the first few minutes (the acute hypoxic ventilatory response (AHVR)) followed by a gradual decline in ventilation over approximately 20 min (the hypoxic ventilatory decline (HVD), often referred to in the American literature as “roll-off”). HVD cannot be attributed entirely to wash-out of carbon dioxide because the decline is still present even when no changes in arterial carbon dioxide partial pressure (an isocapnic exposure) are permitted to occur during hypoxic exposure. At the relief of isocapnic hypoxia, ventilation usually returns rapidly to its baseline or pre-hypoxic value.

Knill, Manninen and Clement showed the marked depressant effect of sub-anaesthetic concentrations of volatile anaesthetics, including enflurane, on AHVR. Their result has been confirmed by several other groups, including for 0.1 minimum alveolar concentration (MAC) of enflurane, 0.1% inspired halothane, 0.1 MAC and 0.22% (0.15 MAC) halothane.

In contrast with the effects of volatile anaesthetics on AHVR, a similar depressant effect on the magnitude of the subsequent ventilatory decline, HVD, has generally not been found. Young, Drummond and Warren and Dahan and colleagues have shown no significant effect of sub-anaesthetic concentrations of halothane on HVD. For isoflurane, Temp, Henson and Ward were unable to show any significant effect of 0.1 MAC of isoflurane on either AHVR or HVD during sustained mildly hypercapnic (end-tidal $P_{CO_2}$ 0.13–0.27 kPa greater than subject’s natural value) hypoxia in adults. Similar results for HVD were reported by Foo and colleagues for equivalent sub-anaesthetic doses of isoflurane. In our previous study we observed no significant reduction in the magnitude of HVD during 0.1 MAC of enflurane.

The finding that AHVR can be greatly attenuated but HVD relatively unaffected is slightly surprising given that, in conscious humans, (i) the magnitude of HVD correlates with the magnitude of AHVR, (ii) other factors that affect AHVR such as almitrine and somatostatin also alter HVD and (iii) in humans who have undergone peripheral chemodenervation, HVD is abolished together with AHVR. It would appear from such results that both AHVR and HVD are determined by the sensitivity of the peripheral chemoreflex loop and functionally correlated. The usual rapid return of ventilation to its pre-hypoxic value after relief of hypoxia suggests that HVD is a direct measure of the decrease over time in chemoreflex sensitivity.

However, in cats, recent studies have shown considerable differences in the form of the ventilatory response to sustained hypoxia between the awake
and anaesthetized state. In awake cats, the form of the ventilatory response to sustained hypoxia is similar to that in awake humans described above. It is clearly asymmetric, with the rapid increase in ventilation at the onset of hypoxia being larger than the rapid decrease at the relief of hypoxia. On the other hand, in anaesthetized cats, the form of this response is much more symmetric with little difference between the magnitudes of the responses at the onset and relief of hypoxia. This results, at the relief of hypoxia, in a decrease in ventilation to below its pre-hypoxic value, sometimes approaching a period of apnoea.

In most human studies using low doses of anaesthetics the usual finding has been that the response remains asymmetric, with the decrease in ventilation at the relief of hypoxia being smaller than the increase in ventilation at the onset of hypoxia. However, one study by Dahan and colleagues using halothane reported a symmetric response.

The purpose of this study was to determine if low doses of enflurane affect HVD, and to convert the form of the ventilatory response in conscious humans from an asymmetric to a symmetric form, in a manner consistent with the differences between awake and anaesthetized cats. In order to examine this without a likelihood of apnoea or near apnoea occurring after relief of hypoxia and an associated uncontrollable increase in end-tidal \( P_{\text{CO}} \), the initial ventilations have to be high enough to allow a symmetric off-transient to occur. The strategy of Khamnei and Robbins of conducting the experiments under hypercapnic conditions was used to achieve this.

**Subjects and methods**

We studied 10 healthy adult volunteers (aged 26.9 (20–51) yr). All subjects received a written and verbal description of the experiments before they gave their consent. None of the subjects was receiving medication at the time of study and all were asked to refrain from taking food for at least 6 h and drinks for 4 h before the experiments. During the experiments in which no enflurane was administered, subjects were asked to watch television. During experiments in which enflurane was administered subjects were asked to shut their eyes in a partially darkened quiet room. Our aim in reducing the stimulus during enflurane sedation was to achieve as great degree of sedation as possible for the dose of enflurane administered, so as to maximize the difference between the awake and sedated state. A pulse oximeter (Ohmeda Biox 3740) continuously measured arterial oxygen saturation via a finger probe. The study was approved by the Central Oxford Research Ethics Committee.

During the experiment subjects were seated in a comfortable chair and breathed through a mouthpiece from an automated gas mixing system designed to regulate end-tidal values, which provided a steady stream of gas of 66 litre min\(^{-1}\). Respiratory volumes were measured with a turbine volume measuring device. Respiratory flows and timing information were obtained using a pneumotachograph. Respired gas was sampled at the mouth and analysed for \( P_{\text{CO}} \), \( P_{\text{O}} \) and enflurane by a mass spectrometer (Airspec 3000, Airspec Ltd., Biggin Hill, Kent, UK). All variables were recorded in real time with a 50-Hz sampling speed by an IBM PC computer. This computer executed a peak-picking program in real time to determine inspiratory and expiratory volumes and durations, and end-tidal \( P_{\text{CO}} \left( P_{\text{CO}} \right) \) and \( P_{\text{O}} \) (\( P_{\text{O}} \)). Breath-by-breath end-tidal values were passed to a second computer controlling the gas mixing system. This computer compared actual \( P_{\text{O}} \left( P_{\text{O}} \right) \) and \( P_{\text{O}} \) with the desired values, and adjusted the inspiratory gas mixture to maintain the desired end-tidal values independently of changes in ventilation. Details of the dynamic end-tidal forcing technique and gas mixing system have been described in more detail elsewhere.

Enflurane was administered using a vaporizer (Penlon Ltd, Abingdon, UK) through which an air flow of 6–10 litre min\(^{-1}\) was used. The mass spectrometer was calibrated using a standard gas mixture of 0.419% enflurane in air (British Oxygen Company, London; enflurane concentration certified to be within the range 0.398–0.440%). The mass number used for enflurane was 51. During experiments in which enflurane was administered the end-expired enflurane concentration was held constant at 0.34% by manual adjustment of the inspired concentration. During experiments in which no enflurane was administered the vaporizer was kept in the off position.

**Experimental design**

Each subject was studied twice, on separate days. On each day four different tests were studied: (1) 0.2 MAC of enflurane with hypoxia, (2) 0.2 MAC of enflurane with euoxia, (3) no enflurane with hypoxia and (4) no enflurane with euoxia. In tests involving a period of hypoxia (hypoxia tests), \( P_{\text{O}} \) was forced as follows: 8 min at 13.3 kPa, 20 min at 6.7 kPa and 8 min at 13.3 kPa. In tests involving no period of hypoxia (euoxia tests), \( P_{\text{O}} \) was held constant at 13.3 kPa for 36 min. In both tests \( P_{\text{O}} \) was increased 0.67 kPa above the subject’s natural value and maintained constant. The order of the tests was randomized and the tests were separated by 30–45-min intervals.

**Data analysis**

Data from each test were averaged over 60-s intervals. To characterize the change in the fast components of the ventilatory response to sustained hypoxia we used four particular 1-min periods, which are illustrated in figure 1. The four periods were: ventilation during the last minute before the step into hypoxia (\( V_{\text{E}1} \), pre-hypoxic or baseline ventilation), peak ventilation during the first 5 min of the hypoxic period (\( V_{\text{E}2} \), peak ventilation), ventilation during the last min of hypoxia (\( V_{\text{E}3} \), depressed ventilation) and minimum ventilation during the first 5 min after return to euoxia (\( V_{\text{E}4} \), post-hypoxic ventilation). The acute hypoxic ventilatory response (on-response, AHVR) was then taken as the
Effect of 0.2 MAC enflurane on ventilatory response to hypoxia

The difference between peak ventilation and pre-hypoxic ventilation ($\bar{V}E_2 - \bar{V}E_1$). The magnitude of the off-response was calculated as the difference in ventilation between the depressed ventilation and post-hypoxic ventilation ($\bar{V}E_3 - \bar{V}E_1$). The decline in ventilation during hypoxia was corrected for changes in ventilation during the euoxia tests. Thus HVD was calculated using the values of ventilation ($\bar{V}E_2$ and $\bar{V}E_3$) measured during euoxia tests corresponding in time to peak and depressed ventilation (fig. 1). We used the formula: $HVD = (\bar{V}E_2 - \bar{V}E_3) - (\bar{V}E_2 - \bar{V}E_1)$.

The significance of differences in baseline ventilation, AHVR, HVD and off-response between the two pharmacological conditions was assessed by analysis of variance (ANOVA; balanced design). The analysis was run within MS Windows for Workgroups 3.11 on a Dell XPS P120c PC, using the Minitab for Windows software package. A probability level of less than 0.05 was taken as statistically significant.

Results

Three of the initial 13 subjects recruited for the study failed to complete the experiments; one because of the excitation, nausea and discomfort during enflurane inhalation and the other two because they found they could not afford the time. The remaining 10 subjects completed the study without any adverse effect. During the enflurane experiments the level of sedation was intense. All of our subjects performed the enflurane experiments with closed eyes. In four subjects we observed airway obstruction with enflurane; this was relieved in all cases by gentle manual extension of the head, traction on the mandible, or both. One subject included in the study had some mild excitation. Mean values for inspired and end-tidal anaesthetic concentrations are shown in table 1. MAC for enflurane was taken to be 1.7%.

End-tidal gas profiles for each test and each pharmacological condition are given in table 2. Figure 2 demonstrates the quality of the end-tidal gas control and ventilatory responses of one subject (No. 960) for the hypoxia and euoxia tests for both pharmacological conditions, each repeated twice. In the hypoxia test the steps of $P_{E0}$ into and out of hypoxia were rapid (fig. 2, left bottom panel; for means see fig. 3c). In the euoxia test, $P_{E0}$ was maintained constant (fig. 2, right bottom panel; for means see fig. 3c). In both tests $P_{ECO2}$ remained constant with the exception of a small increase immediately after the step out of hypoxia in the presence of enflurane (fig. 2, middle panels; for means see fig. 3b).

Figure 3 illustrates mean ventilations for all 10 subjects in the euoxia and hypoxia tests under two pharmacological conditions. All subjects showed biphasic ventilatory responses to sustained hypoxia.

### Table 1

<table>
<thead>
<tr>
<th>Target</th>
<th>Actual</th>
<th>End-tidal (%)</th>
<th>End-tidal (%)</th>
<th>End-tidal (MAC)</th>
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<tbody>
<tr>
<td>End-tidal (%)</td>
<td>Inspired (%)</td>
<td>0.007 (0.002)</td>
<td>0.006 (0.002)</td>
<td></td>
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<tr>
<td>0.34</td>
<td>0.484 (0.013)</td>
<td>0.342 (0.004)</td>
<td>0.201 (0.002)</td>
<td></td>
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<tr>
<td>0.34</td>
<td>0.497 (0.011)</td>
<td>0.352 (0.002)</td>
<td>0.207 (0.001)</td>
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### Table 2

<table>
<thead>
<tr>
<th>Hypoxia</th>
<th>Euoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_{E0}$ (kPa)</td>
<td>$P_{E0}$ (kPa)</td>
</tr>
<tr>
<td>5.91 (0.08)</td>
<td>13.29 (0.01)</td>
</tr>
<tr>
<td>5.99 (0.07)</td>
<td>13.23 (0.01)</td>
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</table>
Table 3  Ventilatory response characteristics (litre min$^{-1}$) to sustained hypoxia for all subjects during control and enflurane conditions

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Control</th>
<th>Enflurane</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>$\dot{V}E_1$</td>
<td>AHVR</td>
</tr>
<tr>
<td>928</td>
<td>20.0</td>
<td>28.2</td>
</tr>
<tr>
<td>956</td>
<td>15.4</td>
<td>11.4</td>
</tr>
<tr>
<td>960</td>
<td>10.7</td>
<td>12.6</td>
</tr>
<tr>
<td>965</td>
<td>11.4</td>
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</tr>
<tr>
<td>966</td>
<td>23.4</td>
<td>45.3</td>
</tr>
<tr>
<td>967</td>
<td>35.3</td>
<td>65.5</td>
</tr>
<tr>
<td>968</td>
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<tr>
<td>969</td>
<td>18.5</td>
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<td>981</td>
<td>15.9</td>
<td>17.5</td>
</tr>
<tr>
<td>Mean</td>
<td>20.9</td>
<td>20.1</td>
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<tr>
<td>SEM</td>
<td>2.0</td>
<td>3.3</td>
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Figure 2  Subject No. 960, individual responses. Minute averages. Ventilation ($\dot{V}E$), end-tidal carbon dioxide partial pressure ($P_e\text{CO}_2$) and end-tidal oxygen partial pressure ($P_e\text{O}_2$) during hypoxia (left) and euoxia (right) tests. Open symbols represent studies without enflurane and closed symbols studies with enflurane.
when no enflurane was administered. The biphasic responses to hypoxia were sometimes less obvious during enflurane sedation. The ventilatory responses to hypoxia were generally greater in the absence of enflurane than during enflurane sedation. In the absence of enflurane in the euoxia test ventilation increased gradually over the whole experimental period (fig. 3A), whereas in the presence of enflurane in the euoxia test, ventilation decreased gradually over most of the time (fig. 3A). In the presence of enflurane, the increase in $P_{E1}$ failed to increase ventilation substantially as was planned (fig. 3A).

Individual values for baseline ventilation, AHVR, HVD and off-responses together with their means are shown in table 3. There was a significant reduction in baseline ventilation ($F = 21.71, P < 0.001$), AHVR ($F = 13.04, P < 0.01$) and off-response ($F = 8.86, P < 0.02$) when comparing enflurane administration with control. In contrast with these findings for baseline ventilation, AHVR and the off-response, there was no significant difference in the magnitude of HVD between the two pharmacological conditions ($F = 1.697, \text{ns}$).

As an alternative to comparing absolute values for AHVR, HVD and off-response with and without enflurane, it is also possible to compare AHVR, HVD and off-responses with and without enflurane when they are expressed as ratios of baseline ventilation ($\hat{V}_E$) before hypoxia is imposed. Under these conditions AHVR/$\hat{V}_E$ and off-response/$\hat{V}_E$ were both reduced significantly by enflurane ($F = 12.85, P < 0.01; F = 12.12, P < 0.01$, respectively), demonstrating that the effect of enflurane was greater on AHVR and off-response than on baseline ventilation. In contrast with the significant findings for AHVR/$\hat{V}_E$ and off-response/$\hat{V}_E$, there was no significant effect for HVD/$\hat{V}_E$ ($F = 0.45, \text{ns}$). This suggests that our study could not distinguish between the magnitude of HVD remaining constant with and without enflurane and the magnitude of HVD diminishing in proportion to baseline ventilation.

In order to determine if our study could distinguish between HVD remaining constant and HVD changing in proportion to AHVR, we compared the effect of enflurane on HVD/AHVR. A parametric test of significance was inappropriate in this case because of a number of small values of AHVR giving rise to very large values for HVD/AHVR. To overcome this, a non-parametric test (Friedman test) was used, which demonstrated a significant increase in HVD/AHVR with enflurane ($S = 6.40, P < 0.02$).

In order to see if peripheral chemoreflex sensitivity to hypoxia remained unchanged during sustained hypoxia, we compared the magnitude of AHVR and off-response in both pharmacological conditions. The off-response was significantly smaller than AHVR in both cases ($t$ test, $P < 0.001$ without enflurane, $P < 0.01$ with enflurane). However, the ratio of off-response to AHVR did not differ significantly with and without enflurane ($F = 0.54, \text{ns}$), suggesting that the proportionate decline in the ventilatory sensitivity to hypoxia was unchanged by enflurane.

**Discussion**

The experiments were performed against a background of mild hypercapnia in order to increase the level of ventilation before induction of hypoxia. The idea behind this was that the magnitude of the rapid decrease in ventilation after relief of hypoxia would then not be limited by the need to maintain some basal level of ventilation, that is ventilation would then be able to decrease well below the pre-hypoxic level but still be above the normal eucapnic level. In this respect our study was unsuccessful, as the level of sedation was sufficiently intense effectively to bring ventilation back to basal levels despite the increase in end-tidal $P_{CO_2}$. Consequently, conclusions relating to the magnitude of the off-transient during enflurane sedation from this study should be drawn with care (see below).

In addition to performing the hypoxia experiments,
we also performed the experiments without hypoxia because we were aware of the possibility that ventilation under the condition of moderate hypercapnia might change gradually with time.10 24 25 These experiments enabled us to control for any gradual change in hypercapnia over time when interpreting the response to sustained hypoxia. We found that under moderate hypercapnic conditions, euoxic ventilation increased gradually over the whole experimental period in subjects exposed to no enflurane, and decreased gradually in subjects exposed to enflurane. This finding was unexpected, and raises the possibility that the effects of constant end-tidal enflurane were not steady throughout the exposure, but rather that the level of sedation increased progressively.

ACUTE HYPOXIC VENTILATORY RESPONSE (AHVR): EFFECT OF LOW-DOSE ENFLURANE

The observation that a sub-anaesthetic concentration of enflurane (0.2 MAC) markedly depressed the ventilatory response to acute hypoxia was no surprise.23 Knill, Manninen and Clement reported a 55% reduction in AHVR at 0.1 MAC of enflurane.2 We found a significant reduction in AHVR of 75%. In our previous study we observed that AHVR was reduced by 20%, 44% and 55% at 0.05, 0.1 and 0.2 MAC of enflurane, respectively.9 This indicated a steep dose–response curve for the effects of sub-anaesthetic concentrations of enflurane on hypoxic drive. The somewhat greater reduction in AHVR found in this study for 0.2 MAC of enflurane compared with our previous study may be because of different levels of stimulation of our subjects in the two studies. In the previous study subjects were asked to watch television and remain attentive, whereas in this study subjects were asked to close their eyes and the room was partially darkened and kept quiet.

HYPOXIC VENTILATORY DECLINE (HVD)

We were unable to detect a significant effect of 0.2 MAC of enflurane on hypoxic ventilatory decline. This is consistent with earlier studies on halothane,4 6 isoflurane7–9 and enflurane3 and supports the notion that AHVR and HVD can be targeted separately and may therefore arise via independent mechanisms. Thus in a functional sense, enflurane would appear to affect the ventilatory response to sustained hypoxia in a manner similar to that of dopamine,26 producing a reduction in AHVR while HVD is unchanged.

We have noted, however, that our study did not have sufficient power to distinguish between the magnitude of HVD remaining constant with and without enflurane and the magnitude of HVD diminishing with enflurane in proportion to baseline ventilation. Our statistical analysis does, however, demonstrate as unlikely that HVD is reduced by enflurane in proportion to AHVR. This in turn suggests that enflurane does not have the effect of modifying the whole ventilatory profile (VE1, AHVR, HVD) at all times by the same proportionate reduction.

It is important, however, to bear in mind one possible interpretation of our measurement of a relatively large HVD (5.5 litre min⁻¹, table 3) in the presence of enflurane, namely that there may have been a progressive intensification of the effect of enflurane on the peripheral chemoreflex during the hypoxia tests and this would have confounded our attempt to measure HVD in the presence of a constant level of anaesthesia. In effect the “acute” component of the ventilatory response to hypoxia may have been steadily declining through a progressive intensification of the effects of enflurane during the 20-min hypoxic exposure, rendering our measurement of HVD an overestimate. It is to be noted that, although the formula for calculating HVD allows for any progressive effects of enflurane on euoxic ventilation, it cannot allow for a progressive depression by enflurane of the peripheral chemoreflex. An experimental observation that supports this notion is that enflurane reversed the normal progressive increase in ventilation observed with hypercapnia during euoxia. The simplest interpretation of this finding is that the effects of enflurane are not steady, but becoming progressively more intense. However, we know of no evidence that the central neural effects of inhalation anaesthesia change progressively with time in the presence of a constant end-tidal pressure of the anaesthetic over the duration studied here.

AHVR 1/5 OFF-TRANSIENT: EFFECT OF LOW-DOSE ANAESTHETICS

Our observation that in the presence of enflurane the rapid decrease in ventilation at cessation of hypoxia was not similar in magnitude to AHVR seems at variance with the findings of Dahan and co-workers.8 They studied the effects of 0.15 MAC of halothane on the ventilatory response to sustained mild hypercapnic hypoxia (end-tidal \(P_{\text{CO}_2}\) 0.13 kPa above subject’s natural value). They observed a small ventilatory undershoot after relief of hypoxia in the absence of anaesthetic, but a larger undershoot in the presence of halothane. Their finding that there was no significant difference in the magnitude of AHVR and the off-response (AHVR = 3.6 litre min⁻¹; off-response = 3.9 litre min⁻¹) in the presence of halothane, suggested that the peripheral reflex sensitivity remained unchanged by sustained hypoxia under these conditions.

Our study was designed to provide sufficient elevation of pre-hypoxic ventilation to enable a symmetric off-transient to occur in the presence of enflurane without the limitation of hypopnoea or apnoea on the transition from hypoxia to euoxia. Under enflurane sedation, however, our technique of using moderate hypercapnia failed to achieve a substantial increase in ventilation above normal levels, and the design must therefore be regarded as having failed in this respect. The extent to which a persistent minimum ventilation linked to wakefulness (or “ventilatory dog-leg”, as it is often known in the context of studies of hypercapnic sensitivity) is retained in humans under sedation remains uncertain, and with it the extent to which ventilation would need to be increased to permit a symmetrical off-response after
a period of sustained hypoxia. It would be informative to repeat administration of enflurane in the presence of a substantially higher level of hypercapnia.

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