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Does a Subanesthetic Concentration of Isoflurane Blunt the Ventilatory Response to Hypoxia?

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The normal ventilatory response to the sudden imposition of sustained hypoxia is characterized by an acute increase followed by a modest decline in ventilation. Since subanesthetic concentrations of potent inhalational anesthetics greatly attenuate the acute response, we hypothesized that ventilation might decrease to less than normoxic levels when hypoxia is sustained. We therefore measured the ventilatory response to 20 min of sustained hypoxia ($P_{ET_{O_2}}$ 45 mmHg) at two levels of strict isocapnia—normocapnia ($P_{ET_{CO_2}}$ 1–2 mmHg above resting) and hypercapnia ($P_{ET_{CO_2}}$ 49 mmHg)—in eight healthy male subjects during inhalation of 0.1 MAC isoflurane or carrier gas (control). An abrupt end-tidal step from normoxia to isocapnic hypoxia was induced using a dynamic end-tidal forcing system. Isoflurane and control experiments were performed on separate days; the order of isoflurane and control days and the order of normocapnia and hypercapnia within days were randomized. Subjects were studied while fasted, always at the same time of day, and were required to watch a documentary videotape to minimize differences in level of consciousness. With normocapnia, there was no difference in ventilation at any time between isoflurane and control (prehypoxic 9.6 ± 1.5 *vs.* 9.5 ± 2.6 l/min, peak hypoxic 24.7 ± 10.4 *vs.* 26.2 ± 10.4 l/min, final hypoxic 15.0 ± 4.4 *vs.* 15.9 ± 3.5 l/min; mean ± SD). With hypercapnia, prehypoxic ventilation increased to the same level for isoflurane and control (24.8 ± 6.7 *vs.* 24.8 ± 9.6 l/min). Although peak hypoxic ventilation was slightly less in isoflurane than in control hypercapnic experiments, this was not significant (49.6 ± 16.3 *vs.* 56.5 ± 24.3 l/min; $P = .22$). But because ventilation also decreased slightly, but not significantly, more in isoflurane than in control hypercapnic experiments, final hypoxic ventilation was less with isoflurane (40.8 ± 13.1 *vs.* 48.5 ± 16.3 l/min; $P < .05$). Our data indicate that 0.1 MAC levels of isoflurane do not affect the ventilatory response to sustained normocapnic hypoxia or to normoxic hypercapnia but do reduce the ventilatory response to sustained hypercapnic hypoxia and may therefore attenuate the normal hypoxic-hypercapnic interaction. (Key words: Anesthetics, volatile: isoflurane. Lungs: ventilation. Oxygen: hypoxia.)

BASED UPON CLINICAL observation and a few experiments in animals anesthetized with barbiturates and opioids, it was long held that the ventilatory response to hypoxia was "rugged and resistant" to the effects of anesthetics.[1,2] In the late 1970s, however, Knill and colleagues began an extensive series of investigations to objectively quantify the ventilatory response to hypoxia in humans anesthetized or sedated with a variety of agents, chiefly the potent inhalational anesthetics.[1,3–7] Based principally on this work, it is now widely quoted that the human ventilatory response to hypoxia is, in fact, exquisitely sensitive to and selectively depressed by inhalational anesthetics.[8]

Anesthetic (1.1 MAC) levels of halothane, enflurane, and isoflurane effectively abolish the ventilatory response to hypoxia, and sedative (0.1 MAC) levels reduce the response by more than 50–80%.[4–6] Furthermore, the reduction in hypoxic sensitivity is much greater than the reduction in hypercapnic sensitivity for the same anesthetic level.[4–6] In particular, the usual synergistic effect of hypercapnia or acidosis on the hypoxic response may be especially vulnerable to inhalational anesthetics.[4,9] This selective attenuation of hypoxic sensitivity appears to occur at the carotid body itself.[10,11]

To measure the ventilatory response to hypoxia, Knill used a variation of Weil's technique of progressive isocapnic hypoxia induced over an 8–10 min period.[4,12] The limitation inherent to this technique is that it describes primarily the first half of the response, the carotid body response.[12] The full ventilatory response to isocapnic hypoxia is characterized by a brisk increase in ventilation for 3–5 min mediated by carotid body stimulation, followed by a relatively slower *decline* from peak ventilation over the next 10–20 min, ending in a final plateau ventilation usually above the normoxic level.[13]

The decline in ventilation has been termed hypoxic ventilatory decline and is mediated by central mechanism(s) that have been only partially elucidated.[14–16] In animals, the carotid body response phase and the hypoxic ventilatory decline phase appear to be independent and to combine in a purely additive fashion.[16] Thus, in the presence of unstimulated or functionally absent carotid bodies in animal preparations, hypoxia causes only a decline in ventilation.[16,17]

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The effects of inhalational anesthetics on the full hypoxic response, including hypoxic ventilatory decline, have not been studied. Knill found, however, that many human subjects anesthetized with halothane (1.1 MAC) showed a net decline in ventilation even over a short 8–10-min duration of progressive hypoxia, especially when hypoxia was superimposed on hypercapnia.[4,7] We surmised that this was due to hypoxic ventilatory decline unopposed by an abolished carotid body response. Since even subanesthetic concentrations of inhalational agents severely blunt the carotid body response, we hypothesized that ventilation during inhalational sedation might also fall below normoxic levels if hypoxia were sustained.

The purpose of this investigation was to determine the effect of subanesthetic concentrations of isoflurane (0.1 MAC) on the full ventilatory response to sustained isocapnic hypoxia (*i.e.*, the carotid body response as well as central hypoxic ventilatory decline) in human subjects under conditions of normocapnia or hypercapnia.

Materials and Methods

Eight healthy men (age 24 ± 5 yr, mean ± SD) participated in these experiments. The study protocol was approved by the UCLA Human Subjects Protection Committee, and subjects gave written informed consent before preliminary testing, which included a medical history, physical examination, resting ECG, and measurement of hemoglobin concentration. Subjects were naive to respiratory physiology, but each had participated in one or more previous studies, and all were thus accustomed to the laboratory apparatus and surroundings, as well as the sensations of hypoxia and/or hypercarbia. None were aware of the anticipated effects of isoflurane beyond the probability that they would feel drowsy.

Since variability of the acute hypoxic response can be considerable,[18] several measures were taken to standardize confounding physiologic factors. Subjects were studied after a minimum 4-hr fast and were asked to refrain from using a list of substances known or thought to be respiratory depressants or stimulants (*i.e.*, alcohol, marijuana, tobacco, chocolate, caffeine-containing drinks, diet pills, and all over-the-counter medications) for at least 16 hr prior to each session. Sessions were always scheduled at the same time of day for a given subject to minimize the potential for diurnal variability. Due to the theoretical concern of greater day-to-day variability,[18,19] possibly because progesterone modulates the acute hypoxic response,[20] women were excluded as subjects. Since sleep depresses the acute hypoxic response by 30–60% depending on sleep stage,[21,22] subjects were required to watch a documentary videotape to minimize differences in level of consciousness between control and isoflurane experiments. If a subject's eyes closed during any experiment, he was gently aroused by speaking his name or touching his arm; only rarely did this cause a discernible change in ventilation or breathing pattern. One subject could not be aroused in this manner (subject 3, during an isoflurane experiment); his results are not noticeably different from those of the others.

Respiratory Measurements

Subjects were seated in a semirecumbent position, and for safety, the ECG and arterial hemoglobin oxygen saturation (Ohmeda Biox 3700 pulse oximeter, Madison, WI) were monitored continuously during the experiments.

Subjects breathed from a high-flow gas mixing chamber through a low deadspace face mask (Vital Signs, 210 ml deadspace, Totawa, NJ). Inhaled and exhaled volumes were measured with a two-directional impeller flowmeter (Sensor Medics VMM 110, Laguna Hills, CA). Airway gases were sampled continuously by mass spectrometer (Perkin-Elmer MGA 1100, Pomona, CA). Flow volume and duration and airway gas concentrations were collected by computer using the TIDAL software package.[23] Breath phases and duration, as well as inspired and end-tidal gas concentrations, were determined from the mass spectrometer and flowmeter signals after correction for gas transport delay. An estimate of arterial hemoglobin oxygen saturation calculated from end-tidal gases using the method of Severinghaus and Naifeh,[24] exhaled minute ventilation, tidal volume, and breathing frequency were determined on a breath-by-breath basis and stored for later analysis. Gas volumes were corrected to body temperature, ambient pressure, and saturated conditions.

The technique of dynamic end-tidal forcing was used to control end-tidal O_2 and CO_2 tensions independent of changes in ventilation or mixed venous return. The concepts of dynamic end-tidal forcing have been described elsewhere;[25] the equipment currently used in the laboratory to achieve dynamic end-tidal forcing is diagrammed in figure 1. In brief, a computer-driven high-flow stepper-motor-valve gas mixing system adjusts the inspired concentration of CO_2 and O_2 on a breath-by-breath basis to force the desired end-tidal conditions. As ventilation changes, the system alters the composition of the inspired gas to maintain constant end-tidal tensions. A combination of predictive and adaptive control algorithms in the computer software allows precise regulation of end-tidal gas tensions over prolonged time periods and can also accomplish abrupt transitions in end-tidal O_2 and/or CO_2 (fig. 2).

The gas mixing chamber itself is conceptually equivalent to a T-piece but is capable of handling gas flows in excess of 400 l/min. To conserve isoflurane in this study, the chamber was modified to accept a fixed 6 l/min flow of N_2 from an isoflurane vaporizer (Ohio Medical Model

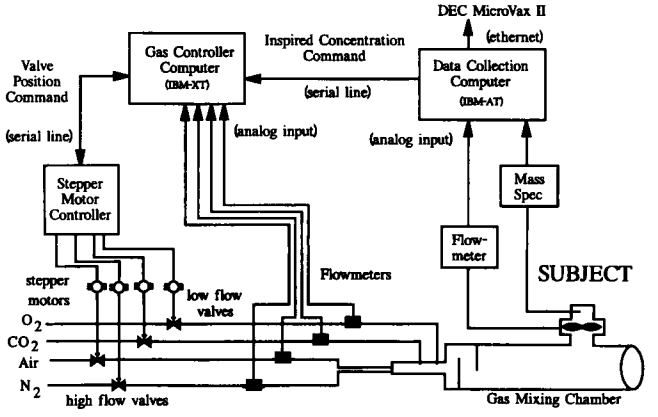

FIG. 1. A computer-controlled system for dynamic end-tidal forcing. The desired time course for end-tidal gases is preprogrammed in the data collection computer. The data computer determines the composition of inspired gases necessary to achieve the desired end-tidal concentrations and passes that composition to the gas controller computer. The controller computer determines the flow of each of four gases that will achieve the inspired gas composition and passes valve position commands to the stepper motor controller. The stepper motors can control the flow of each gas to within 10–20 ml/min for low flow valves (O_2 and CO_2) and to within 0.2–2.0 l/min, depending on flow, for the high flow valves (air and N_2). Solid state flowmeters provide instantaneous feedback to the gas controller computer, allowing readjustment of the flow valves up to 20 times per second. The data collection computer determines tidal volume, breath phase, and airway gas concentration from the mass spectrometer and flowmeter signals. An adaptive control algorithm adjusts inspired gas composition for discrepancies between desired and actual end-tidal concentrations. Figure 2 shows the two steps into hypoxia (normocapnic and hypercapnic) produced by the system for subject 1.

100F, Madison, WI); additional flow (a computer-controlled mixture of N_2, O_2, CO_2, and air) was limited to 60 ± 3 l/min. By constraining total system gas flow to 66 ± 3 l/min, a stable inspired concentration of isoflurane in the range of 0–0.5% could be achieved by hand adjustment of the vaporizer. With this configuration, entrainment of room air does not occur to measured ventilations greater than 150 l/min; chamber response time, however, is slow compared to that achieved with greater total flows (note that the first breath of the hypoxic steps in figure 2 does not reach 0 inspired O_2). Partial rebreathing can also occur at sufficiently high minute ventilations in this configuration, but this does not affect the ability to control end-tidal gas tensions. Gases are individually humidified before entering the chamber and exhausted to an outside ventilation system beyond the chamber.

PROTOCOL

Subjects completed two 40-min experiments separated by 40 min of rest on each of 2 days. Each experiment consisted of a 20-min period for uptake and equilibration of isoflurane or carrier gas (control), followed by an abrupt transition to a 20-min period of isocapnic hypoxia. The four experiments differed only in the presence or absence of isoflurane and in which of two levels of isocapnia was maintained for that experiment.

Control and isoflurane experiments were performed on separate days since residual brain levels of isoflurane prevent randomization within a reasonable time period on the same day.[3] The order of control and isoflurane days was randomized among subjects. To study the effect of isoflurane on the interaction between hypoxia and hypercapnia, both control and isoflurane experiments were performed at two levels of isocapnia. $P_{ET_{CO_2}}$ was maintained either 1–2 mmHg above the subject's resting $P_{ET_{CO_2}}$ (normocapnia) or at 49 mmHg (hypercapnia). The order of normocapnic and hypercapnic experiments was randomized within each study day.

For the first minute of all experiments, subjects breathed room air from the gas mixing system (a technical consideration). For the remaining 19 min of the uptake and equilibration period, $P_{ET_{O_2}}$ was controlled to 114 mmHg ($F_{ET_{O_2}}$ = 0.15), a value slightly greater than normal room air levels. At 20 min, $P_{ET_{O_2}}$ was abruptly stepped to the hypoxic value of 45 mmHg ($F_{ET_{O_2}}$ = 0.059), where it was maintained for the 20-min hypoxic period.

Following the first minute of all experiments, CO_2 was controlled to an *inspired* value of 7.6 mmHg (F_ICO_2 = 0.01) for 9 min. In our experience, this is the minimum amount of inspired CO_2 necessary to accomplish end-tidal CO_2 forcing with normal ventilatory fluctuations; it typically increases $P_{ET_{CO_2}}$ ~ 1 mmHg and increases resting ventilation ~ 1–2 l/min. For the remaining 10 min of the uptake and equilibration period, and for the 20-min hypoxic period, $P_{ET_{CO_2}}$ was held at the level achieved by the 1% CO_2 inhalation for normocapnic experiments or at 49 mmHg for hypercapnic experiments.

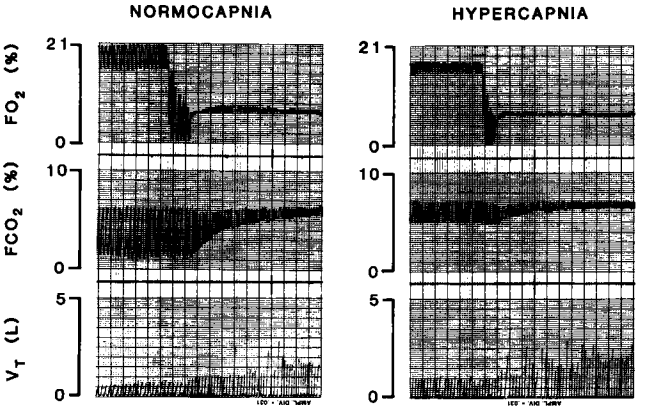

FIG. 2. Strip chart recording of airway O_2 (F_{O_2}), airway CO_2 (F_{CO_2}), and tidal volume (V_T) across hypoxic steps during a normocapnic experiment (*left*) and a hypercapnic experiment (*right*) in a representative subject (subject 1). One box equals 10 s at this paper speed.

For isoflurane experiments, isoflurane was added to the gas mixing chamber utilizing an over-pressure technique (maximum inspired concentration 0.4%) to bring the subject's end-tidal concentration to a target value of 0.125% (age-adjusted 0.1 MAC)[26] within 3–4 min. End-tidal isoflurane concentration was determined from the mass spectrometer signal and displayed on a breath-by-breath basis as feedback to the vaporizer operator (always J. A. T. or L. C. H.). The 20-min uptake and equilibration period thus provided four or five time constants for brain uptake at a constant end-tidal isoflurane concentration.[27] For control experiments, the same carrier gas (N_2 at 6 l/min) was directed through the vaporizer and added to the gas mixing chamber, but the vaporizer remained in the "off" position.

Statistical Analysis

Three time periods were defined for use in statistical comparisons: the 2 min immediately prior to the hypoxic step (prehypoxic); the four contiguous 30-s segments (*i.e.*, 2 min) with the highest average minute ventilation (peak hypoxic); and the final 5 min of hypoxia (final hypoxic). Breath-by-breath data for each subject were averaged over these intervals. No peak hypoxic ventilation fell outside the first 7 min of hypoxia. Comparisons between time intervals and between control and isoflurane experiments were performed using ANOVA with post-hoc Newman-Keuls testing. Significance was accepted at the 0.05 level. Statistical analysis was performed with the SOLO computer software (BMDP Statistical Software, Los Angeles, CA).

Results

$P_{ET_{O_2}}$ and $P_{ET_{CO_2}}$ did not differ between control and isoflurane at any time for either normocapnic or hypercapnic experiments (table 1). The greater variability of $P_{ET_{CO_2}}$ and calculated Sa_{O_2} during normocapnic experiments reflects differences in the subjects' resting $P_{ET_{CO_2}}$ (and therefore differences in target CO_2 control level) rather than the accuracy of dynamic end-tidal forcing. Calculated hemoglobin oxygen saturation was significantly less for the same $P_{ET_{O_2}}$ during hypercapnic experiments due to the Bohr effect on the hemoglobin dissociation curve.

End-tidal isoflurane concentration was 0.124 ± 0.005% for isoflurane experiments during normocapnia and 0.123 ± 0.005% for isoflurane experiments during hypercapnia. End-tidal isoflurane concentration was 0 for control experiments (fig. 3).

With normocapnia (fig. 3 and table 2), there was no difference in mean ventilation, tidal volume, or breathing frequency between control and isoflurane experiments. Neither the acute stimulation nor the subsequent decline in ventilation was affected by isoflurane. As shown in figure 4, only one subject demonstrated the marked blunting of the acute hypoxic response expected with isoflurane (subject 6). Conversely, one subject exhibited a markedly *greater* hypoxic response with isoflurane (subject 1). The responses of the other subjects were consistent with the mean data.

During hypercapnic experiments (fig. 3 and table 2), ventilation began at a similar level for control and isoflurane and increased to the same level with the imposition of hypercapnia during the prehypoxic period. Thus, the ventilatory response to hypercapnia was unchanged by isoflurane. Peak hypoxic ventilation during hypercapnia was reduced with isoflurane but the difference from control was not statistically significant ($P = .22$). Final hypoxic ventilation during hypercapnia, however, was significantly lower with isoflurane.

TABLE 1. Mean End-tidal CO_2 ($P_{ET_{CO_2}}$), End-tidal O_2 ($P_{ET_{O_2}}$), and Hemoglobin Oxygen Saturation (Sa_{O_2}) during Normocapnic and Hypercapnic Experiments

	Normocapnia		Hypercapnia	
	Control	Isoflurane	Control	Isoflurane
$P_{ET_{CO_2}}$ (mmHg)				
Prehypoxic	41.6 ± 1.7	41.3 ± 2.0	49.0 ± 0.3	49.0 ± 0.1
Peak hypoxic	42.1 ± 1.4	41.8 ± 2.0	49.1 ± 0.2	49.2 ± 0.3
Final hypoxic	41.6 ± 1.6	41.6 ± 2.0	49.0 ± 0.0*	49.0 ± 0.0*
$P_{ET_{O_2}}$ (mmHg)				
Prehypoxic	113.2 ± 0.9	113.3 ± 1.3	114.1 ± 0.4	114.0 ± 0.6
Peak hypoxic	44.7 ± 0.2	44.7 ± 0.1	45.0 ± 0.2	44.9 ± 0.1
Final hypoxic	45.0 ± 0.1	45.1 ± 0.2	45.0 ± 0.0*	45.0 ± 0.1
Sa_{O_2}‡ (%)				
Prehypoxic	98.4 ± 0.1	98.4 ± 0.2	98.2 ± 0.9	97.8 ± 0.0*
Peak hypoxic	79.6 ± 1.1	79.8 ± 1.6	74.4 ± 0.3†	74.1 ± 0.3†
Final hypoxic	80.2 ± 1.2	80.1 ± 1.3	74.5 ± 0.1†	74.5 ± 0.1†

Values are mean ± SD
* SD less than 0.05.
† Significantly different from normocapnic value, $P < .05$.
‡ Hemoglobin O_2 saturation calculated from end-tidal P_{CO_2} and P_{O_2}.

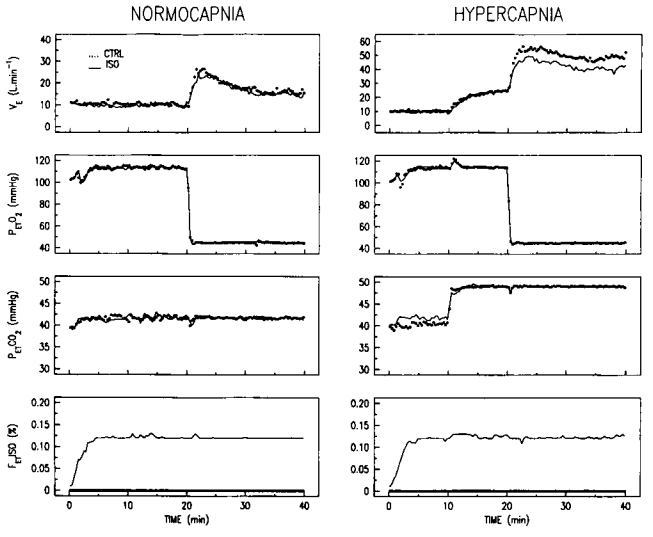

FIG. 3. Mean minute ventilation (V_E), end-tidal O_2 (PET_{O_2}), end-tidal CO_2 (PET_{CO_2}), and end-tidal isoflurane (FET_{ISO}) concentration for normocapnic (*left*) and hypercapnic (*right*) experiments. Open circles = control experiments; solid lines = isoflurane experiments. Data presented are ensemble averages of individual breath-by-breath data for eight subjects, time-averaged over 20-s intervals.

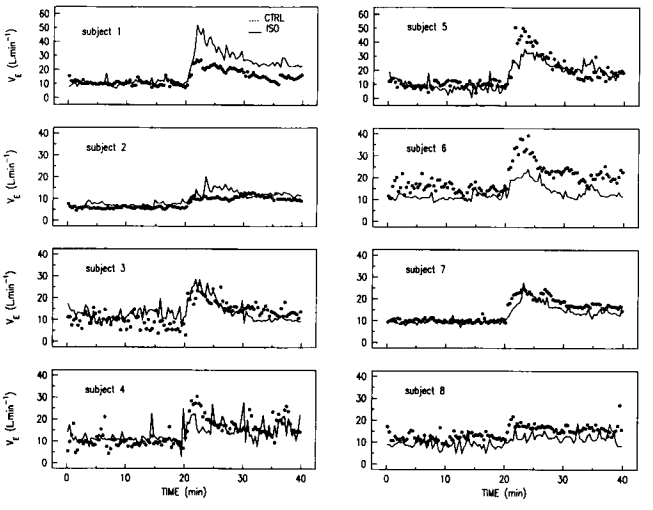

FIG. 4. Minute ventilation (V_E) for each of eight individual subjects for control (open circles) and isoflurane (solid lines) experiments during normoxia. Data presented are individual breath-by-breath data, time-averaged over 20-s intervals.

Hypoxic ventilatory decline occurred due to a significant reduction in tidal volume without a significant change in breathing frequency (table 2). The magnitude of the decline was unaffected by isoflurane.

Discussion

We designed these experiments to study the two phases of the ventilatory response to sustained hypoxia in humans. To do so, we sought to take advantage of a well established and widely quoted drug effect—namely, the selective attenuation of the acute ventilatory response to hypoxia by inhalational anesthetics.[4–6] To our knowledge the effect of any of these drugs on the ventilatory response to sustained hypoxia has not been previously investigated. We expected the acute hypoxic response to be reduced by at least 50–80% with subanesthetic isoflurane[4–6] and hypothesized that final ventilation might decrease to less than normoxic levels because of the effect of hypoxic ventilatory decline.

TABLE 2. Mean Minute Ventilation (V_E), Tidal Volume (V_T), and Breathing Frequency (f_R) during Normocapnic and Hypercapnic Experiments

	Normocapnia		Hypercapnia	
	Control	Isoflurane	Control	Isoflurane
V_E (l/min)				
Prehypoxic	9.5 ± 2.6	9.6 ± 1.5	24.8 ± 9.6	24.8 ± 6.7
Peak hypoxic	26.2 ± 10.4	24.7 ± 10.4	56.5 ± 24.3	49.6 ± 16.3
Final hypoxic	15.9 ± 3.5*	15.0 ± 4.4*	48.5 ± 16.3	40.8 ± 13.1*†
Δ	10.3 ± 8.1§	9.7 ± 7.2§	7.9 ± 10.9§	8.8 ± 9.2§
V_T (l)				
Prehypoxic	0.53 ± 0.22	0.53 ± 0.11	1.17 ± 0.51	1.11 ± 0.33
Peak hypoxic	1.27 ± 0.75	1.06 ± 0.34	2.15 ± 0.94	1.93 ± 0.72
Final hypoxic	0.83 ± 0.33*	0.75 ± 0.18*	1.80 ± 0.64*	1.61 ± 0.53*‡
Δ	0.44 ± 0.44§	0.31 ± 0.57§	0.36 ± 0.33§	0.33 ± 0.27§
f_R (min^{-1})				
Prehypoxic	16 ± 3	16 ± 2	19 ± 4	19 ± 3
Peak hypoxic	19 ± 5	20 ± 5	23 ± 5	22 ± 5
Final hypoxic	18 ± 4	18 ± 4	23 ± 5	22 ± 4
Δ	1 ± 2	2 ± 4	0 ± 2	0 ± 3

Values are mean ± SD.
Δ = peak hypoxic value minus final hypoxic value.
* Significantly different from peak hypoxic values, $P < .05$.
† Significantly different from control value, $P < .05$.
‡ NS *versus* control value, $P = .06$.
§ Significantly different from 0, $P < .05$, one-tailed t test.

Surprisingly, the subjects did not demonstrate the well established drug effect. The eight subjects responded to normocapnic hypoxia very similarly with and without 0.1 MAC isoflurane; neither the acute increase nor the subsequent decrease in ventilation was affected. Moreover, even in the one circumstance in which isoflurane significantly reduced ventilation (*i.e.*, the final hypoxic ventilation during hypercapnic experiments), the magnitude of the reduction was much less than 50%. The lack of dramatic effect was consistent among subjects (fig. 4).

Since our experiments anticipated a large isoflurane effect, and therefore, were not designed in a way to detect a small effect, it is legitimate to ask how large an isoflurane effect the study might have missed (type II error). The acute individual isoflurane responses in normocapnic experiments ranged from 0.49 to 2.18 times control response, with a mean response of 0.99 times control and a standard deviation of 0.53. The 95% confidence limits calculated from these normocapnic values place the true (population) isoflurane response between 0.55 and 1.43 times control. Similarly, 95% confidence limits for the hypercapnic experiments place the true (population) isoflurane response between 0.60 and 1.05 times acute control response. Although broad, these confidence intervals clearly exclude Knill's corresponding inhalational values of ~0.20–0.50 times control (*i.e.*, 50–80% reductions).[4–6]

Thus, the major finding of the study is the inability to reproduce the large, dramatic reductions of the acute hypoxic ventilatory response previously reported with 0.1 MAC concentrations of inhalational agents. A small to moderate reduction, however, can not be excluded by the data.

The total number of individual subjects in Knill's extensive series of experiments was 121.[28] Thus, as he has recently stated, any uncertainty in the result "would seem to arise not so much from the type and number of subjects studied previously as from the fact that all reported (human) studies have been undertaken by a single group."[28] Nevertheless, the number of subjects Knill studied specifically at 0.1 MAC isoflurane was only five,[5] and the effect he found was somewhat less than he found with halothane and enflurane at 0.1 MAC.[4,6] Although Knill does not report the variability of effect in his subjects, it seems probable that his isoflurane confidence limits would overlap with ours in the area of a 20–30% reduction. Thus, one possible explanation is that isoflurane, in contrast to enflurane and halothane, may produce a small reduction at 0.1 MAC—a reduction that we did not detect and which Knill over-estimated. At other concentrations, however, Knill repeatedly and consistently found similar effects with all three halogenated agents.[3–7,10,28] Therefore, we have carefully examined other reasons why our experiments with isoflurane did not demonstrate an effect.

Recently, two independent groups have also reported results (animal and human) apparently at odds with those of Knill's group. In contrast to Knill's 0.1 MAC results in humans, Koh and Severinghaus found 0.5% halothane (~0.5 MAC) did not significantly depress the hypoxic response in goats.[29] This finding could be attributed to a species difference. Indeed, in prior studies in dogs[30,31] and cats,[11] deep inhalational anesthesia (1.0–2.5 MAC) significantly depressed but never abolished the hypoxic response, suggesting the human response might be uniquely sensitive to inhalational agents. Most recently, however, Sjogren *et al.* have claimed that human hypoxic drive is *not* depressed by 1% isoflurane.[32] The interpretation of Sjogren's study is severely limited because isocapnia was not maintained and end-tidal CO_2 differed significantly between awake and isoflurane states, but an increase in ventilation and inspiratory drive was not abolished when hypoxia was induced under isoflurane anesthesia.

Because the difference between our results and those of Knill's group may be related to methodologic differences, a careful comparison of the methods employed is warranted. The method of randomization we used was very similar to that used in all of Knill's studies, with control and isoflurane experiments conducted on different days. Since variability of the hypoxic response is greater between days than within days,[18] this experimental design biased each study toward not finding a significant drug effect. We have already noted the broad confidence limits of our study; presumably, Knill's confidence limits were no better, especially as he studied fewer subjects at isoflurane 0.1 MAC. Theoretically, the confidence limits for either set of experiments would have been narrowed by performing control and isoflurane experiments on the same day, or by studying more subjects.

Both our protocol and Knill's allowed at least 20 min for anesthetic uptake and equilibration, and stable end-tidal concentrations of isoflurane were achieved well before hypoxic tests were performed.[5,27] We used an age-adjusted isoflurane MAC of 1.28%[26] and achieved 0.124 ± 0.005% as our average 0.1 MAC end-tidal concentration; Knill *et al.*[5] do not specifically report an end-tidal isoflurane concentration at 0.1 MAC, but achieved an end-tidal concentration of 1.30 ± 0.1% at 1.1 MAC, suggesting a 0.1 MAC value slightly less than ours.

Although we did not monitor the EEG, we made an effort to ensure a comparable state of consciousness between control and isoflurane sedation, and with one exception, we believe our subjects were fundamentally awake. Whatever state of consciousness was achieved, however, we do not believe it differed significantly from that of Knill's subjects who during inhalational sedation were "drowsy . . . but easily rousable (with) full recall of the experiment afterwards"[3] and who were able to sit

in a chair throughout the experiment.[3,5] Although sleep significantly reduces hypoxic sensitivity,[21,22] it also reduces hypercapnic sensitivity[33]; neither we nor Knill saw a reduction in hypercapnic sensitivity with 0.1 MAC isoflurane. Audiovisual stimulation, such as our documentary videotape, may minimally alter breathing pattern, but does not affect overall minute ventilation.[34]

The equipment we used was considerably different from that used by Knill's group. The combination of high gas flows, precise stepper motor valves, and several loops of feed-forward/feed-back computer control allows our dynamic end-tidal forcing system to adjust inspired gases on a breath-by-breath basis, producing very accurate and reproducible end-tidal (arterial) stimuli. Knill controlled inspired gases by hand adjustment.[4] Our data allow us to calculate that a 1 mmHg difference in isocapnic level between isoflurane and control experiments would produce a 25–30% difference in peak hypoxic response; thus, a consistent bias of 2–3 mmHg in end-tidal CO_2 would need to exist to conceal or to create an effect as dramatic as Knill found. While we believe automated control is preferable, we find it implausible that this methodologic difference alone could result in such a large bias in either study without detection. Finally, although Knill's experiments typically began in hyperoxia ($F_IO_2 \sim 0.95$) and our experiments began from normoxia, one set of Knill's halothane experiments did begin in normoxia and the results are not dramatically different.[4]

One methodologic difference, however, may be significant. In our study, hypoxia was induced as an abrupt step in end-tidal oxygen achieved by several breaths of no inspired oxygen (fig. 2). In the two recent studies cited above, hypoxia was induced as an abrupt step to a new inspired oxygen.[29,34] In Knill's studies, however, hypoxia was induced as a gradual ramp decline in oxygen over 8–10 min.[4,5,12] To our knowledge, the correlation between ventilatory responses to the gradual *versus* sudden onset of hypoxia has not been studied. Some evidence, however, suggests the rate of change in hypoxic stimuli may affect the resultant ventilation. Bertholon *et al.* exposed human subjects to a staircase sequence of hypoxic levels and found the highest ventilation achieved differed significantly depending on the length of time spent at each level even though the levels of hypoxia were the same.[35] Moreover, children with congenital central hypoventilation syndrome (CCHS) have no consistent ventilatory response to gradual onset of hypoxia[36] but have a nearly normal response to abrupt changes into hypoxia.[37] If a lesion or anomaly in children with CCHS produces a different response to a gradual *versus* sudden onset of hypoxia, could isoflurane produce a similar difference?

A simple explanation for such a difference might be offered by the biphasic nature of the ventilatory response to hypoxia itself. The expression of these two phases is subtly different when hypoxia is induced gradually (*i.e.*, as a "ramp") than when it is induced abruptly (*i.e.*, as a "step"). Because hypoxic ventilatory decline is induced gradually over the course of a slow ramp, the peak ventilation of a ramp represents not only the acute increase in ventilation but also some hypoxic ventilatory decline, the amount of decline depending inversely on the rate of the ramp. For a step, on the other hand, the peak ventilation represents almost exclusively the acute increase. Thus, the peak ventilatory response to a step will be greater than to a ramp to the same hypoxic level. If isoflurane delayed the time course of the acute hypoxic response or sped the onset of hypoxic ventilatory decline, then one *should* find different peaks depending upon how hypoxia is induced. Our data, however, show no difference in time course or magnitude of either the acute response or the decline with isoflurane (figs. 3 and 4).

Although the lack of an attenuation in hypoxic sensitivity by subanesthetic isoflurane is the most interesting finding of the study, the data demonstrate several other points as well. Hypercapnic sensitivity also was unaffected by subanesthetic isoflurane since prehypoxic ventilation was the same for isoflurane and control hypercapnic experiments; this is in agreement with Knill's findings for all inhalational agents.[4–6] And although peak hypoxic ventilation during hypercapnic hypoxia was not statistically different between isoflurane and control, final hypoxic ventilation was lower with isoflurane. This is consistent with previous findings that the normal hypoxic-hypercapnic interaction is especially sensitive to depression by inhalational anesthetics.[4,30,31]

A new finding of this study is the demonstration that subanesthetic (0.1 MAC) isoflurane did not significantly affect hypoxic ventilatory decline. Given the generalized depressant effects of inhalational anesthetics on the CNS, this may be surprising. On the other hand, the available evidence from animal and human studies suggests hypoxic ventilatory decline is mediated by an accumulation of inhibitory neurotransmitters, possibly GABA[17,38,39] or adenosine,[40] near the respiratory centers in the medulla. If so, the effect may be receptor and/or pathway specific. Dahan and Ward have shown that midazolam, presumably by modulation of GABA-A receptors, exaggerates hypoxic ventilatory decline in humans.[41] Although inhalational agents have been shown to increase synaptosomal GABA concentrations,[42] this may not be a significant effect at this level of isoflurane. The dose-response curve for the effect of isoflurane on the ventilatory response to sustained hypoxia, including hypoxic ventilatory decline, should be investigated.

In summary, we could not demonstrate that subanesthetic (0.1 MAC) concentrations of isoflurane affect either

the acute hypoxic response or hypoxic ventilatory decline, if hypoxia is induced as an abrupt step from normoxia under conditions of normocapnia. In addition, 0.1 MAC isoflurane did not affect the increase in ventilation seen with hypercapnia. However, when hypoxia was superimposed on hypercapnia, isoflurane reduced the final hypoxic ventilation. The data suggest a specific effect of isoflurane on the hypoxic-hypercapnic interaction. The difference between our results and those of Knill's group may indicate that subanesthetic isoflurane's effect on acute hypoxic sensitivity is less than previously reported, or may be related to a difference in the rate of change of the hypoxic stimulus between the two studies, such that the ventilatory response to an abrupt step into hypoxia is different from the response to a more gradual ramp into hypoxia.

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References

1. Knill RL, Clement JL: Variable effects of anaesthetics on the ventilatory response to hypoxaemia in man. Can Anaesth Soc J 29: 93–99, 1982
2. Comroe JH: The peripheral chemoreceptors, Handbook of Physiology, Section 3: Respiration Volume I. Washington, DC, American Physiological Society, 1964, pp 557–583
3. Gelb AW, Knill RL: Subanesthetic halothane: Its effect on regulation of ventilation and relevance to the recovery room. Can Anaesth Soc J 25:488–494, 1978
4. Knill RL, Gelb AW: Ventilatory responses to hypoxia and hypercapnia during halothane sedation and anesthesia in man. ANESTHESIOLOGY 49:244–251, 1978
5. Knill RL, Kieraszewicz HT, Dodgson BG, Clement JL: Chemical regulation of ventilation during isoflurane sedation and anaesthesia in humans. Can Anaesth Soc J 30:607–614, 1983
6. Knill RL, Manninen PH, Clement JL: Ventilation and chemoreflexes during enflurane sedation and anaesthesia in man. Can Anaesth Soc J 26:353–360, 1979
7. Knill RL, Clement JL, Gelb AW: Ventilatory responses mediated by peripheral chemoreceptors in anaesthetized man. Adv Exp Med Biol 99:67–77, 1978
8. Knill RL, Gelb AW: Peripheral chemoreceptors during anesthesia: Are the watchdogs sleeping? (editorial). ANESTHESIOLOGY 57: 151–152, 1982
9. Knill RL, Clement JL: Ventilatory responses to acute metabolic acidemia in humans awake, sedated, and anesthetized with halothane. ANESTHESIOLOGY 62:745–753, 1985
10. Knill RL, Clement JL: Site of selective action of halothane on the peripheral chemoreflex pathway in humans. ANESTHESIOLOGY 61:121–126, 1984
11. Davies RO, Edwards MW, Jr., Lahiri S: Halothane depresses the response of carotid body chemoreceptors to hypoxia and hypercapnia in the cat. ANESTHESIOLOGY 57:153–159, 1982
12. Weil JV, Byrne-Quinn E, Sodal IE, Friesen WO, Underhill B, Filley GF, Grover RF: Hypoxic ventilatory drive in normal man. J Clin Invest 49:1061–1072, 1970
13. Easton PA, Slykerman LJ, Anthonisen NR: Ventilatory response to sustained hypoxia in normal adults. J Appl Physiol 61:906–911, 1986
14. Neubauer JA, Melton JE, Edelman NH: Modulation of respiration during brain hypoxia. J Appl Physiol 68:441–451, 1990
15. Vizek M, Pickett CK, Weil JV: Biphasic ventilatory response of adult cats to sustained hypoxia has central origin. J Appl Physiol 63:1658–1664, 1987
16. Ward DS, Berkenbosch A, DeGoede J, Olievier CN: Dynamics of the ventilatory response to central hypoxia in cats. J Appl Physiol 68:1107–1113, 1990
17. Melton JE, Neubauer JA, Edelman NH: GABA antagonism reverses hypoxic respiratory depression in the cat. J Appl Physiol 69:1296–1301, 1990
18. Sahn S, Zwillich C, Dick N, McCullough R, Lakshminarayan S, Weil J: Variability of ventilatory responses to hypoxia and hypercapnia. J Appl Physiol 43:1019–1025, 1977
19. Schoene RB, Robertson HT, Pierson DJ, Peterson AP: Respiratory drives and exercise in menstrual cycles of athletic and nonathletic women. J Appl Physiol 50:1300–1305, 1981
20. Javaheri S, Guerra LF: Effects of domperidone and medroxyprogesterone acetate on ventilation in man. Respir Physiol 81:359–370, 1990
21. Berthon-Jones M, Sullivan CE: Ventilatory and arousal responses to hypoxia in sleeping humans. Am Rev Respir Dis 125:632–639, 1982
22. Douglas NJ, White DP, Weil JV, Pickett CK, Martin RJ, Hudgel DW, Zwillich CW: Hypoxic ventilatory response decreases during sleep in normal men. Am Rev Respir Dis 125:286–289, 1982
23. Jenkins JS, Valcke CP, Ward DS: A programmable system for acquisition and reduction of respiratory physiological data. Ann Biomed Eng 17:93–108, 1989
24. Severinghaus JW, Naifeh KH: Accuracy of response of six pulse oximeters to profound hypoxia. ANESTHESIOLOGY 67:551–558, 1987
25. Swanson GD, Bellville JW: Step changes in end-tidal CO2: Methods and implications. J Appl Physiol 39:377–385, 1975
26. Stevens WC, Dolan WM, Gibbons RT, White A, Eger EI, II, Miller RD, DeJong RH, Elashoff RM: Minimum alveolar concentrations (MAC) of isoflurane with and without nitrous oxide in patients of various ages. ANESTHESIOLOGY 42:197–200, 1975
27. Eger EI, II: Anesthetic Uptake and Action. Baltimore, Williams & Wilkins, 1974, pp 82–89
28. Knill RL: Uncertainties about the ventilatory response to hypoxaemia (letter). Br J Anaesth 67:223–224, 1991
29. Koh SO, Severinghaus JW: Effect of halothane on hypoxic and hypercapnic ventilatory responses of goats. Br J Anaesth 65: 713–717, 1990
30. Hirshman CA, McCullough RE, Cohen PJ, Weil JV: Depression of hypoxic ventilatory response by halothane, enflurane and isoflurane in dogs. Br J Anaesth 49:957–963, 1977
31. Weiskopf RB, Raymond LW, Severinghaus JW: Effects of halothane on canine respiratory responses to hypoxia with and without hypercarbia. ANESTHESIOLOGY 41:350–360, 1974
32. Sjogren D, Ebberyd A, Sollevi A, Lindahl SGE: Ventilatory responses to hypoxia in awake and anesthetized humans (abstract). ANESTHESIOLOGY 75:A1102, 1991
33. Gothe B, Altose MD, Goldman MD, Cherniack NS: Effect of quiet sleep on resting and CO2-stimulated breathing in humans. J Appl Physiol 50:724–730, 1981
34. Mador MJ, Tobin MJ: Effect of alterations in mental activity on

the breathing pattern in healthy subjects. Am Rev Respir Dis 144:481–487, 1991

35. Bertholon JF, Eugene M, Labeyrie E, Teillac A: A dynamic analysis of the ventilatory response to hypoxia in man. J Physiol (Lond) 408:473–492, 1989
36. Paton JY, Swaminathan S, Sargent CS, Keens TG: Hypoxic and hypercapnic ventilatory responses in awake children with congenital central hypoventilation syndrome. Am Rev Respir Dis 140:368–372, 1989
37. Gozal D, Marcus CL, Shoseyov D, Keens TG: Intact peripheral chemoreceptor function in children with the congenital central hypoventilation syndrome (abstract). Clin Res 40:68A, 1992
38. Taviera da Silva AM, Hartley B, Hamosh P, Quest JA, Gillis RA: Respiratory depressant effects of GABA A- and B-receptor agonists in the cat. J Appl Physiol 62:2264–2272, 1987
39. Yamada KA, Norman WP, Hamosh P, Gillis RA: Medullary ventral surface GABA receptors affect respiratory and cardiovascular function. Brain Res 248:71–78, 1982
40. Easton PA, Anthonisen NR: Ventilatory response to sustained hypoxia after pretreatment with aminophylline. J Appl Physiol 64:1445–1450, 1988
41. Dahan A, Ward DS: Effect of I.V. midazolam on the ventilatory response to sustained hypoxia in man. Br J Anaesth 66:454–457, 1991
42. Cheng S-C, Brunner EA: Effects of anesthetic agents on synaptosomal GABA disposal. ANESTHESIOLOGY 55:34–40, 1981