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Influences of Subanesthetic Isoflurane on Ventilatory Control in Humans

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Background: **The purpose of this study was to quantify in humans the effects of subanesthetic isoflurane on the ventilatory control system, in particular on the peripheral chemoreflex loop. Therefore we studied the dynamic ventilatory response to carbon dioxide, the effect of isoflurane wash-in upon sustained hypoxic steady-state ventilation, and the ventilatory response at the onset of 20 min of isocapnic hypoxia.**

Methods: **Study 1: Square-wave changes in end-tidal carbon dioxide tension (7.5–11.5 mmHg) were performed in eight healthy volunteers at 0 and 0.1 minimum alveolar concentration (MAC) isoflurane. 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 (apneic threshold). Study 2: The ventilatory changes due to the wash-in of 0.1 MAC isoflurane, 15 min after the induction of isocapnic hypoxia, were studied in 11 healthy volunteers. Study 3: The ventilatory responses to a step decrease in end-tidal oxygen (end-tidal oxygen tension from 110 to 44 mmHg within 3–4 breaths; duration of hypoxia 20 min) were assessed in eight healthy volunteers at 0, 0.1, and 0.2 MAC isoflurane.**

Results: **Values are reported as means ± SE. Study 1: The peripheral carbon dioxide sensitivities averaged 0.50 ± 0.08 (control) and 0.28 ± 0.05 $l \cdot min^{-1} \cdot mmHg^{-1}$ (isoflurane; $P < 0.01$). The central carbon dioxide sensitivities (control 1.20 ± 0.12 *vs.* isoflurane 1.04 ± 0.11 $l \cdot min^{-1} \cdot mmHg^{-1}$) and off-sets (control 36.0 ± 0.1 mmHg *vs.* isoflurane 34.5 ± 0.2 mmHg) did not differ between treatments. Study 2: Within 30 s of exposure to 0.1 MAC isoflurane, ventilation decreased significantly, from 17.7 ± 1.6 (hypoxia, awake) to 15.0 ± 1.5 $l \cdot min^{-1}$ (hypoxia, isoflurane). Study 3: At the initiation of hypoxia ventilation increased by 7.7 ± 1.4 (control), 4.1 ± 0.8 (0.1 MAC; $P < 0.05$ *vs.* control), and 2.8 ± 0.6 (0.2 MAC; $P < 0.05$ *vs.* control) $1 \cdot min^{-1}$. The subsequent ventilatory decrease averaged 4.9 ± 0.8 (control), 3.4 ± 0.5 (0.1 MAC; difference not statistically significant), and 2.0 ± 0.4 (0.2 MAC; $P < 0.05$ *vs.* control) $1 \cdot min^{-1}$. There was a good correlation between the acute hypoxic response and the hypoxic ventilatory decrease ($r = 0.9$; $P < 0.001$).**

Conclusions: **The results of all three studies indicate a selective and profound effect of subanesthetic isoflurane on the peripheral chemoreflex loop at the site of the peripheral chemoreceptors. We relate the reduction of the ventilatory decrease of sustained hypoxia to the decrease of the initial ventilatory response to hypoxia. (Key words: Anesthetics, volatile: isoflurane. Lungs, ventilation: acute hypoxic response; dynamic hypercapnic response; hypoxic ventilatory decrease. Methods: dynamic end-tidal forcing; isocapnia. Receptors: carotid bodies; central chemoreceptors; peripheral chemoreceptors.)**

IN humans halothane, at subanesthetic concentrations, influences the metabolic control of breathing by selectively affecting the peripheral chemoreflex loop at the site of the peripheral chemoreceptors. Knill and Clement observed that hypoxia-driven minute ventilation ($\dot{V}_E$) decreased by about 35% within 1 min of exposure to halothane (0.15–0.30% inspired concentration).[1] In another study they studied the effects of 0.1 minimum alveolar concentration (MAC) halothane on the ventilatory response to acute isocapnic metabolic acidosis *via* infusion of L-arginine hydrochloride.[2] During normoxia they observed a decrease of the $\dot{V}_E$–H^+ response by about 60%. In previous studies we performed step decreases in end-tidal oxygen tension ($P_{ET_{O_2}}$) at the background of a constant end-tidal carbon dioxide tension ($P_{ET_{CO_2}}$) and step increases in $P_{ET_{CO_2}}$ during normoxia.[3,4] From the hypercapnic responses we determined the por-

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tions of the ventilatory carbon dioxide sensitivities of the peripheral and central chemoreflex loops. At 0.05 and 0.1 MAC halothane the peripheral carbon dioxide sensitivity decreased by 30% and 70%, respectively, whereas the central carbon dioxide sensitivity did not show a significant change.[3] Upon exposure to hypoxia the ventilatory increase above normoxic baseline at 0.05, 0.1, and 0.15 MAC halothane was about 80%, 35%, and 25%, respectively.[3,4] These studies[1–4] provide abundant evidence for the selective site of action of subanesthetic halothane in humans.

Currently, results from studies on the effects of isoflurane on ventilatory control are more ambiguous than those on subanesthetic halothane. Whereas some investigators have found little or no effect of isoflurane on the ventilatory response to hypoxia or hypercapnia,[5–7] others have found an appreciable depression and concluded that isoflurane selectively impairs all responses mediated by the peripheral chemoreceptors.[8,9] We attribute these differences to variations in study conditions and techniques.[3,8]

The aim of our current studies is to determine the influences of subanesthetic isoflurane on the metabolic control of ventilation in healthy volunteers. First, with the use of the "dynamic end-tidal forcing" technique we applied square-wave changes in $P_{ET_{CO_2}}$ against a background of normoxia. The ventilatory responses, measured on a breath-to-breath basis, then is partitioned into a fast, peripheral component and a slow, central component using a two-compartment model.[3,10–12] Second, in analogy to the initial study by Knill and Clement,[1] we applied step increases in end-tidal isoflurane concentration (~0.1 MAC)§ during sustained-hypoxia driven steady-state $\dot{V}_E$. This will allow us to examine the effects of subanesthetic isoflurane on the peripheral chemoreceptors when brain concentrations (and sedative effects) of isoflurane are still nonsignificant. Finally, we performed step decreases in $P_{ET_{O_2}}$ against a background of strict iso-normocapnia. Hypoxia was maintained for 20 min. We determined the ventilatory increase from baseline after 3–5 min of hypoxia, the acute hypoxic response, and the subsequent ventilatory decrease, the hypoxic ventilatory decrease.

Materials and Methods

Subjects and Apparatus

Eleven healthy, nonsmoking subjects (two women and nine men, aged 22–35 yr) took part in the experimental protocols, which were approved by the Leiden University Committee on Medical Ethics. These were "trained" subjects: all had participated in several other studies on ventilatory control. All were unfamiliar with respiratory physiology but received information on the risks of the study and had given informed consent. The subjects were asked to refrain from stimulants and depressants for at least 12 h before the study.

During the study the subjects were in a semirecumbent position. An oronasal mask was fitted before the experiment started. The airway gas flow was measured with a pneumotachograph connected to a differential pressure transducer (model 270, Hewlett-Packard, Andover, MA) and electronically integrated to yield a volume signal. This signal was calibrated with a motor-driven piston pump (stroke volume 1 l, at a frequency of 20/min). 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/min from a gas mixing system, consisting of four mass flow controllers (F201, F202, F203, Bronkhorst High Tec, Veenendaal, The Netherlands) with which the flows of oxygen, carbon dioxide, nitrogen, and isoflurane in nitrogen could be set individually at the desired levels. Flows were calibrated with flow resistance standards (Godart, Bilthoven, The Netherlands). A Programmable Digital Processor microcomputer (11/23, Digital Equipment Corporation, Ireland) provided control signals to the mass flow controllers, so that 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/min) passed through the isoflurane vaporizer. During the initial part of the study the vaporizer was kept in the off position.

The oxygen and carbon dioxide concentrations of the inspired and expired gases were measured with a gas monitor (Multicap, Datex, Helsinki, Finland) by paramagnetic and infrared analysis, respectively. The gas monitor was calibrated with gas mixtures of known

§ 1 MAC isoflurane = 1.25% at ages 22–35 yr. Stevens WC, Dolan WM, Gibbons RT, White A, Eger EI II, Miller RD, DeJong RH, Elashoff RM: Minimum alveolar concentration (MAC) of isoflurane with and without nitrous oxide in patients of various ages. ANESTHESIOLOGY 42: 197–200, 1975.

concentrations. The isoflurane concentration was measured at the mouth with a Datex monitor (Ultima, Helsinki, Finland). This monitor was calibrated with a gas mixture of isoflurane (in air) of known concentration. A pulse oximeter (Satellite Plus, Datex) continuously measured the arterial oxygen saturation with a finger probe (Sp_{O_2}). Throughout the study the electrocardiogram was monitored. $\dot{V}_E$, tidal volume, respiratory frequency, Sp_{O_2}, $P_{ET_{CO_2}}$, and $P_{ET_{O_2}}$ were calculated and stored on a breath-to-breath basis.

Study Design

The dynamic ventilatory response to carbon dioxide (study 1), the response to 0.1 MAC isoflurane wash-in on sustained hypoxia-driven steady-state $\dot{V}_E$ (study 2) and the ventilatory response at the initiation of sustained hypoxia (study 3) were determined on different morning sessions, each at least 1 week apart. To force dynamically the $P_{ET_{O_2}}$ and $P_{ET_{CO_2}}$ to follow a prescribed pattern in time we used a "dynamic end-tidal forcing" system.[11] Each session started with a 30-min relaxation period. Thereafter, resting $P_{ET_{CO_2}}$ was determined at the end of 15 min of steady-state $\dot{V}_E$ with no inspired carbon dioxide. Subsequently the $P_{ET_{CO_2}}$ was increased about 0.8–1.4 mmHg above the individual resting values ($P_{ET_{CO_2}}'$) and maintained constant at this level throughout the session in studies 2 and 3. In study 1, the initial steady-state $\dot{V}_E$ was determined at $P_{ET_{CO_2}}'$. $P_{ET_{CO_2}}'$ was determined for each experimental session.

Study 1: The dynamic ventilatory response to normoxic hypercapnia. Eight subjects participated in this study (two women and six men). The experiments were performed at a background of normoxia ($P_{ET_{O_2}}$ 110 mmHg). After the determination of resting values and $P_{ET_{CO_2}}'$ the experiments started. For each experiment the $P_{ET_{CO_2}}$ was forced as follows: (1) 5–10 min at $P_{ET_{CO_2}}'$; (2) a step increase of 7.5–11.5 mmHg within 3–4 breaths; this hypercapnic level was maintained for 6–8 min; and (3) a rapid decrease within 3–4 breaths to its original value and kept constant for another 6–8 min. Each subject performed two or three experiments without isoflurane and two or three at 0.1 MAC isoflurane. Control experiments always preceded isoflurane experiments. The $\dot{V}_E$–carbon dioxide responses during isoflurane inhalation were performed after a 20-min equilibration period (end-tidal isoflurane concentration 0.125%).

Study 2: Isoflurane wash-in during sustained isocapnic hypoxia. All 11 subjects participated in this study. The $P_{ET_{O_2}}$ was forced according to the following pattern: (1) 10 min at 110 mmHg; (2) a rapid decrease to 45 mmHg; (3) maintenance at 45 mmHg for 20 min. After hypoxic $\dot{V}_E$ had reached a steady state (after about 15 min of hypoxia) the isoflurane end-tidal concentration was increased from zero to the target level (end-tidal fraction 0.125%) within 4–6 breaths.

Study 3: The ventilatory response to sustained isocapnic hypoxia. The eight subjects of study 1 participated in this study. The $P_{ET_{O_2}}$ was forced according to the following pattern: (1) 10 min at 110 mmHg; (2) a rapid decrease to 45 mmHg within 2 or 3 breaths; (3) maintenance at 45 mmHg for 20 min; (4) a 10-min hyperoxic period (inspired fraction >0.7). Each subject performed three experiments in the following order: one control, one at 0.1 MAC and one at 0.2 MAC isoflurane. Between experiments there was a 30-min resting period. The end-tidal fraction of isoflurane was brought to 0.125% (for the 0.1 MAC experiments) or 0.25% (for the 0.2 MAC experiments) within 5 min by means of an "overpressure" technique. Thereafter a 20-min equilibrium period preceded the hypoxic challenge.

Throughout the isoflurane trials, the end-tidal fraction of isoflurane was maintained at the target level by manipulation of the isoflurane vaporizer by one of the authors (A.D. or M.v.d.E.).

Data Analysis

Study 1. The steady-state relation of $\dot{V}_E$ to $P_{ET_{CO_2}}$ at constant $P_{ET_{O_2}}$ in man is described by:

$$\dot{V}_E = (G_P + G_C)(P_{ET_{CO_2}} - B) \quad (1)$$

where G_P = the carbon dioxide sensitivity of the peripheral chemoreflex loop; G_C = the carbon dioxide sensitivity of the central chemoreflex loop; and B = the apneic threshold or extrapolated $P_{ET_{CO_2}}$ of the steady-state ventilatory response to carbon dioxide at zero $\dot{V}_E$. The sum of G_P and G_C is the total carbon dioxide sensitivity (G_{TOT}).

For the analysis of the dynamic response of the ventilation we used a two-compartment model[3,10–12]:

$$\tau_P \, d/dt \, \dot{V}_P(t) = G_P(P_{ET_{CO_2}}[t - T_P] - B) - \dot{V}_P(t) \quad (2)$$

$$\tau_C \, d/dt \, \dot{V}_C(t) = G_C(P_{ET_{CO_2}}[t - T_C] - B) - \dot{V}_C(t) \quad (3)$$

where τ_P and τ_C = the time constants of the peripheral and central chemoreflex loops, respectively; $\dot{V}_P(t)$ and $\dot{V}_C(t)$ = the outputs of the peripheral and central chemoreflex loops, respectively; $P_{ET_{CO_2}}[t - T_P]$ = the stimulus to the peripheral chemoreflex loop delayed by the peripheral transport delay time (T_P); and $P_{ET_{CO_2}}[t - T_C]$

= the stimulus to the central chemoreflex loop delayed by the central transport delay time (T_C).

To model τ_C of the ventilatory on-transient (τ_{ON}) to be different from that of the off-transient (τ_{OFF}), τ_C is written as:

$$\tau_C = \tau_{ON}x + (1 - x)\tau_{OFF} \quad (4)$$

where x = 1 when the $P_{ET_{CO_2}}$ is high and x = 0 when $P_{ET_{CO_2}}$ is low.

In most experiments a small drift in ventilation was present. We therefore included a drift term (Ct) in our model. The total ventilatory response $\dot{V}_E(t)$ is made up of the contributions of the central and peripheral chemoreflex loops, Ct, and a measurement noise term (W(t)):

$$\dot{V}_E(t) = \dot{V}_P(t) + \dot{V}_C(t) + Ct + W(t) \quad (5)$$

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_P and T_C, with increments of 1 s and with $T_P \leq T_C$ were tried until a minimum in the residual sum of squares was found. The minimum time delay was chosen, arbitrarily, to be 1 s, and τ_P was constrained to be at least 0.3 s.

Study 2. Mean values of the breath-to-breath $\dot{V}_E$ over five identical time segments were evaluated and expressed as absolute values and percentage of awake normoxic baseline $\dot{V}_E$. We calculated mean values for the last 2 min of normoxia before hypoxia (the awake normoxic data point) and for the 30-s period before the isoflurane wash-in (the awake hypoxic data point). During wash-in mean values were determined over periods 15–30, 30–60, 90–120, and 150–180 s after the start of isoflurane inhalation.

Study 3. The experiments were evaluated by taking mean values of the breath-to-breath $\dot{V}_E$ over identical time segments: period A = the final 2 min of normoxic $\dot{V}_E$ before the induction of sustained hypoxia; period B = min 3 and 4 of hypoxia; and period C = min 19 and 20 of hypoxia. The difference in $\dot{V}_E$ between periods B and A is termed the acute hypoxic response, and the difference between periods B and C is termed the hypoxic ventilatory decrease.

Inclusion Criteria

At the start and end of experiments in studies 1 and 3 we recorded the central nervous system (CNS) arousal state of the subjects by applying a five-point scale: 0 = normal alertness; 1 = drowsy, open eyes; 2 = closed eyes, opened by verbal command; 3 = closed eyes, opened by touching the subject; and 4 = closed eyes, unarousable.

Data were included for analysis if the subjects were in scale 0 for the control, scale 2 for the 0.1 MAC and scale 3 for the 0.2 MAC isoflurane experiments. Furthermore, during the experiments the subjects were continuously observed by one of the investigators (A.D. or M.v.d.E.). Data from an experiment were discarded when obstructive apnea or an apparent change of the CNS arousal state occurred (*e.g.*, limb movement, eye opening, restlessness).

Statistical Analysis

To detect the significance of differences between the treatments of study 1, a two-way analysis of variance was performed on parameters B, G_P, G_C, G_{TOT}, and G_P/G_{TOT} using a mixed model. As the data were unbalanced, the variance components were estimated by weighted means analysis.[13]

A two-way analysis of variance was performed on averaged $\dot{V}_E$ of the different periods (absolute and relative values) of study 2, and the acute hypoxic response and the hypoxic ventilatory decrease of study 3. Differences between periods were tested with the Student-Newman-Keuls test.

Probability levels <0.05 were considered significant. All values are means ± SE.

Results

Study 1

We obtained data from 19 control and 20 isoflurane experiments. Two isoflurane experiments were discarded because of arousal during the hypercapnic period, in one case because of obstructive apnea. G_{TOT} averaged 1.7 ± 0.1 $l \cdot min^{-1} \cdot mmHg^{-1}$ for the control experiments. At 0.1 MAC isoflurane there was a significant decrease to 1.3 ± 0.3 $l \cdot min^{-1} \cdot mmHg^{-1}$ ($P < 0.01$; fig. 1, top). The apneic threshold did not differ between treatments (control 36.0 ± 0.1 mmHg *vs.* isoflurane 34.5 ± 0.2 mmHg). The model fits to a control and an isoflurane experiment of one subject are shown in figure 1 (middle and bottom). They demonstrate that the contribution of the peripheral chemoreflex loop was decreased during isoflurane inhalation without much change of the contribution of the central chemoreflex loop. G_P decreased from 0.50 ± 0.08

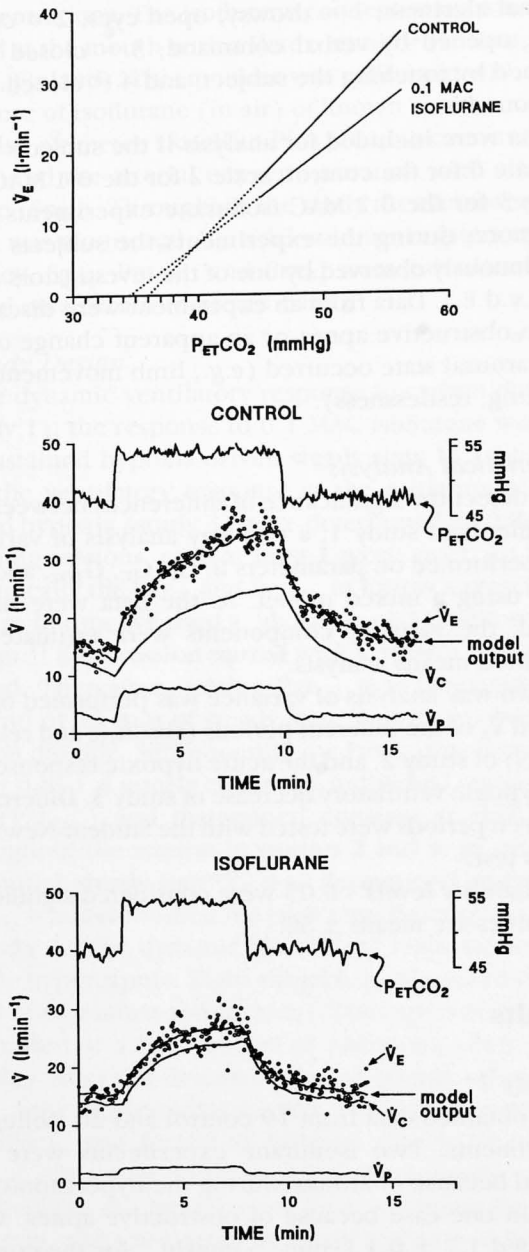

Fig. 1. (*Top*) The mean steady-state ventilatory response to carbon dioxide without and with 0.1 MAC isoflurane of all subjects. The inhalation of 0.1 MAC isoflurane reduced the ventilatory carbon dioxide sensitivity by about 25% without significantly affecting the extrapolated end-tidal carbon dioxide tension ($P_{ET}CO_2$) at zero minute ventilation ($\dot{V}_E$). (*Middle*) Model fit to a control experiment of subject 429. Each dot = 1 breath. The model output is the sum of the output of the central chemoreflex loop ($\dot{V}_C$), output of the peripheral chemoreflex loop ($\dot{V}_P$), a trend term, and measurement noise (not shown). The ratio of the ventilatory carbon dioxide sensitivity of the peripheral chemoreflex loop (G_P) to total ventilatory carbon dioxide sensitivity (G_{TOT}) = 0.2. (*Bottom*) Model fit to an experiment at 0.1 MAC isoflurane in subject 429. G_P/G_{TOT} is reduced to 0.1.

(control) to 0.28 ± 0.05 l·min^{-1}·mmHg^{-1} (isoflurane, $P < 0.01$); G_C did not show a significant change (control 1.20 ± 0.12 *vs.* isoflurane 1.04 ± 0.11 l·min^{-1}·mmHg^{-1}). The ratio G_P/G_{TOT} showed a 45% decrease from 0.37 ± 0.04 (control) to 0.20 ± 0.03 (isoflurane, $P < 0.01$). In figure 2 the mean values of B, G_P, G_C, and G_P/G_{TOT} of each subject for the two treatments are shown in scatter diagrams.

Study 2

In figure 3 (left) the response of one subject is displayed. It shows the biphasic response to a step decrease in $P_{ET}O_2$ and the immediate ventilatory decrease at the inhalation of isoflurane (end-tidal tension increased from zero to about 0.9 mmHg in 4 breaths). A biphasic response was observed in the initial (awake) part of the experiments in all subjects. Peak ventilation, determined between min 3–5 of hypoxia, was 153 ± 11% of baseline $\dot{V}_E$. The new steady-state $\dot{V}_E$ reached before isoflurane wash-in (*i.e.*, the awake hypoxic data point) was 127 ± 7% of baseline $\dot{V}_E$. The ventilatory change due to isoflurane occurred significantly within the first 30 s (fig. 3, right) of isoflurane wash-in. $\dot{V}_E$ decreased to 107 ± 7%, 108 ± 8.1%, 104 ± 7.2%, and 101 ± 9% of baseline in $\dot{V}_E$ in periods 15–30, 30–60, 90–120, and 150–180 s of isoflurane wash-in, respectively (fig. 3). The mean values of $\dot{V}_E$, $P_{ET}O_2$, $P_{ET}CO_2$ and the end-tidal isoflurane tensions of the different periods are collected in table 1.

Study 3

All subjects completed this study without problems, none of the experiments had to be discarded. In figure 4 the acute hypoxic responses at 0, 0.1, and 0.2 MAC isoflurane from one subject are plotted indicating the dose dependent depression of the acute hypoxic response. We observed a decrease of baseline $\dot{V}_E$ at 0.1 and 0.2 MAC isoflurane compared with control ($P < 0.05$) (table 2). The levels of Sp_{O_2} and $P_{ET}O_2$ in periods B and C and the changes in $P_{ET}O_2$, Sp_{O_2} and $P_{ET}CO_2$ between periods B and A ($\Delta_{A\rightarrow B}$) and B and C ($\Delta_{B\rightarrow C}$) did not differ significantly among treatments. The mean values of the parameters of periods A, B and C are collected in table 2. The acute hypoxic responses averaged 7.7 ± 1.4 l·min^{-1} (the ventilatory response to acute hypoxia per percentage drop in Sp_{O_2} = 0.44 ± 0.08 l·min^{-1}·%$^{-1}$) in the control experiments, 4.1 ± 0.8 l·min^{-1} (0.25 ± 0.05 l·min^{-1}·%$^{-1}$) in the 0.1 MAC isoflurane experiments ($P < 0.05$ *vs.* control), and 2.8

Fig. 2. Scatter diagrams of the m
in each subject of the apneic thr
(*top left*), central carbon dioxide
(G_C) (*top right*), peripheral carb
sensitivity (G_P) (*bottom left*), an
of G_P to total ventilatory carb
sensitivity (G_{TOT}) (*bottom right*)
and isoflurane (iso) experim
subject is represented by the sa
in all diagrams.

±0.6 l·min^{-1} (0.16 ± 0.0
MAC isoflurane experimen
The hypoxic ventilatory
control, 3.4 ± 0.5 fo 0.1
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tilatory response to sustain

Fig. 3. (*Left*) Effect of a step
end-tidal isoflurane tension (
0 to approximately 0.9 mm
tained hypoxia-driven minute
($\dot{V}_E$) in subject 415 at min 17 o
hypoxia. (*Right*) Mean effect o
to isoflurane on sustained hyp
$\dot{V}_E$. Data points are means ± SE
$P_{ET_{O_2}}$ and $\dot{V}_E$ (percentage of
normoxic $\dot{V}_E$). The last expirati
isoflurane was indexed at time
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hand. *$P < 0.05$ *versus* hypo
(circles).

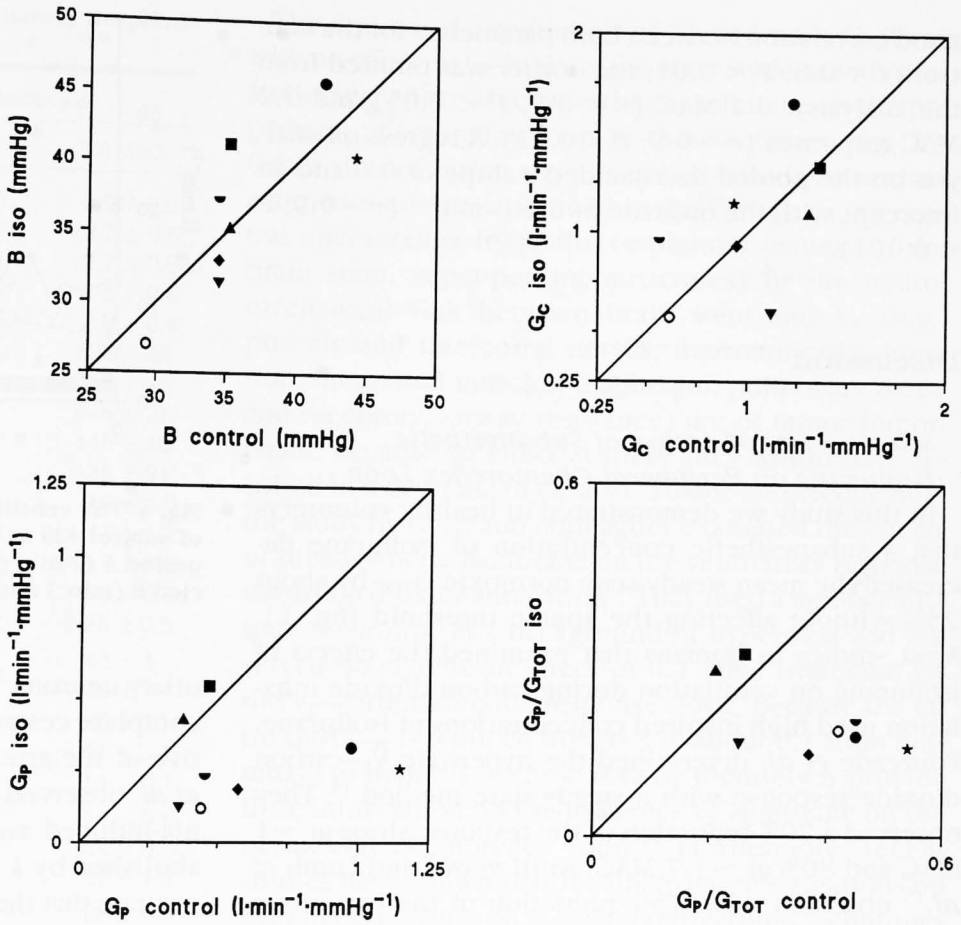

Fig. 2. Scatter diagrams of the mean values in each subject of the apneic threshold (B) (*top left*), central carbon dioxide sensitivity (G_C) (*top right*), peripheral carbon dioxide sensitivity (G_P) (*bottom left*), and the ratio of G_P to total ventilatory carbon dioxide sensitivity (G_{TOT}) (*bottom right*) for control and isoflurane (iso) experiments. Each subject is represented by the same symbol in all diagrams.

± 0.6 l·min^{-1} (0.16 ± 0.04 l·min^{-1}·%$^{-1}$) in the 0.2 MAC isoflurane experiments ($P < 0.05$ *vs.* control).

The hypoxic ventilatory decrease was 4.9 ± 0.8 for control, 3.4 ± 0.5 for 0.1 MAC isoflurane (difference not statistically significant), and 2.0 ± 0.4 l·min^{-1} for 0.2 MAC experiments ($P < 0.05$ *vs.* control). The ventilatory response to sustained isocapnic hypoxia (*i.e.*, the ventilatory increase after 20 min of hypoxia per percentage drop in Sp_{O_2}) was 0.16 ± 0.07 for control, 0.04 ± 0.03 for 0.1 MAC isoflurane ($P < 0.05$ *vs.* control), and 0.04 ± 0.02 l·min^{-1}·%$^{-1}$ for 0.2 MAC isoflurane experiments ($P < 0.05$ *vs.* control).

In figure 5A we plotted the acute hypoxic response against the hypoxic ventilatory decrease. There was a

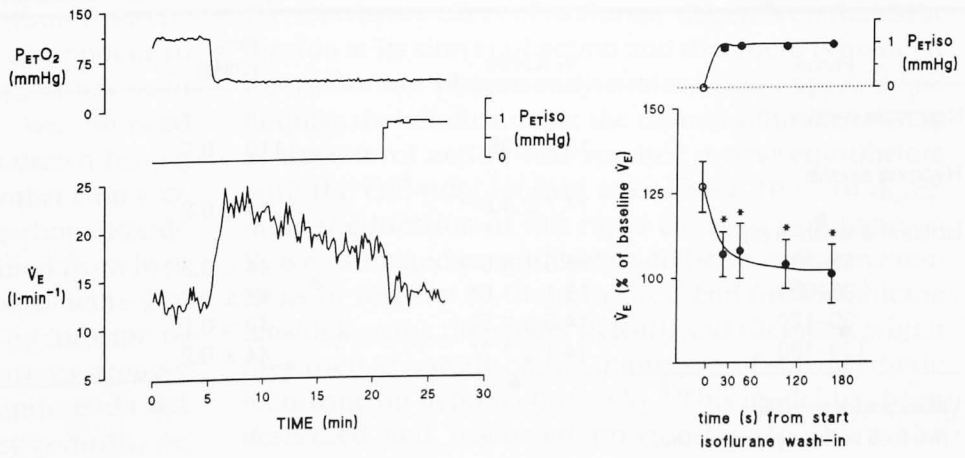

Fig. 3. (*Left*) Effect of a step increase in end-tidal isoflurane tension ($P_{ET_{iso}}$) from 0 to approximately 0.9 mmHg on sustained hypoxia-driven minute ventilation ($\dot{V}_E$) in subject 415 at min 17 of isocapnic hypoxia. (*Right*) Mean effect of exposure to isoflurane on sustained hypoxia-driven $\dot{V}_E$. Data points are means ± SE (n = 11) of $P_{ET_{iso}}$ and $\dot{V}_E$ (percentage of prehypoxic normoxic $\dot{V}_E$). The last expiration without isoflurane was indexed at time 0. The lines through the data points were drawn by hand. *$P < 0.05$ *versus* hypoxia awake (circles).

good correlation between both parameters for the control ($r = 0.8$; $P < 0.05$; the outlier was omitted from the analysis), 0.1 MAC ($r = 0.7$; $P < 0.05$) and 0.2 MAC responses ($r = 0.9$; $P < 0.01$). A regression analysis on the pooled data yielded a slope of 0.6 and an intercept with the ordinate of 0.6 $l \cdot min^{-1}$ ($r = 0.9$; $P < 0.001$).

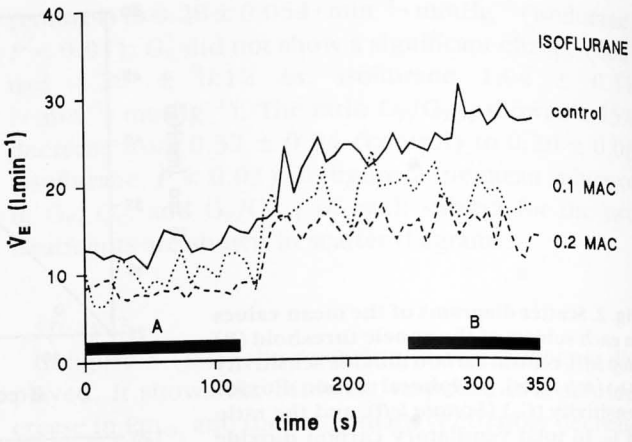

Fig. 4. The ventilatory responses to acute isocapnic hypoxia of subject 429 at 0, 0.1, and 0.2 MAC isoflurane. Solid bars = period A (2-min period before induction of hypoxia) and period B (min 3 and 4 of hypoxia). $\dot{V}_E$ = minute ventilation.

Discussion

Selective Site of Action of Subanesthetic Isoflurane on Peripheral Chemoreflex Loop

In this study we demonstrated in healthy volunteers that a subanesthetic concentration of isoflurane decreased the mean steady-state normoxic G_{TOT} by about 25% without affecting the apneic threshold (fig. 1). Most studies in humans that examined the effects of isoflurane on ventilation during carbon dioxide inhalation used high inspired concentrations of isoflurane. Fourcade *et al.* determined the hyperoxic $\dot{V}_E$–carbon dioxide response with a steady-state method.[14] They observed a 70% reduction of the response slope at ~1 MAC and 80% at ~1.7 MAC. Knill *et al.*[9] and Lumb *et al.*[15] observed a 70–75% reduction of the hyperoxic carbon dioxide response slope at 1.1 and 1 MAC isoflurane, respectively, using a non–steady-state technique. Part of this reduction is related to the decrease of the relative contribution of the rib cage to carbon dioxide stimulated ventilation[15] and part to a general depression of the central respiratory neuronal drive.

A study in vagotomized paralyzed dogs demonstrated a profound depressant effect at anesthetic isoflurane concentrations on the inspiratory and expiratory medullary neurons.[16] Isoflurane MAC fractions >2.0 caused complete cessation of phrenic nerve activity, irrespective of the arterial carbon dioxide tension. Hirshman *et al.* observed in tracheotomized dogs that hypercapnia-induced augmentation of the hypoxic drive was abolished by 1.5 MAC isoflurane.[17] These studies demonstrate that the reduction in carbon dioxide sensitivity (G_{TOT}) at anesthetic concentrations of isoflurane originates within the CNS and at peripheral sites (*i.e.*, at one or more of the components of the peripheral chemoreflex loop and at the processes between the controller and ventilatory pump).

To locate the site of action of *subanesthetic* isoflurane we determined the steady-state characteristics and dynamics of the central and peripheral chemoreflex loops using the noninvasive dynamic end-tidal forcing technique.[3,10–12] This technique

Table 1. Effects of Subanesthetic Isoflurane on Sustained Hypoxia-driven Ventilation

Period	$\dot{V}_E$ (L/min)	$P_{ET_{O_2}}$ (mmHg)	$P_{ET_{CO_2}}$ (mmHg)	$P_{ET_{ISO}}$ (mmHg)
Normoxia awake	13.8 ± 06	110 ± 0.5	44 ± 0.7	—
Hypoxia awake	17.7 ± 1.6	44 ± 0.2	44 ± 0.7	—
Isoflurane wash-in (s)				
15–30	15.0 ± 1.5*	44 ± 0.3	44 ± 0.7	0.90 ± 0.07
30–60	15.1 ± 1.6*	44 ± 0.2	44 ± 0.6	0.92 ± 0.03
90–120	14.5 ± 1.5*	44 ± 0.2	44 ± 0.7	0.92 ± 0.03
150–180	14.1 ± 1.7*	44 ± 0.2	44 ± 0.7	0.96 ± 0.04

Values are mean ± SE.

* $P < 0.05$ *versus* hypoxia awake.

Table 2. The Effect of Isoflurane on the Ventilatory Response to Sustained Hypoxia

			Isoflurane	
		Control	0.1 MAC	0.2 MAC
$\dot{V}_E$ (L/min)	A	14.5 ± 0.9	10.8 ± 0.5	9.9 ± 0.5
	B	22.2 ± 1.9	14.9 ± 0.7	12.7 ± 0.5
	C	17.3 ± 1.4	11.5 ± 0.4	10.7 ± 0.5
	Δ_{A-B}	7.7 ± 1.4	4.1 ± 0.8*	2.8 ± 0.6*
	Δ_{B-C}	4.9 ± 0.8	3.4 ± 0.5	2.0 ± 0.4*
V_T (ml/breath)	A	848 ± 37	683 ± 37	638 ± 42
	B	1166 ± 54	898 ± 41	783 ± 45
	C	941 ± 63	725 ± 39	645 ± 27
	Δ_{A-B}	318 ± 50	215 ± 40*	145 ± 46*
	Δ_{B-C}	224 ± 28	173 ± 31	138 ± 31*
f (breaths/min)	A	17 ± 1.1	16 ± 0.8	16 ± 1.0
	B	19 ± 1.2	17 ± 0.8	17 ± 1.2
	C	19 ± 0.9	16 ± 0.8	17 ± 1.0
	Δ_{A-B}	1.9 ± 0.7	0.5 ± 0.3	0.5 ± 0.8
	Δ_{B-C}	0.4 ± 0.7	0.4 ± 0.2	−0.25 ± 0.5
$P_{ET_{CO_2}}$ (mmHg)	A	44 ± 0.8	44 ± 1	45 ± 1
	B	44 ± 0.8	44 ± 1	45 ± 1
	C	44 ± 0.9	44 ± 1	45 ± 1
	Δ_{A-B}	−0.3 ± 0.1	−0.4 ± 0.1	−0.01 ± 0.1
	Δ_{B-C}	−0.1 ± 0.1	−0.2 ± 0.1	0.1 ± 0.1
$P_{ET_{O_2}}$ (mmHg)	A	112 ± 0.5	111 ± 0.6	111 ± 0.6
	B	44 ± 0.7	44 ± 1.1	46 ± 0.7
	C	45 ± 0.6	45 ± 1.0	47 ± 1.3
Sp_{O_2} (%)	A	98 ± 0.2	98 ± 0.2	98 ± 0.3
	B	80 ± 0.4	81 ± 0.6	81 ± 0.5
	C	79 ± 0.3	79 ± 0.4	79 ± 0.5
$P_{ET_{ISO}}$ (mmHg)	A	—	0.97 ± 0.00	1.86 ± 0.02
	B	—	0.95 ± 0.01	1.88 ± 0.02
	C	—	0.96 ± 0.01	1.86 ± 0.01

Δ_{A-B} = period A to period B; Δ_{B-C} = period B to period C. *$P < 0.05$ *versus* control.

nique.[3,10–12] This technique involves the application of steps in $P_{ET_{CO_2}}$ and a mathematical model to separate the dynamic response 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. This method has been validated extensively in cats.[12,18,19] We showed previously[3] in humans that conclusions drawn from a study on the effects of subanesthetic halothane on ventilatory control with dynamic end-tidal carbon dioxide forcing were consistent with those obtained from hypoxic studies[3,20] and from a study in which acute isocapnic metabolic acidosis was induced by infusion of L-arginine hydrochloride.[2] These observations strongly support the overall validity of the dynamic end-tidal forcing technique in studying ventilatory control.

The finding of a reduction of G_P and ratio G_P/G_{TOT} with no effect on G_C in six of the eight subjects indicates a selective effect of subanesthetic isoflurane on the peripheral chemoreflex loop in these subjects (fig. 2). Other sites of action with respect to steady-state characteristics of ventilation within the CNS (*e.g.*, the central chemoreflex loop, the respiratory centers in the brain stem, supra-pontine structures) or the neuromechanical link between brain stem and $\dot{V}_E$ (*e.g.*, phrenic and intercostal nerves, neuromuscular junction, intercostal muscles, diaphragm, pulmonary tissue and receptors, airway resistance) are of minor importance, because an effect at these sites would have resulted in a decrease of G_C also. To our knowledge only the study by Knill and colleagues examined the effects of subanesthetic isoflurane on the ventilatory response to carbon dioxide inhalation.[9] They used a non–steady-state technique at a background of hyperoxia and observed no significant effect of 0.1 MAC isoflurane on the $\dot{V}_E$–carbon dioxide response slope. Because the ratio G_P/G_{TOT} is reduced from 0.3 to about 0.1 from normoxia to hyperoxia, these data by themselves provide little information on the influence of isoflurane on the peripheral chemoreflex loop.[10] Furthermore, recent studies have shown that results from investigations on the effects of drugs on G_C using rebreathing techniques are difficult to interpret.[21,22]

The results of the isoflurane wash-in study are in agreement with those of the dynamic hypercapnic study and furthermore pinpoint the effect of subanesthetic isoflurane at the site of the peripheral chemoreceptors. After induction of isocapnic hypoxia and $\dot{V}_E$ had reached a new steady state, the isoflurane end-tidal tension was increased from zero to about 0.1 MAC within 4–6 breaths and maintained constant at this level for 3 min. Isoflurane caused a ventilatory change predominantly within the first 30 s of wash-in. We assume that the ventilatory effect of isoflurane depends on the tissue tension at its site(s) of action and that there is no delay for isoflurane pharmacodynamics. Our experimental findings then indicate that the tissue isoflurane tension at the site of action had reached a near-equilibrium with the end-tidal tension after about 30 s. To determine the location of this rapid effect of isoflurane on $\dot{V}_E$ we estimated carotid body and brain isoflurane tensions in relation to the measured end-tidal isoflurane tensions, using the model of Knill and Clement, which they used in a study on the influences of subanesthetic halothane on hypoxia-driven $\dot{V}_E$.[1] This model has been described and discussed previously.[1] In short, the

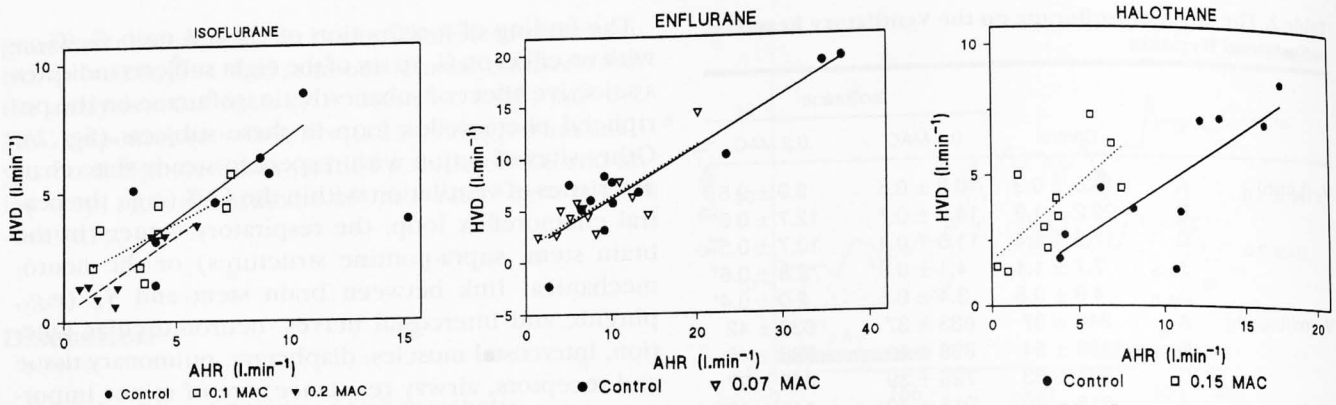

Fig. 5. Acute hypoxic response (AHR) *versus* hypoxic ventilatory decrease (HVD). (*Left*) Effects of isoflurane. The data points and the linear regressions are plotted for control (solid line), 0.1 MAC (dotted line), and 0.2 MAC isoflurane (dashed line). The outlier in the control data (AHR = 15.2, HVD = 3.9 $l \cdot min^{-1}$) was omitted from the linear regression analysis. Linear regression on the pooled data yielded a slope of 0.6 and an intercept with the ordinate of 0.6 $l \cdot min^{-1}$ ($r = 0.9$; $P < 0.001$) (not shown). Data from this study. (*Middle*) Effects of enflurane. Linear regression is shown through the data points for control (solid line) (n = 12; $r = 0.9$; $P < 0.001$) and 0.07 MAC enflurane (dotted line) (n = 12; $r = 0.8$; $P < 0.001$). Regression of the pooled data yielded a slope of 0.5 and intercept with the ordinate of 1.2 $l \cdot min^{-1}$. Data from Nagyova *et al.*[33] (*Right*) Effects of halothane. Linear regression is shown through the data points for control (solid line) (n = 10; slope = 0.4; intercept with the ordinate = 0.3 $l \cdot min^{-1}$; $r = 0.8$; $P < 0.01$) and 0.15 MAC halothane (dotted line) (n = 10; slope = 0.6; intercept with the ordinate = 1.7 $l \cdot min^{-1}$; $r = 0.7$, $P < 0.05$). Data from Dahan *et al.*[4]

model assumes that the isoflurane tissue uptake follows first order, perfusion limited kinetics and that the delivery of isoflurane from the lung to the tissues is delayed by a circulatory transit time. We assumed that the transport delay time from the lung to the carotid bodies is 7 s and to the brain 14 s,‖ and that the time constants for isoflurane uptake is 7 s for the carotid bodies and 4 min for the brain.[1,23] The model may overestimate the tissue tension of isoflurane because it does not take into account any end-tidal–to–arterial gradient for isoflurane or a diffusion time for isoflurane into the tissues. The results of the estimations are shown in figure 6. After 30 s of isoflurane inhalation, the carotid body isoflurane tension was estimated at about 90% of end-tidal, whereas the brain isoflurane tension was estimated at about 8% of end-tidal. Taking into account the limitations of the model, these estimations indicate that the experimentally observed ventilatory change, with respect to its dynamics, is well explained by an effect at the site of the peripheral chemoreceptors. The findings of Ponte and Sadler[24] in a study in cats and rabbits that the exposure of isoflurane into the inspired gases during normoxia and normocapnia caused a marked decrease of spontaneous peripheral chemoreceptors discharge over the 1st min, further strengthen our reasoning. The results of studies 1 and 2 lead to the conclusion that the effector site of subanesthetic isoflurane with respect to ventilatory control is located within the peripheral chemoreflex loop at the peripheral chemoreceptors.

A noteworthy observation in our study is that two subjects demonstrated relatively similar peripheral drives during control and isoflurane carbon dioxide experiments (fig. 2). Previously we performed steps in $P_{ET_{CO_2}}$ during hyperoxia and determined the peripheral carbon dioxide sensitivities.[10] We reported two subsets of response: in some subjects the existence of the peripheral component was doubtful or absent, whereas in others it averaged about one fourth of G_{TOT}. These findings suggest that several populations of carotid body response to various stimuli exist. It may well be that these differences in carotid body response are biologically determined. In a recent study Tankersley *et al.*[25] challenged eight inbred strains of mice to hypercapnia under normoxic and hyperoxic conditions. Their results indicated that genetic determinants determined the interstrain variation in ventilatory responses. Furthermore, hypoxic and hypercapnic ventilatory responses appeared to be influenced by different genetic mechanisms. Molecular studies on anesthetic action at the carotid bodies are necessary to elucidate this matter.

‖ Dahan A: The ventilatory response to carbon dioxide and oxygen in man: methods and implications. Ph.D. Thesis. Leiden, Leiden University, 1990.

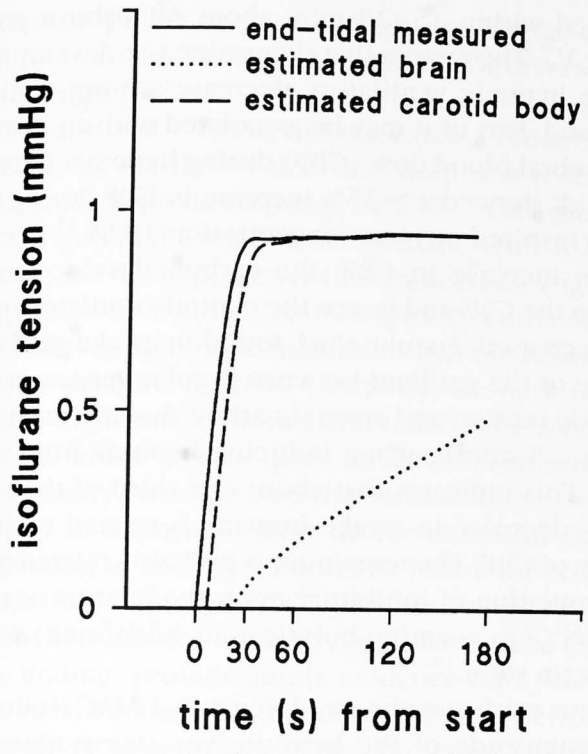

Fig. 6. Estimation of the carotid body and brain isoflurane tension and the measured end-tidal tension during the first 3 min of isoflurane wash-in.

The Ventilatory Response to Hypoxia

The Acute Hypoxic Response. We demonstrated a 50% and 65% reduction of the acute hypoxic responses at 0.1 and 0.2 MAC isoflurane, respectively. These observations are in agreement with the findings of Knill *et al.*[9]: at 0.1 MAC isoflurane they observed a 50% reduction of the ventilatory response to isocapnic hypoxia. At first, this may seem surprising taking into account the difference in the stimulus waveform: Knill *et al.*[9] applied a progressive decrease of the $P_{ET_{O_2}}$ to 6% over an 8- to 10-min period; we applied a decrease of the $P_{ET_{O_2}}$ to 5.9% within 2 or 3 breaths and kept this hypoxic level constant. When isocapnic hypoxia is induced as a step and sustained longer than 3–5 min, the ventilatory response is biphasic. The initial ventilatory increase, which is of peripheral origin, is followed by a slow ventilatory decrease, originating within the CNS. A slow progressive decrease in oxygen concentration over 8–10 min will therefore yield a response that is contaminated by central effects. The similarity in results of the studies of Knill *et al.*[9] and ours may be explained by the decrease of the magnitude of the central depressive effects of hypoxia by subanesthetic isoflurane.

In two studies Temp *et al.*[5,6] examined the sensitivity of the acute hypoxic response to 0.1 MAC isoflurane by applying a stimulus waveform similar to ours. In both studies they did not find a significant effect of subanesthetic isoflurane although they concluded that a moderate reduction could not be excluded. We attribute the difference in outcome of their and our investigations to the study conditions and the environment in which the subjects underwent the hypoxic procedures: the subjects of Temp *et al.*[5,6] were aroused through touch, visual and auditory input to prevent eye closure; our subjects performed the experiments in quiet room with closed eyes and with rigid avoidance of arousal during an experiment. In a previous study[8] we tested the influence of audiovisual input on the acute hypoxic response without and with 0.1 MAC isoflurane. A depressant effect of isoflurane was found only when external input to the subjects was absent. We argued that the audiovisual input activated conscious or behavioral ventilatory control that made the proper assessment of metabolic ventilatory control impossible.[8]

Sjögren *et al.*[7] studied the influences of isoflurane on the ventilatory response to hypoxia without and with $P_{ET_{CO_2}}$ control. At 0.6 MAC isoflurane they found a 50% reduction of the isocapnic ventilatory response to hypoxia compared with isocapnic control. These findings indicate a much lesser depressant effect of isoflurane than observed in our study (50% depression at already 0.1 MAC). Furthermore, the magnitude of their control isocapnic hypoxic responses was half of that measured in our group of subjects ($\sim$0.2 *vs.* 0.44 $l \cdot min^{-1} \cdot \%^{-1}$). We relate these differences to variations in protocol. Sjögren *et al.* performed experiments in patients awaiting elective surgery. Apart from the effects of the unfamiliarity with the apparatus and procedure, the performance of experiments before surgery may have had an important influence on the study outcome because of suprapontine mechanisms. Our subjects did appear to be well accustomed to the apparatus and underwent the experimental procedure several times before these studies. Perhaps more important, in contrast to our strict $P_{ET_{CO_2}}$ control between treatments (table 2), Sjögren *et al.*[7] allowed a $P_{ET_{CO_2}}$ increase of about 3.8 mmHg during the isoflurane experiments compared with control.

Foo *et al.*[26] investigated the interaction of subanesthetic isoflurane and domperidone (a selective dopamine D_2 receptor antagonist) on the ventilatory response to sustained isocapnic hypoxia in 20 male sub-

jects. They observed a 17% reduction of the acute hypoxic response at 0.1 MAC isoflurane. Although administration of domperidone decreased the depression of the initial response, a significant interaction with isoflurane could not be demonstrated. Similar to our study, they applied a square-wave change in Sp_{O_2} from 100% to 80%. However, their subjects were asked to remain awake and aroused with auditory and manual arousal when they appeared "asleep." With electroencephalographic monitoring they observed that the time spent asleep was less than 5 min spread over their 20-min measurement period. The arousal may explain the lesser magnitude of the depression of the acute hypoxic response compared with our results. The authors argue that the inability to observe an interaction between isoflurane and domperidone suggests that the mechanism of the depressant effect of isoflurane on the acute hypoxic response is not mediated *via* dopamine, a neurotransmitter in the carotid bodies.

The results of our studies[3,4,8] and those of Knill *et al.*,[9] Temp *et al.*,[5,6] Sjögren *et al.*,[7] and Foo *et al.*[26] demonstrate clearly that many seemingly small differences among protocols may affect the study outcome significantly. When we consider in this perspective the recent debate on the effects of subanesthetic concentrations of isoflurane on ventilatory control,[3–7,26–33] it is indisputable that 0.1 MAC isoflurane, halothane and enflurane profoundly affect ventilatory control in general and the acute hypoxic response in particular *via* their influence on the peripheral chemoreflex loop when examined in a quiet laboratory with strict $P_{ET_{CO_2}}$ control. However, in patients in the postoperative period, when the depressant effects on the peripheral chemoreflex loop are still present, additional drives may at times prevent a depressant effect of subanesthetic isoflurane or any other volatile anesthetic from becoming apparent (for instance because of pain or stimulation from recovery room personnel). At other times, when these drives are not present, residual anesthetics may lead to hypoventilation, hypercapnia, hypoxia and lessened ability to overcome obstructive apnea, all of which may be associated with significant morbidity.

Hypoxic Ventilatory Decrease. The ventilatory response to sustained isocapnic hypoxia shows an initial ventilatory increase. The origin of this increase, the acute hypoxic response, is at the carotid bodies. After 3–5 min, because of the central depressant effects of hypoxia of longer duration ventilation decreases (hypoxic ventilatory decrease).[34] A new steady-state $\dot{V}_E$ is reached within 15–20 min, about 30% above prehypoxic $\dot{V}_E$. The factors that determine the development of the hypoxic ventilatory decrease are not well understood. Part of it may be associated with an increase of cerebral blood flow (CBF) during hypoxia. Kety and Schmidt showed a ~35% increase in CBF during hypoxia (inspired oxygen concentration 10%).[35] Because of the increase in CBF, the carbon dioxide tension within the CNS and hence the central ventilatory drive are decreased. Suzuki *et al.* found in awake man a decrease of the gradient between jugular venous carbon dioxide tension and arterial carbon dioxide tension of about 1.5 mmHg when inducing hypoxia from room air.[36] This indicates that about one third of the ventilatory decrease in awake humans is related to an increase of CBF. The remainder is probably related to the accumulation of inhibitory neuromodulators or transmitters (*e.g.*, γ-amino butyric acid, adenosine) within the brain stem.[37–39]

In our study we observed that at 0.1 MAC isoflurane the magnitude of the hypoxic ventilatory decrease was decreased but did not quite reach the level of significance. On the other hand, 0.2 MAC isoflurane decreased the magnitude of the hypoxic ventilatory decrease by 60%. This reduction may be caused by an effect of isoflurane on CBF. However, it is improbable that isoflurane at the end-tidal concentrations we have used altered (*i.e.*, decreased) the CBF response to hypoxia. The reduction of the hypoxic ventilatory decrease may then be related to a decrease in net concentration of inhibitory substances in the brain stem. In humans changing the output from the peripheral chemoreceptors changes the magnitude of the hypoxic ventilatory decrease. Almitrine causes an increase of the acute hypoxic response and the hypoxic ventilatory decrease,[37] whereas the reverse is true for somatostatin.[39] We showed that decreasing the peripheral drive with isoflurane caused the reduction of the hypoxic ventilatory decrease. Furthermore, at all three treatments the relation between the acute hypoxic response and the hypoxic ventilatory decrease remained present among subjects with little difference in slopes and intercepts (fig. 5A). Nagyova *et al.*[33] made a similar observation with 0.07 MAC enflurane (fig. 5B). These findings suggest that the afferent information from the carotid bodies determines the magnitude of the hypoxic ventilatory decrease due to "central" modulation of the peripheral input into the release of inhibitory substances near sites within the CNS that determine $\dot{V}_E$ (such as

facilitation of the release at high peripheral drives [*e.g.*, by almitrine] and the reverse at low drives [*e.g.*, by isoflurane]).[39]

Halothane at 0.15 MAC did not cause a reduction of the hypoxic ventilatory decrease despite a reduction of the acute hypoxic response by 65%.[4] This caused a leftward shift of the relation between the acute hypoxic response and the hypoxic ventilatory decrease (fig. 5C). Compared with control, 100% hypoxic ventilatory decrease during halothane inhalation was obtained with 65% less peripheral drive. Currently, we have no satisfactory explanation for this difference in behavior between halothane and the other inhalational anesthetics.

In summary, we observed that subanesthestic isoflurane had an important effect on the chemical control of breathing in healthy volunteers. Isoflurane reduced G_P with little influence on G_C. The ventilatory response to acute hypoxia was affected proportionally to the G_P. These findings provide ample evidence for a selective effect of subanesthetic isoflurane on the peripheral chemoreflex loop. Furthermore, the rapid ventilatory decrease due to isoflurane wash-in on steady-state hypoxic ventilation indicates that the site of action is located at the peripheral chemoreceptors. Our studies, together with those of others,[1–4,33] demonstrate that subanesthetic isoflurane, halothane, and enflurane in this respect behave in the same fashion.

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Heat Balance
Temperature

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Background: **Once triggered,**
tory vasoconstriction is remar
further hypothermia. Protecti
striction-induced decrease in c
distribution of body heat. How
butions of each mechanism h
cordingly, we evaluated overal
of heat within the body during
Methods: **Nine minimally c**
anesthetized with propofol and
an ≈22°C environment. They w
vasoconstriction and for 3 h s
ance was determined from the
heat loss (thermal flux transdu
duction (oxygen consumption
tents were determined from 1
ten skin temperatures, and "
constrained by vasoconstrictio
calculated by subtracting the e
(overall heat balance multiplie
the trunk and head) from the a
esophageal temperature multip
man tissue and the weight of t
represents the amount by wh
which would be expected base
suming that the change was e
the body.
Results: **Vasoconstriction an**
creased heat loss but not to the
sequently, heat loss exceede

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