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Effects of Subanesthetic Halothane on the Ventilatory Responses to Hypercapnia and Acute Hypoxia in Healthy Volunteers

Albert Dahan, M.D., Ph.D., Maarten J. L. J. van den Elsen, M.D.,* Aad Berkenbosch, Ph.D.,† Jacob DeGoede, Ph.D.,† Ida C. W. Olievier,‡ Jack W. van Kleef, M.D., Ph.D.,§ James G. Bovill, M.D., Ph.D.‖*

Background: **The peripheral chemoreceptors are responsible for the ventilatory response to hypoxia (acute hypoxic response) and for 30% of the normoxic hypercapnic ventilatory response. To quantify the effects of subanesthetic concentrations of halothane on the respiratory control system, in particular on the peripheral chemoreceptors, we studied the response of humans to carbon dioxide and oxygen at two subanesthetic concentrations of halothane.**

Methods: **Square-wave changes in end-tidal carbon dioxide tension (7.5–11.3 mmHg) and step decreases in end-tidal oxygen tension (arterial hemoglobin oxygen saturation 82 ± 2%; duration of hypoxia 5 min) were performed in nine healthy male subjects during 0, 0.05 (HA-1), and 0.1 minimum alveolar concentration (HA-2) halothane. Each hypercapnic response was separated into a fast, peripheral component and a slow, central component, characterized by a time constant, carbon dioxide sensitivity, time delay, and off-set.**

Results: **Fifty-six carbon dioxide responses and 27 oxygen responses were obtained. The peripheral carbon dioxide sensitivities averaged to 0.76 ± 0.14 $l \cdot min^{-1} \cdot mmHg^{-1}$ (control), 0.50 ± 0.12 $l \cdot min^{-1} \cdot mmHg^{-1}$ (HA-1), and 0.30 ± 0.08 $l \cdot min^{-1} \cdot mmHg^{-1}$ (HA-2; $P < 0.01$ *vs.* control). The central carbon dioxide sensitivity did not differ significantly among treatment groups (control, 1.47 ± 0.22 $l \cdot min^{-1} \cdot mmHg^{-1}$; HA-1, 1.41 ± 0.51 $l \cdot min^{-1} \cdot mmHg^{-1}$; and HA-2, 1.23 ± 0.30 $l \cdot min^{-1} \cdot mmHg^{-1}$). The time constants of the central chemoreflex loop showed a large decrease during the administration of 0.1 minimum alveolar concentration halothane. The acute hypoxic response declined from 15.0 ± 3.9 $l \cdot min^{-1}$ to 10.9 ± 2.9 $l \cdot min^{-1}$ (HA-1) and 4.8 ± 1.4 $l \cdot min^{-1}$ (HA-2; $P < 0.01$ *vs.* control and HA-1). All values are means ± SEM.**

Conclusions: **The results show depression of the ventilatory responses to hypoxia and hypercapnia during inhalation of subanesthetic concentrations of halothane. The depression is attributed to a selective effect of halothane on the peripheral chemoreflex loop. The oxygen and carbon dioxide responses mediated by the peripheral chemoreceptors are affected proportionally. It is argued that the decrease in central time constants is caused by an effect of halothane on central neuronal dynamics. (Key words: Anesthetics, volatile: halothane. Lung, ventilation: acute hypoxic response, hypercapnic response. Methods: dynamic end-tidal forcing. Receptors: peripheral chemoreceptors, central chemoreceptors.)**

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SEVERAL studies have dealt with the effects of volatile anesthetics on the chemical control of breathing. Duffin *et al.*[1] showed in humans that the ventilatory response to two breaths of oxygen was absent during inhalation of 1 minimum alveolar concentration (MAC) halothane. Knill and coworkers[2–6] investigated the effects of halothane, enflurane, and isoflurane on the hypoxic ventilatory response and the hypercapnic ventilatory response in humans. They found that 0.1 MAC of any of these three halogenated anesthetic agents reduced the hypoxic ventilatory response by 50–75% without much affecting the hypercapnic ventilatory response. Inhalation of 1.1 and 2.0 MAC abolished the response to oxygen and severely blunted the response to carbon dioxide. They concluded that these volatile anesthetics selectively and severely depress the peripheral che-

* Resident, Department of Anesthesiology, University Hospital Leiden.

† Associate Professor of Physiology, Department of Physiology, University of Leiden.

‡ Technical Assistant, Department of Physiology, University of Leiden.

§ Professor of Anesthesiology and Chairman, Department of Anesthesiology, University Hospital Leiden.

‖ Professor of Anesthesiology, Department of Anesthesiology, University Hospital Leiden.

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Address reprint requests to Dr. Dahan: Department of Anesthesiology, University Hospital Leiden, P.O. Box 9600, 2300 RC Leiden, The Netherlands.

moreflex loop in humans at subanesthetic concentrations.[7] Furthermore, in animal studies, there are indications that halothane has a depressant effect on the peripheral chemoreceptors. Davies *et al.*[8] showed in cats that 0.5–1.0% halothane inhalation reduced chemoreceptor activity recorded from single-fiber preparations of the sinus nerve during hypoxia to 58% of control response. In dog studies, halothane completely abolished the interactive effect of oxygen and carbon dioxide on minute ventilation ($\dot{V}_E$).[9,10]

On the other hand, Clergue *et al.*[11] found that during halothane anesthesia (inspired fraction [F_I] 1.5%) in humans, administration of oxygen after breathing air resulted in a small but significant decrease in $\dot{V}_E$. This suggests that the peripheral chemoreflex loop still is active during the inhalation of a high concentration of halothane. Temp *et al.*[12] were not able to show in humans an effect on the ventilatory response to a step decrease in end-tidal partial pressure of oxygen ($P_{ET_{O_2}}$) during exposure to 0.1 MAC isoflurane. In addition, at higher doses of isoflurane (0.6–1.2 MAC), the hypoxic ventilatory response was not abolished completely in humans.[13–15] In cats, Berkenbosch and coworkers[16,17] found that 0.5–1.5% halothane depressed the central and peripheral chemoreflex loops to the same extent. A recent study in goats did not reveal depression of the hypoxic ventilatory response during 0.5% halothane inhalation.[18] These studies suggest that volatile anesthetics do not depress or abolish selectively the ventilatory drive from the peripheral chemoreceptors.

The studies on the effects of subanesthetic concentrations of volatile anesthetics are of particular interest from a clinical point of view. Low concentrations of anesthetics do occur postoperatively, and in addition, hypoxia and hypoventilation are not uncommon during transportation to and stay in the anesthesia care unit.[2,19,20] Depression of the peripheral chemoreflex loop at subanesthetic concentrations of halothane, enflurane, and isoflurane could leave a patient without defense against hypoxia and hypercapnia. The studies that address this issue are those of Temp *et al.*[12] and Knill *et al.*[2–6] Temp *et al.* argue that the discrepancy between their findings and those of Knill *et al.* may be the result of a difference in the method of inducing hypoxia. Knill's group used a progressive decrease in oxygen concentration over 8–10 min to obtain the hypoxic ventilatory response; Temp *et al.* used a sudden decrease in $P_{ET_{O_2}}$. The ventilatory response to a step decrease in $P_{ET_{O_2}}$ is biphasic: The initial increase in $\dot{V}_E$ is followed within 5 min by a slow decline.[21] The hyperventilatory response is thought to be of peripheral origin, the slow decline most probably originates within the central nervous system.[22,23] A slow progressive decrease in oxygen concentration over 10 min therefore will yield a response that is contaminated by central effects. Problems in interpretation could occur if a drug is tested that alters the central effect of hypoxia. For instance, an increase of the magnitude or an earlier onset of the hypoxic ventilatory decline caused by 0.1 MAC halothane could explain Knill *et al.*'s[2–6] larger decline of hypoxic ventilatory response compared with the data of Temp *et al.*[12] Assessing the initial response to a sudden step decrease in $P_{ET_{O_2}}$ avoids difficulties in interpretation.

The main aim of this study is to quantify the influences of two subanesthetic levels of halothane (F_I 0.076% and 0.15%) on the respiratory control system, in particular on the peripheral chemoreflex loop. We will do so by using the "dynamic end-tidal forcing technique" to perform square-wave changes in end-tidal carbon dioxide tension ($P_{ET_{CO_2}}$) against a background of normoxia. The ventilatory response, measured on a breath-to-breath basis, then is partitioned into a fast, peripheral dynamic component and a slow, central dynamic component using a two-compartment model.[24–26] To the best of our knowledge, no such study has been performed during halothane inhalation. Furthermore, using the dynamic end-tidal forcing technique, we will perform steps into short time hypoxia against a background of normocapnia to obtain a selective stimulus to the peripheral chemoreflex loop.

Materials and Methods

Subjects

Nine male subjects (aged 23–33 yr) took part in this experimental protocol, which was approved by the Leiden University Ethics Committee. The subjects had no history of cardiovascular, respiratory, or liver disease and had normal serum chemistry (based on liver and kidney function tests) and electrocardiograms. Subjects who had received anesthesia in the 6-month period before this study were excluded. All subjects were uninformed regarding respiratory physiology but did receive information on the nature and risks of the study. After giving informed consent, they were familiarized with the experimental procedure and apparatus before the study started. The subjects were asked to refrain

from using stimulants and depressants at least 12 h before the experiments. After arrival at the laboratory, they rested for 45 min. During an experiment (or run), they were in a semirecumbent position and listened to music of their choice through headphones.

Experimental Design

To study the ventilatory response to hypoxia and hypercapnia, we used the dynamic end-tidal forcing technique. With this technique, we are able to force the end-tidal gas tensions dynamically to follow a prescribed pattern in time by manipulating the inspired gas concentrations independently of the ventilatory response (fig. 1).[24-26]

The experiments in protocol I consisted of normoxic steps into and out of hypercapnia. After a period of steady-state $\dot{V}_E$ with $P_{ET_{CO_2}}$ slightly raised above resting values (0.5–1 mmHg), $P_{ET_{CO_2}}$ was increased by 7.5–11.3 mmHg in a stepwise fashion and kept constant for 6–8 min. Subsequently, $P_{ET_{CO_2}}$ was returned to its original value and kept constant for another 6–8 min. During the experiment, $P_{ET_{O_2}}$ was maintained at 110 mmHg. Each subject performed at least one control run, one during the inhalation of 0.076% halothane, and one during the inhalation of 0.15% halothane. The maximum number of runs obtained was three per treatment.

The experiments in protocol II consisted of isocapnic steps into hypoxia. After a period of steady-state $\dot{V}_E$ during which the $P_{ET_{CO_2}}$ was raised slightly above resting values (0.5–1 mmHg) and $P_{ET_{O_2}}$ was at 110 mmHg, the $P_{ET_{O_2}}$ was decreased rapidly to 44 mmHg to attain an arterial hemoglobin oxygen saturation (Sp_{O_2}) (obtained from pulse oximetry) of 82 ± 2%. After 5 min of hypoxia, hyperoxia (F_I oxygen > 0.7) was introduced for 10 min. The $P_{ET_{CO_2}}$ was kept constant, within 0.4 mmHg (SD). Each subject performed three hypoxic runs: one control, one during the inhalation of 0.076% halothane, and one during the inhalation of 0.15% halothane.

Before a drug experiment, the subject started inhaling halothane at twice the desired concentration for 5 min, after which the halothane was set at the appropriate concentration (F_I 0.076% or 0.15%). After at least 15 min of equilibration time data collection started. Between halothane runs, the subjects inhaled room air. Before and at the end of each individual run, we "determined" the level of sedation of the subjects. If, in both instances, a subject opened his eyes after his name was called, we accepted the experiment for analysis; if not, we discarded data from that run. After each run, we obtained information on the patient's awareness of time and space through a short interview. Protocols I and II were performed on one day. The order of runs in our study was fixed so control runs were performed before drug runs, and the runs during inhalation of 0.076% halothane were performed before the runs during inhalation of 0.15% halothane. In each treatment, the order of hypoxic and hypercapnic experiments was chosen arbitrarily. Between runs, there was a 10–15 min rest period.

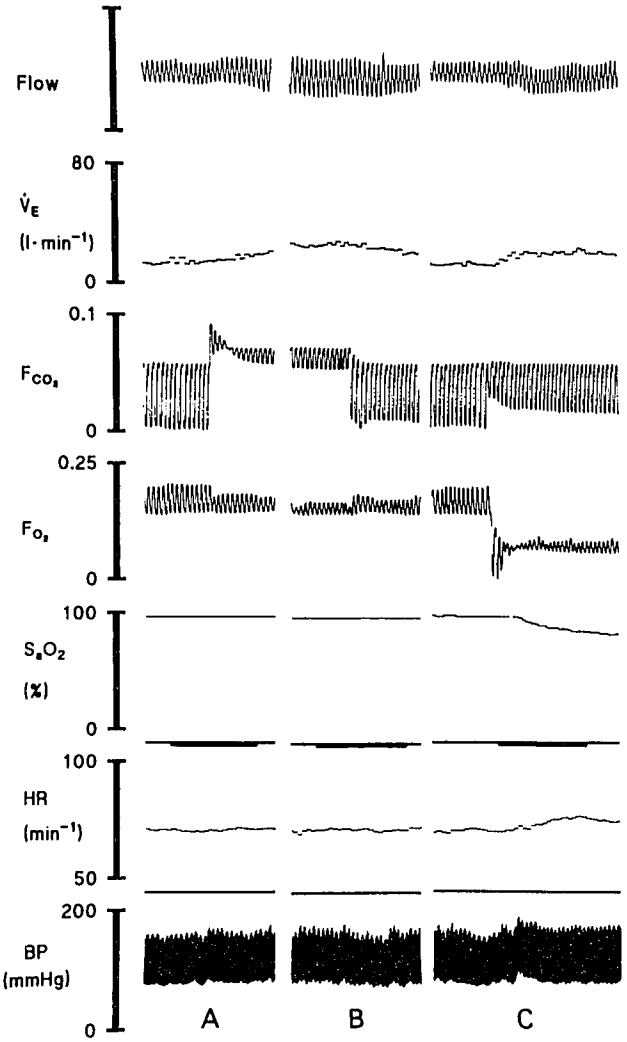

Fig. 1. Recording of a transition into hypercapnia (*A*), out of hypercapnia (*B*), and into hypoxia (*C*) of control runs of subject no. 315. Flow is not calibrated. The thick horizontal bars denote 1-min periods. HR = heart rate; BP = blood pressure.

Apparatus

An oronasal mask was fitted to the face of each subject. Each subject then was instructed to breathe through his mouth to minimize changes in airway resistance during an experiment. The mask allows normal movements of mouth and lips and is considered less disruptive to normal breathing than a mouthpiece. The airway gas flow was measured with a pneumotachograph (Fleisch #3, Switzerland) connected to a differential pressure transducer (Hewlett Packard model 270, USA) and electronically integrated to yield a volume signal.[27] This signal was calibrated with a motor-driven piston pump (stroke volume of 1 l at a frequency of 20 min^{-1}). Corrections were made for the changes in gas viscosity due to changes in oxygen concentration of the inhaled gas mixture. The pneumotachograph was connected to a T-piece. One arm of the T-piece received a gas mixture with a flow of 50 $l \cdot min^{-1}$ from a gas mixing system, consisting of four mass-flow controllers (Bronkhorst High Tec, F201/F202/F203, Bilthoven, The Netherlands), with which the flow of oxygen, carbon dioxide, nitrogen, and halothane in nitrogen could be set individually at a desired level. Flows were calibrated with flow-resistance standards (Godart, The Netherlands). A PDP 11/23 microcomputer provided control signals to the mass-flow controllers so the composition of the inspiratory gas mixture could be adjusted to force the $P_{ET_{CO_2}}$ and $P_{ET_{O_2}}$ to follow a specific pattern in time. Part of the nitrogen (5 $l \cdot min^{-1}$) passed through the halothane vaporizer. During control experiments, the vaporizer was kept in the "off" position.

The oxygen and carbon dioxide concentrations of the inspired and expired gasses were measured with a gas monitor (Datex Multicap, Finland). The concentration of halothane was measured in the outflow limb of the vaporizer with an infrared absorption monitor (Beckman LB-2, USA). A Datex Satellite Plus (Finland) continuously measured Sp_{O_2} (*via* a finger probe) and the electrocardiogram. Blood pressure was monitored beat-to-beat *via* a finger cuff (Ohmeda 2300 Finapress, USA).[28] The following parameters were stored on a breath-to-breath basis for further analysis: $\dot{V}_E$, tidal volume, respiratory frequency (f), Sp_{O_2}, $P_{ET_{CO_2}}$, and $P_{ET_{O_2}}$.

Data Analysis

For the analysis of the dynamic response of ventilation to a step-wise change in $P_{ET_{CO_2}}$ (protocol I), we used a two-compartment model.[24-26]

$$\tau_c \frac{d}{dt}\dot{V}_c(t) + \dot{V}_c(t) = G_c[P_{ET_{CO_2}}(t - T_c) - B]$$

$$\tau_p \frac{d}{dt}\dot{V}_p(t) + \dot{V}_p(t) = G_p[P_{ET_{CO_2}}(t - T_p) - B]$$

$\dot{V}_c(t)$ and $\dot{V}_p(t)$ are the outputs of the central and peripheral chemoreflex loops. $P_{ET_{CO_2}}(t - T_c)$ is the stimulus to the central chemoreflex loop delayed by the central transport delay time, T_c. $P_{ET_{CO_2}}(t - T_p)$ is the input to the peripheral chemoreflex loop delayed by the peripheral transport delay time, T_p. The parameters G_c and τ_c are the carbon dioxide sensitivity and time constant, respectively, of the central chemoreflex loop. The corresponding parameters of the peripheral chemoreflex loop are denoted G_p and τ_p. B is the apneic threshold (extrapolated $P_{ET_{CO_2}}$ of the steady-state $\dot{V}_E$-$P_{ET_{CO_2}}$ response at zero $\dot{V}_E$).

To model the central time constant of ventilatory on-transient to be different from the off-transient, τ_c is written as:

$$\tau_c = \tau_{on}x + (1 - x)\tau_{off}$$

in which x = 1 when $P_{ET_{CO_2}}$ is high, and x = 0 when $P_{ET_{CO_2}}$ is low.

In most experiments, a small drift in the ventilation was present. We therefore included a drift term (Ct) in the total ventilatory response, which is made up of the sum of the contributions of the central and peripheral chemoreflex loops:

$$\dot{V}_E = \dot{V}_c + \dot{V}_p + Ct$$

The parameters of the model were estimated by fitting the model to the breath-to-breath data with a least-squares method. To obtain optimal time delays, a "grid search" was applied, and all combinations of T_c and T_p with increments of 1 s and with $T_c \geq T_p$ were tried until a minimum in the residual sum of squares was found. The minimal time delay was chosen, somewhat arbitrarily, to be 1 s, and τ_p was constrained to be at least 0.3 s.

We evaluated the experiments of protocol II by taking mean values of breath-to-breath ventilation over identical time segments of each run. We calculated mean values for the final 2 min of normoxic ventilation before induction of hypoxia (period A) and for minutes 3 and 4 after exposure to hypoxia (period B). We defined the difference in $\dot{V}_E$ between these two periods as the acute hypoxic response.

Table 1. The Effect of Inhaling 0.076% and 0.15% Halothane on the Dynamic Response to Hypercapnia

	Control	Halothane	
		F_I 0.076%	F_I 0.15%
No. of runs	20	18	18
B (mmHg)	35.9 ± 1.15	35.7 ± 1.23	34.0 ± 1.83
G_c ($l \cdot min^{-1} \cdot mmHg^{-1}$)	1.47 ± 0.22	1.41 ± 0.21	1.23 ± 0.19
G_p ($l \cdot min^{-1} \cdot mmHg^{-1}$)	0.74 ± 0.14	0.51 ± 0.12*	0.30 ± 0.08†
G_p/G_{tot}	0.32 ± 0.06	0.24 ± 0.06*	0.19 ± 0.05†
τ_{on} (s)	232.7 ± 40.3	141.8 ± 34.7	88.7 ± 15.3†
τ_{off} (s)	161.0 ± 29.7	102.3 ± 22.1	60.7 ± 11.4†
τ_p (s)	12.8 ± 2.9	5.8 ± 1.7	7.1 ± 1.5
T_c (s)	17.9 ± 1.4	17.5 ± 1.9	16.0 ± 1.6
T_p (s)	6.6 ± 0.7	6.8 ± 0.7	7.6 ± 1.6

Values are means of the subject mean ± SE. $G_{tot} = G_c + G_p$.

* $P < 0.05$ *versus* control.

† $P < 0.01$ *versus* control.

Statistical Analysis

To detect the significance of differences among the three treatment groups in protocol I, a two-way analysis of variance was performed on the parameters B, G_p, G_c, G_p/G_{tot}, τ_{on}, τ_{off}, τ_p, T_c, T_p using a mixed model. As the data were unbalanced, the variance components were estimated by weighted means analysis. Estimated treatment means were compared with each other using the method of least significant differences.[29]

For protocol II, a two-way analysis of variance was performed on the acute hypoxic response and the changes in tidal volume, respiratory frequency, Sp_{O_2}, PET_{O_2}, and PET_{CO_2} between periods B and A of the three treatment groups. Differences between treatments were tested with the Student–Newman–Keuls test.

A probability level of 0.05 was chosen for differences to be significant. All values presented are means ± SE unless otherwise stated.

Results

All nine subjects completed both protocols without problems. In figure 1, an actual recording of a transition into hypercapnia (A), out of hypercapnia (B), and into hypoxia (C) is shown for control runs of one subject (no. 315). It shows the control of PET_{O_2} and PET_{CO_2} through manipulation of the inspired gas concentrations. None of the halothane runs had to be rejected because of an excessive depth of sedation. Most subjects performed experiments during inhalation of 0.076% halothane with open eyes. During inhalation of 0.15% halothane, all subjects opened their eyes without difficulty when their names were called. None of the subjects showed any behavioral or ventilatory changes suggestive of sleep.

For protocol I, 66 runs were obtained. Data from ten were discarded because of an irregular pattern of breathing (table 1). The model fits to a typical control and a halothane (F_I 0.15%) experiment of one subject are shown in fig. 2. They demonstrate that the contribution of the peripheral chemoreflex loop is decreased during halothane inhalation, without much change in

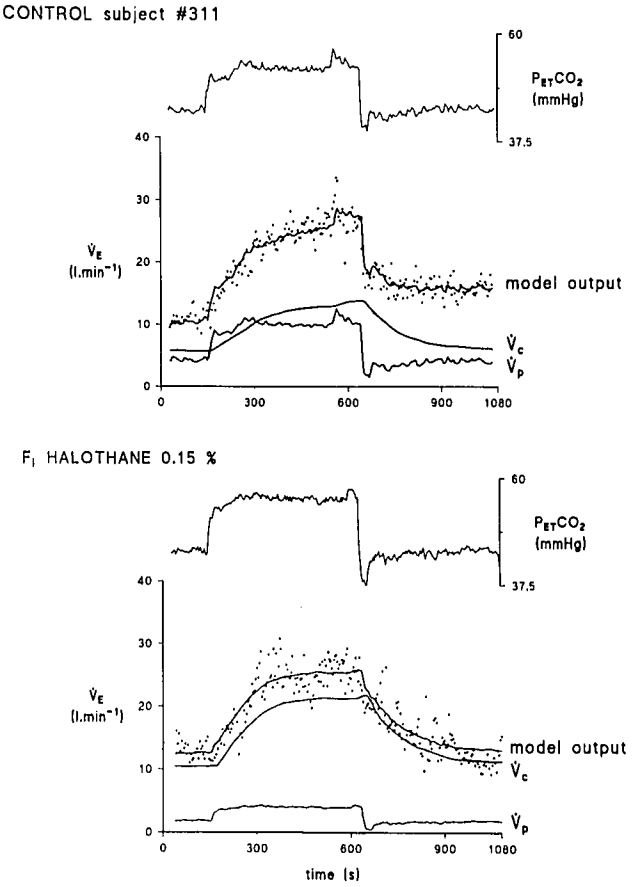

Fig. 2. Model fits to a control run (*top*) and run during inhalation of 0.15% halothane (*bottom*) of subject no. 311. Each dot represents one breath. The model output is the sum of $\dot{V}_c$, $\dot{V}_p$, and a trend term (not shown). Parameter values are for control: B = 37.5 mmHg, G_c = 0.9 $l \cdot min^{-1} \cdot mmHg^{-1}$, G_p = 0.6 $l \cdot min^{-1} \cdot mmHg^{-1}$, τ_{on} = 143 s, τ_{off} = 150 s, τ_p = 0.3 s, T_c = 17 s, T_p = 7 s, and C = 305 $ml \cdot min^{-2}$. F_I = 0.15%: B = 33.8 mmHg, G_c = 1.0 $l \cdot min^{-1} \cdot mmHg^{-1}$, G_p = 0.2 $l \cdot min^{-1} \cdot mmHg^{-1}$, τ_{on} = 95 s, τ_{off} = 157 s, τ_p = 0.3 s, T_c = 25 s, T_p = 9 s, and C = −13 $ml \cdot min^{-2}$.

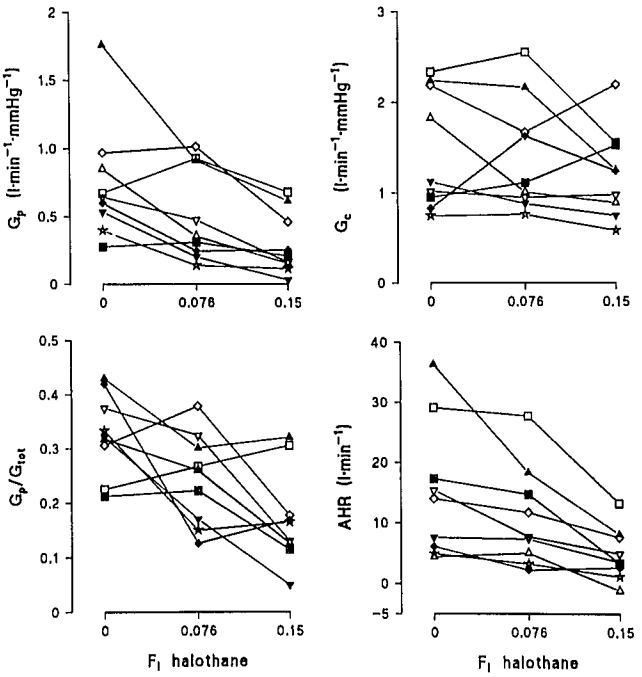

Fig. 3. Mean values of G_p, G_c, G_p/G_{tot}, and the acute hypoxic response (AHR) of each subject at an F_I halothane of 0, 0.076%, and 0.15%. Each subject has the same symbol in each plot. $G_{tot} = G_c + G_p$.

the contribution of the central chemoreflex loop. The mean values of the subject means of all parameters are shown in table 1. Fig. 3 shows the mean values of G_c, G_p, and G_p/G_{tot} of each subject for each treatment. During inhalation of 0.076% halothane, parameter G_p decreased by about 30% and ratio G_p/G_{tot} by 25% ($P < 0.05$ *vs.* control). Inhalation of 0.15% halothane reduced the peripheral carbon dioxide sensitivity and the ratio G_p over G_{tot} by about 60 and 40%, respectively ($P < 0.01$ *vs.* control). The time constants of the central chemoreflex loop were reduced to about one third of control values. The apneic thresholds, peripheral time constants, and central and peripheral time delays did not differ significantly among any of the three treatments.

For protocol II, 27 responses were obtained, and none had to be discarded. The levels of Sp_{O_2} and $P_{ET_{O_2}}$ in period B and the changes in $P_{ET_{CO_2}}$, $P_{ET_{O_2}}$, and Sp_{O_2} between periods B and A did not differ significantly among treatments (table 2). Figure 4 shows the responses of two subjects (nos. 306 and 309). It clearly illustrates the effect of halothane on the acute hypoxic response. For all runs, the acute hypoxic response averaged to 15.0 ± 3.9 l·min^{-1} in the control run, 10.9 ± 2.9 l·min^{-1} in the 0.076% halothane (NS) run, and 4.8 ± 1.4 l·min^{-1} in the 0.15% halothane run ($P < 0.01$ *vs.* control and 0.076% halothane). This was due to changes in tidal volume as well as breathing frequency.

In figure 5, we plotted the mean response of the peripheral chemoreflex loop ($\Delta \dot{V}_p$) per treatment of each subject obtained from protocol I (stimulus $P_{ET_{CO_2}}$ = 11.3 mmHg) against their acute hypoxic counterpart from protocol II. There was a good correlation between $\Delta \dot{V}_p$ and the acute hypoxic response ($r = 0.84$; $P < 0.0001$).

Discussion

In this study we observed that subanesthetic concentrations of halothane have an important impact on the chemical control of breathing in humans. The responses to both carbon dioxide and oxygen are affected. Spe-

Table 2. The Effect of Inhaling 0.076% and 0.15% Halothane on Acute Hypoxic Response

		Halothane	
	Control	F_I 0.076%	F_I 0.15%
$\dot{V}_E$ (l·min^{-1})			
A	14.6 ± 0.8	13.3 ± 0.7	13.8 ± 1.4
B	29.6 ± 4.3	24.2 ± 3.4	18.6 ± 1.8
Δ	15.0 ± 3.9	10.9 ± 2.9	4.8 ± 1.4*
V_T (ml)			
A	862 ± 55	825 ± 47	765 ± 48
B	1,450 ± 160	1,252 ± 120	1,012 ± 71
Δ	588 ± 133	428 ± 104	247 ± 72*
f (breaths/min)			
A	17.2 ± 0.8	16.5 ± 1.0	18.0 ± 1.0
B	20.0 ± 1.0	19.2 ± 1.2	18.7 ± 1.3
Δ	2.9 ± 0.7	2.7 ± 0.9	0.7 ± 0.6*
$P_{ET_{CO_2}}$ (mmHg)			
A	43.7 ± 0.4	43.7 ± 0.4	43.7 ± 0.4
B	42.9 ± 0.4	43.7 ± 0.4	43.3 ± 0.3
Δ	−0.8 ± 0.4	−0.08 ± 0.4	−0.5 ± 0.3
$P_{ET_{O_2}}$ (mmHg)			
A	110.3 ± 0.5	109.8 ± 0.4	109.6 ± 0.6
B	43.5 ± 0.5	43.7 ± 0.6	44.3 ± 0.6
Sp_{O_2} (%)			
A	98.3 ± 0.3	98.5 ± 0.2	98.2 ± 0.3
B	81.8 ± 0.6	82.3 ± 0.8	81.6 ± 0.6

Values are mean ± SE; n = 9.

A = 2-min period before induction of hypoxia; B = min 3 and 4 of hypoxia; Δ = period B − period A.

* $P < 0.01$ *versus* control and 0.076% halothane.

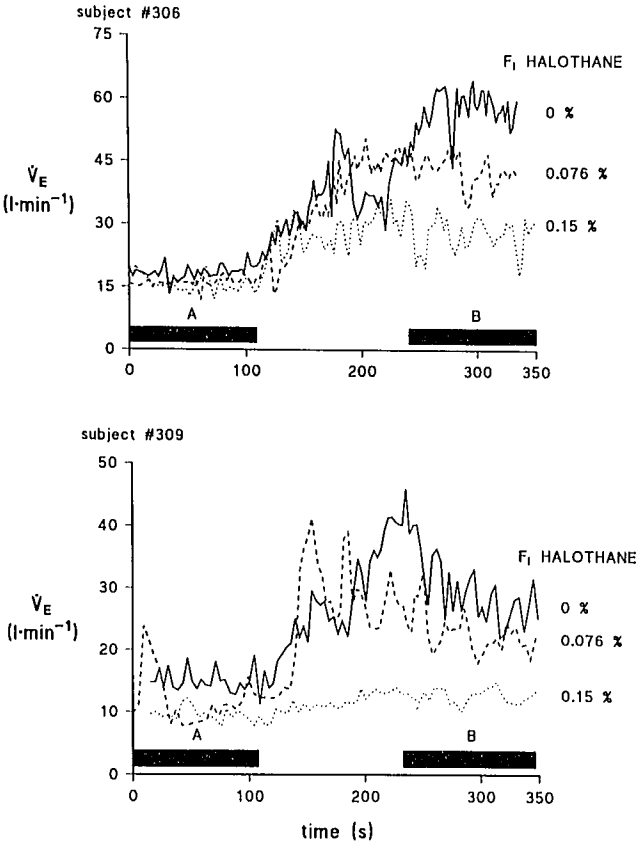

Fig. 4. The ventilatory responses to hypoxia of subjects no. 306 (*top*) and no. 309 (*bottom*) during inhalation of 0.076% and 0.15% halothane. The black bars represent periods A (2 min before hypoxia) and B (minutes 3 and 4 of hypoxia). The responses for subject no. 306 were 36.3 l·min^{-1} for the control run, 18.3 l·min^{-1} for the F_I 0.076% run, and 8.1 l·min^{-1} for the F_I 0.15% run. The responses for subject no. 309 were 17.3 l·min^{-1} for the control run, 14.7 l·min^{-1} for the F_I 0.076% run, and 3.3 l·min^{-1} for the F_I 0.15% run. F_I = inspired fraction.

cifically, halothane reduced the acute hypoxic response and the peripheral carbon dioxide sensitivity but had little influence on the central carbon dioxide sensitivity. This indicates a selective effect of halothane on the peripheral chemoreflex loop.

Critique of Methods

We performed control and all drug experiments on one day. The order of experiments was fixed to control, 0.076% halothane, and 0.15% halothane. There are several reasons for this approach. We did not want to expose our group of volunteers to halothane more than once in a short time span to minimize the risk of inducing halothane-related disease. We also did not want to perform control and drug experiments on separate days, because day-to-day variability of the ventilatory responses to both hypoxia and hypercapnia is more significant than within-day variability.[30,31] A randomized cross-over study on one day leads to excessively long sessions and the discomfort of the subjects. Furthermore, because halothane is not eliminated completely within a short time period, an influence on subsequent experiments (control or 0.076% halothane experiment) cannot be excluded.[32-34] Because the differences between treatments could have been small, we opted to use a protocol in which the run-to-run variability was minimal.

We did not determine the level of sedation in our subjects specifically. Experiments were accepted for analysis if subjects were able to open their eyes on command at the beginning and end of each run. Similar to the findings of Knill *et al.*,[2] we observed that during the 0.076% halothane experiments, all subjects were sedated only lightly, were well aware of time and space, and had no memory defects. Inhaling halothane at 0.15% increased the level of sedation, but the subjects still had the ability to respond to command, as was observed also by Knill *et al.*[3] and Newton *et al.*[35] Furthermore, our data showed no effect of 0.1 MAC halothane on resting ventilation, pattern of breathing, or $P_{ET_{CO_2}}$. It is a matter of opinion to perform experiments

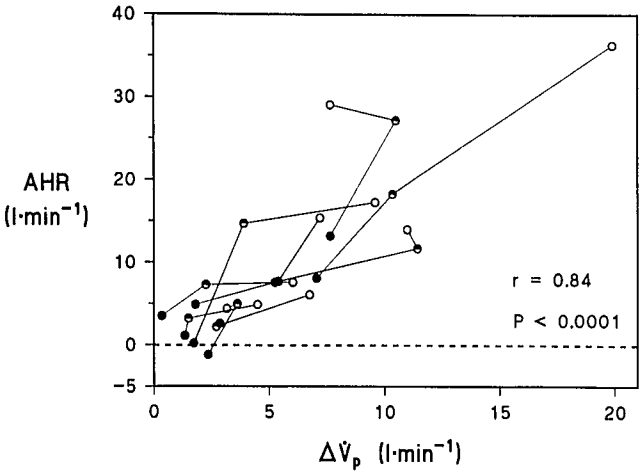

Fig. 5. Plot of the mean response of the peripheral chemoreflex loop ($\Delta \dot{V}_p$) per treatment of each subject against the acute hypoxic response (AHR). $\Delta \dot{V}_p$ was obtained by multiplying G_p by a 11.3 mmHg $P_{ET_{CO_2}}$ stimulus. Open circles = control; half-full circles = F_I halothane 0.076%; closed circles = F_I halothane 0.15%. The data points of each subject are connected. F_I = inspired fraction.

on subjects who can be aroused easily. In comparable clinical situations, the patients may not be easily arousable at all. To compare our results with the literature, we restricted ourselves to arousable subjects.

Our subjects inhaled 0.15% halothane for 5 min, followed by 0.076% for 15 min, after which data collection started. Twenty min of inhaling halothane will result in an alveolar to inspired halothane fraction of about 0.55.[32-34] The MAC of our volunteers was approximately 0.84%.[36] It is reasonable to assume there was a MAC value of 0.05 and 0.1 for the experiments during inhalation of 0.076% and 0.15% halothane, respectively. In the remainder of the discussion, we therefore will refer to the experiments during inhalation of 0.076% halothane as 0.05 MAC experiments and during inhalation of 0.15% as 0.1 MAC experiments.

To study the effects of halothane on the ventilatory control system, we used the "dynamic end-tidal forcing" technique. We performed steps in $P_{ET_{O_2}}$ and $P_{ET_{CO_2}}$ and used a mathematical model to separate the dynamic response to carbon dioxide into a fast and a slow ventilatory component. The fast component is attributed to the peripheral chemoreflex loop, the slow component to the central chemoreflex loop.[24-26,37,38] This technique has been validated extensively in cats,[25,37,38] and there is no reason to doubt that this would not hold also for humans. In several studies in humans and animals, this technique has been used successfully.[24-26,39-43]

Characteristics of Components

The parameter values of the dynamic response to carbon dioxide in the control runs (table 1) are consistent with our findings in previous studies.[26,39] The carbon dioxide response curves of all three treatments intersect close to the abscissa (*i.e.,* there was no effect of halothane on the apneic threshold). The decrease in G_p, ratio of G_p over G_{tot}, and acute hypoxic response suggests an appreciable influence of halothane on the peripheral chemoreceptors, but other sites of action also have to be considered. The effects may be on the respiratory center, in the central nervous system, or on the neuromechanical link between brainstem and $\dot{V}_E$: motor neuron, neuromuscular junction, respiratory muscle, and lung tissue. An effect on the link between brainstem and $\dot{V}_E$ at the inspired concentrations of halothane we have used is not very likely. An effect of halothane on the integrating centers and thus on both peripheral and central chemoreflex loops cannot be excluded. Although it was not significant, there was a trend of G_c to decrease at 0.1 MAC halothane. This suggests that there was a small, if any, effect on the respiratory center with respect to steady-state characteristics at 0.1 MAC halothane. The selective effect of subanesthetic halothane on the peripheral chemoreflex loop that we observed is in good agreement with the observation of a prompt decrease of hypoxia-driven $\dot{V}_E$ on exposure to halothane (F_I 0.15–0.30%) and the finding of a large decrease by halothane of the $\dot{V}_E$–H^+ response in man (see below).[4,44] The finding of no effect of halothane on the hypoxic response in goats and no selectivity of depression of the peripheral and central chemoreflex loops in cats probably is due to species differences.[16-18]

An interesting finding in our study is the decrease in central time constants that occurred with halothane. There are several possible mechanisms for this effect. An increase in initial brain blood flow ($\dot{Q}_b$) or an increase in brain blood flow reactivity to carbon dioxide ($\Delta\dot{Q}_b/\Delta$ carbon dioxide tension [P_{CO_2}]) causes a decrease in τ_{on} and τ_{off}.[45] It is improbable, however, that at 0.1 MAC, the speeding up of the central response to carbon dioxide is caused by a change in the level of initial $\dot{Q}_b$, because halothane causes an increase in $\dot{Q}_b$ in a dose-dependent manner detectable from 0.6 MAC on only.# To our knowledge, there are no studies that investigated the effects of subanesthetic concentrations of halothane on the relationship between brain blood flow and arterial P_{CO_2}. At high MACs, a decrease in $\Delta\dot{Q}_b/\Delta P_{CO_2}$ is found.[46] This is attributed to near maximal vasodilation of the brain vessels by an action of halothane on the smooth muscle or on the vasomotor center. At constant initial brain blood flow, an increase in $\Delta\dot{Q}_b/\Delta P_{CO_2}$ leads to a decrease in G_c.[45] As we did not observe a significant change in central carbon dioxide sensitivity, the effect of 0.1 MAC halothane on $\Delta\dot{Q}_b/\Delta P_{CO_2}$ was probably small and therefore is of minor importance in the decrease of the central time constants.

Because it is clear that 0.1 MAC halothane could not have affected initial brain blood flow or blood flow reactivity to carbon dioxide, another mechanism must be responsible for the reduction of central time constants with halothane. Besides $\dot{Q}_b$ and $\Delta\dot{Q}_b/\Delta P_{CO_2}$, central neuronal dynamics also determine the

Eger EI: Isoflurane (Forane): A Compendium and Reference, 2nd edition. Madison, Anaquest, 1984, pp 79–90.

magnitude of the central time constants.[26,45,47,48] Without the activation of neuronal dynamics, *i.e.*, with only brain blood flow dynamics, the magnitude of the central time constants would be roughly three times smaller in our control experiments.[26,45] In cats, a step change in arterial P_{CO_2} results in a change in respiratory activity (obtained from integrated phrenic nerve activity) that lags behind the change in central stimulus (expressed by medullary extracellular fluid $[H^+]$).[47,48] This lagging is attributed to central neuronal dynamics (respiratory after-discharge). In awake humans, neuronal dynamics become apparent after a period of voluntary hyperventilation. The hyperpnea is maintained and shows an exponential-like decline.[49] It is possible that 0.1 MAC halothane decreases the central time constants by affecting the respiratory center *via* inactivation of central neuronal dynamics. Further studies are needed to clarify the influences of subanesthetic concentrations of halothane on cerebral blood flow reactivity to carbon dioxide and, in particular, on central neuronal dynamics.

Quantitative Effects of Halothane on Peripheral Chemoreflex Loop

Our finding of a significant depression of the hypoxic ventilatory response by a subanesthetic concentration of halothane is in good agreement with the findings of Knill *et al.*[2,3] (fig. 6A). With halothane at 0.05 MAC, they observed a 50% decline of the hypoxic ventilatory response, and at 0.1 MAC, there was a 70% decline. Our results show that at 0.05 MAC halothane, the acute hypoxic response was decreased but did not quite reach the level of significance ($P > 0.05$). On the other hand, 0.1 MAC halothane decreased the response by 68%. This implies that the method of inducing hypoxia (a progressive decline as performed by Knill or a step decrease as performed by us) did not lead to differences in study outcome. The ventilatory response to a step decrease in arterial hemoglobin oxygen saturation is biphasic, and only the initial hyperventilatory response is of peripheral origin.[21–23] The slow decline in $\dot{V}_E$, which starts after approximately 5 min of hypoxia, is attributed to the depressive effects of hypoxia, which originates within the central nervous system.[22] A slow, progressive decrease in oxygen concentration over 10 min therefore will yield a response that has characteristics of both the peripheral hypoxic response and the "central" hypoxic ventilatory decline.[12,50] Because the depression in Knill's studies[2,3] and ours was similar, it

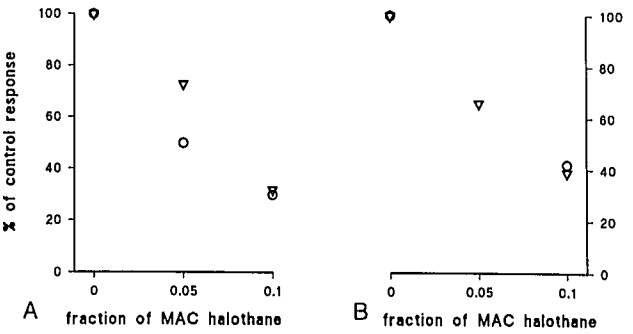

Fig. 6. (*A*) The effects of halothane on the hypoxic ventilatory response. ▽ = data calculated from this study; ○ = data from Gelb and Knill[2] and Knill and Gelb.[3] (*B*) The effects of halothane on the response of the peripheral chemoreceptors to carbon dioxide (▽) and H^+ (○). ▽ = data calculated from this study; ○ = data from Knill and Clement.[44]

suggests that halothane at subanesthetic concentrations changes the magnitude of the hypoxic ventilatory decline. Studies on the influence of halothane on hypoxic ventilatory decline, however, are needed to clarify this matter.

Knill *et al.*[2,3] did not observe a change in hypercapnic ventilatory response in their 0.05 and 0.1 MAC experiments. To obtain the hypercapnic ventilatory response Knill *et al.* used Read's rebreathing method.[51] This method challenges the respiratory control system with a step-ramp carbon dioxide input against a background of hyperoxia.[30,51] In normoxia, G_p is about 30% of G_{tot} but declines to about 10% in hyperoxia.[26] Presumably, Knill *et al.* used Read's rebreathing method to test selectively the effects of halothane on the central chemoreceptor-mediated response to carbon dioxide. We remark in passing that it recently has been shown that the use of Read's rebreathing method to test the influences of drugs on the central chemoreflex loop leads to problems in the interpretation of the results.[30,45,52,53] In a separate study, Knill and Clement[44] studied the effects of acute isocapnic metabolic acidosis through infusion of L-arginine hydrochloride on $\dot{V}_E$ in humans. Their results imply that acute, moderate metabolic acidosis increases ventilation mainly through stimulation of the peripheral chemoreceptors. In normoxia, they observed that a 58% decrease of the $\dot{V}_E$–H^+ response resulted from 0.1 MAC halothane. This corresponds well with our finding of a 61% reduction of the carbon dioxide sensitivity of the peripheral chemoreceptors by 0.1 MAC halothane (fig. 6B).

We observed a decrease in total carbon dioxide sensitivity with 0.1 MAC at normoxia. Because the dynamic

end-tidal forcing technique provides information on the contribution to total $\dot{V}_E$ of the central and peripheral chemoreflex loop as well as on their dynamics, we were able to localize the influences of halothane on the carbon dioxide sensitivity of the peripheral chemoreflex loop and the time course of the central chemoreflex loop. Our findings on the effects of halothane on the peripheral carbon dioxide response and the acute hypoxic response lead to similar conclusions. Furthermore, studying the effects of halothane on the peripheral chemoreceptors by intravenous infusion of acid,[44] a method completely different from ours, gives (quantitative) results similar to those we obtained with the dynamic end-tidal forcing technique.

Halothane Versus *Isoflurane*

It is of special clinical interest to consider the question of whether our findings are unique to halothane or apply to other inhalation anesthetics as well. Recently, Temp *et al.*[12] tested the influence of isoflurane on the hypoxic ventilatory response. They performed steps into hypoxia during inhalation of 0.1 MAC isoflurane and found no significant effect on the acute hypoxic response (drug response, 99% of control value). We did observe a significant decrease of the acute hypoxic response at 0.1 MAC halothane (drug response, 30% of control value). At least two reasons for the difference in results may be proposed: differences in protocol or a truly different effect of isoflurane on the response to hypoxia. We performed control and halothane experiments on a single day. In the study of Temp *et al.*,[12] control and isoflurane responses were studied on different days. This introduces an increase in run-to-run variability (see above). Our subjects relaxed in a semirecumbent position in a room separate from the investigators. They were never touched or addressed during an experiment. All subjects listened to quiet music by headphones and were not aware of noise from the mass flow controllers or flowing gasses. The subjects of Temp *et al.*[12] were required to watch a documentary videotape and were touched or addressed regularly. It is quite possible that this procedure introduced the sensitive confounding effects of central nervous system stimulation on the response to hypoxia.[54–57] We are well aware of the effects of eye closure, sedation, and "sleep" on the control of breathing.[58–60] Because these features are inherent properties of the drug that we tested, we decided to accept their occurrence and considered their influence on breathing an intrinsic drug effect. Evidently Temp *et al.*[12,58] were interested in studying isoflurane without the loss of "the wakefulness drive to breathe." We were more concerned with changes of the level of sedation during an experiment and therefore avoided external stimuli that could have affected the assessment of the chemical regulation of breathing. The lack of effect of 0.1 MAC halothane on the level of resting $\dot{V}_E$, pattern of breathing, and $P_{ET_{CO_2}}$ strengthens our impression that none of our subjects was "sleeping" during the experiments.

The differences in protocol may explain, at least partly, the large differences in outcome of the isoflurane studies of Temp *et al.*[12] and Knill *et al.*[6] and our halothane study. There also is some evidence, however, that isoflurane behaves differently than halothane. Although not designed for this purpose, the study of Sjögren *et al.*[13] suggests that 0.9 MAC isoflurane also does not affect the ventilatory response to acute hypoxia in humans. With hypoxia, they observed a significant increase in respiratory rate and ventilatory drive during isoflurane anesthesia when compared to control values. In this study, the $P_{ET_{CO_2}}$ was not kept constant, and the decrease in Sp_{O_2} showed a small difference between treatments, which makes the interpretation of the results more difficult. Furthermore, their control hypoxic response was exceedingly small. Two other abstracts by the same group of investigators show that 0.6–1.2 MAC isoflurane depressed the isocapnic hypoxic ventilatory response by 50–70%.[14,15] Control hypoxic responses in these studies were small (a decrease in Sp_{O_2} to 75%: an increase in $\dot{V}_E$ of approximately 4.5 $l \cdot min^{-1}$ *vs.* a decrease in Sp_{O_2} to 82%: increase in $\dot{V}_E$ 15 $l \cdot min^{-1}$ in our study), and the drug responses were performed 30 min after induction of anesthesia with propofol. The results of these three studies[13–15] suggest that the peripheral chemoreflex loop is more resistant to the effects of isoflurane than those of halothane.

Our findings have important clinical implications. If we extrapolate our data to 0.15 MAC halothane and higher, both the acute hypoxic response and peripheral carbon dioxide sensitivity will be virtually zero. In the postoperative period, a spontaneously breathing patient who still has low concentrations of halothane in his body will react to hypoxia with a severely depressed or even without hyperventilatory response. If further studies indeed show that, in contrast to halothane, the acute hypoxic response at (sub)anesthetic levels of isoflurane is sustained, the use of isoflurane would be suggested for those patients who depend solely on a drive from their pe-

ripheral chemoreceptors for normal breathing as well as for other patients prone to hypoxia.

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