Ventilatory Response to Hypoxia in Humans

Influences of Subanesthetic Desflurane

Albert Dahan, M.D., Ph.D.,* Elise Sarton, M.D.,† Maarten van den Elsen, M.D.,‡ Jack van Kleef, M.D., Ph.D.,‡ Luc Teppema, Ph.D.,§ Aad Berkenbosch, Ph.D.¶

**Background:** At low dose, the halogenated anesthetic agents halothane, isoflurane, and enfurane depress the ventilatory response to isocapnic hypoxia in humans. In the current study, the influence of subanesthetic desflurane (0.1 minimum alveolar concentration [MAC]) on the isocapnic hypoxic ventilatory response was assessed in healthy volunteers during normocapnia and hypercapnia.

**Methods:** A single hypoxic ventilatory response was obtained at each of 4 target end-tidal partial pressure of oxygen concentrations: 75, 53, 44, and 38 mmHg, before and during 0.1 MAC desflurane administration. Fourteen subjects were tested at a normal end-tidal partial pressure of carbon dioxide (43 mmHg), with 9 subjects tested at an end-tidal carbon dioxide concentration of 49 mmHg (hypercapnia). The hypoxic sensitivity (S) was computed as the slope of the linear regression of inspired minute ventilation (V̇E) on (100 – S纯O₂). Values are mean ± SE.

**Results:** Sensitivity was unaffected by desflurane during normocapnia (control: S = 0.45 ± 0.07 l/min % S纯O₂ vs. 0.1 MAC desflurane: S = 0.43 ± 0.09 l/min % S纯O₂). With hypercapnia S decreased by 30% during desflurane inhalation (control: S = 0.74 ± 0.09 l/min % S纯O₂ vs. 0.1 MAC desflurane: S = 0.55 ± 0.06 l/min % S纯O₂, P < 0.05).

**Conclusions:** On the basis of the data, subanesthetic desflurane has no detectable effect on the normocapnic hypoxic ventilatory response sensitivity. However, the carbon dioxide-induced augmentation of the hypoxic response was reduced. This indicates that subanesthetic desflurane affects the chemoreceptors at the carotid bodies. (Key words: Anesthesics, volatile: desflurane, Methods, dynamic end-tidal forcing, isoflurane, Receptors, peripheral: carotid bodies, Ventilation: hypercapnia; hypoxic response; normocapnia. Respiration: regulation.)

**DESFLURANE,** an inhalational anesthetic introduced in clinical practice in 1992, reduces the ventilatory response to carbon dioxide at anesthetic concentrations (minimum alveolar concentration [MAC] fraction ≥ 0.8). At these alveolar concentrations, the regulation of breathing is affected via depression of the central neuronal respiratory drive, the peripheral drive from the carotid bodies, and/or the efferent pathways between controller and ventilatory pump. In the current study, we investigated the effects of subanesthetic desflurane (0.1 MAC) on ventilatory control, in particular on the responses mediated via the carotid bodies. Studies in humans performed in our laboratory consistently showed that halothane and isoflurane at MAC-fractions ranging from 0.05 to 0.2 reduced the ventilatory responses that originated at the carotid bodies (i.e., the hypoxic ventilatory response and the ventilatory carbon dioxide sensitivity of the peripheral chemoreceptors). We expected that subanesthetic desflurane would behave in a similar fashion, despite its somewhat distinctive pharmacodynamic properties apparent at higher inspired concentrations that may be related to the control of breathing: airway irritation, and a significant increase in sympathetic activity that occurs with rapidly increasing the MAC-fraction from 0.5 to 1.0 or 1.5.

Our main aim in the current study was to assess the influence of 0.1 MAC desflurane on the ventilatory response to hypoxia at constant normocapnia and hypercapnic levels in healthy young volunteers. This al-

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* Staff Anesthesiologist, Department of Anesthesiology, Leiden University Hospital.
† Resident, Department of Anesthesiology, Leiden University Hospital.
‡ Professor and Chairman, Department of Anesthesiology, Leiden University Hospital.
§ Assistant Professor of Physiology, Department of Physiology, Leiden University.
¶ Associate Professor of Physiology, Department of Physiology, Leiden University.

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lowed us to examine the effects of desflurane on the augmentation of the hypoxic response by carbon dioxide, an effect believed to originate at the peripheral chemoreceptors.

Materials and Methods

Subjects and Apparatus

After approval by the Leiden University Committee on Medical Ethics, 1 healthy, aged 24–30 yr subjects (5 women) without a history of smoking, drug, or alcohol abuse were selected for the study. None had participated in other respiratory studies. Before the studies, the subjects participated in a training session to become familiarized with the protocol and apparatus. The magnitude of the hypoxic response was not measured in these training sessions. The subjects were advised not to eat or drink for the 6 h before the study. This procedure was identical to that used in our earlier studies.

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 (Fleisch, Lausanne, Switzerland) 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 strokes/min). The pneumotachograph was connected to a T piece. One arm of the T piece received a gas mixture, with a flow of 45 l/min from a gas mixing system that consisted of four mass flow controllers (F201–F203, Bronkhurst High Tec, Veenendaal, The Netherlands) with which the flow of oxygen, carbon dioxide, nitrogen, and desflurane in nitrogen could be set individually at a desired level. Flows were calibrated with flow resistance standards (Godart, Bilthoven, The Netherlands). A Programmable Digital Processor 11/23 microcomputer (Digital Equipment Corporation, Maynard, MA) provided control signals to the mass flow controllers, so that the composition of the inspiratory gas mixture could be adjusted to force the end-tidal oxygen tension ($\text{P}_{\text{et}}\text{O}_2$) to follow a specific pattern in time while the end-tidal carbon dioxide tension ($\text{P}_{\text{et}}\text{CO}_2$) is kept constant. Part of the nitrogen (5 l/min) passed through the desflurane vaporizer (Tec 6, Ohmeda, West Yorkshire, United Kingdom). 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 (Datex Multicap, Helsinki, Finland) by paramagnetic and infrared analysis, respectively. The gas monitor was calibrated with gas mixtures of known concentrations delivered by a gas-mixing pump (Wösthoff, Bochum, Germany). The desflurane concentration was measured at the mouth with a Datex monitor (Capnomac Ultima, Helsinki, Finland). A pulse oximeter (Datex Satellite Plus, Helsinki, Finland) continuously measured the arterial hemoglobin-oxygen saturation via a finger probe (S$_\text{a}$O$_2$). Throughout the study, the electrocardiograph was monitored. Inspiratory minute ventilation ($V_i$), tidal volume ($V_t$), respiratory rate (RR), $S\text{O}_2$, $P\text{et}CO_2$, and $P\text{et}O_2$ were stored on a breath-to-breath basis.

Study Design

The ventilatory responses to hypoxia at the background of normocapnia (Normocapnic Studies) and the responses at a background of hypercapnia (Hypercapnic Studies) were determined on different morning sessions, at least 1 week apart. Four hypoxic responses were obtained before and during desflurane administration at the following target end-tidal oxygen fractions: 0.10 ($P\text{et}O_2 \sim 75$ mmHg), 0.07 ($P\text{et}O_2 \sim 53$ mmHg), 0.058 ($P\text{et}O_2 \sim 44$ mmHg), and 0.050 ($P\text{et}O_2 \sim 38$ mmHg; fig. 1).

Each session started with a 30-min relaxation period. Thereafter, individual resting $P\text{et}CO_2$ was determined at the end of 10 min of steady-state $V_i$ with no inspired carbon dioxide. Subsequently, the $P\text{et}CO_2$ was increased by 2 mmHg in the normocapnic studies and 8 mmHg in the hypercapnic studies. This level was maintained throughout the control and desflurane studies.

Hypoxia was induced with a “dynamic end-tidal forcing” system: steps from normoxia ($P\text{et}O_2 \sim 110$ mmHg) into hypoxia (target $P\text{et}O_2$ level obtained within 4–8 breaths) were applied. Hypoxia was maintained for 3 min, after which normoxia was reintroduced. Between hypoxic challenges there was a 10- to 15-min interlude. For each study (control-normocapnia; control hypercapnia; desflurane-normocapnia; desflurane-hypercapnia), the subjects were allocated randomly to 1 of 24 possible study sequences (fig. 1).

The control studies always preceded the desflurane hypoxic studies. The end-tidal fraction of desflurane was brought to 0.72% (~0.1 MAC) within 1 min by means of an “overpressure” technique. Thereafter a
10- to 15-min equilibration period preceded the hypoxic challenges.

Data Analysis
Hypoxic sensitivity—The average $V_t$ of the last 30 s of each hypoxic challenge was calculated. In addition, normoxic ventilation was determined before the hypoxic challenges longer than 30 s. This yielded 5 $V_t$ $S_\text{O}_2$ data points.

We expressed $V_t$ as a linear function of arterial oxygen-hemoglobin desaturation:

$$S = [V_t - V_t(0)]/[100 - S_{\text{O}_2}]$$

where $S$ is the hypoxic sensitivity and $V_t(0)$ the ventilation at normoxia ($S_{\text{O}_2} = 98\%$). The parameters were determined by linear regression of $V_t$ on $(100 - S_{\text{O}_2})$. Similar procedures were performed for respiratory rate and tidal volume.

Inclusion Criteria
One of the investigators (AD, ES, or MvdE) continuously observed the subjects. During the study, soft music was played, but there was no visual stimulation. Experiments were performed in a normal lighted room that was sealed off from the data acquisition- and endtidal steering-apparatus.

At the start and end of the studies, 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 in response to verbal command;
3 = closed eyes, opened in response to touch; and
4 = closed eyes, unarousable.

Data were included for analysis if the subjects were in scale 0 for control and scales 0, 1, or 2 for the desflurane studies. In addition, data were discarded when a subject displayed discomfort during the study.

Statistical Analysis
To detect a significant difference (in the normocapnic and hypercapnic studies) between the control and desflurane studies, a Student’s $t$ test was performed on the $S$, $V_t(0)$, $\Delta V_t/\Delta S_{\text{O}_2}$, $\Delta RR/\Delta S_{\text{O}_2}$, respiratory rate at normoxia (RR(0)), and tidal volume at normoxia ($V_t(0)$). Probability levels $<0.05$ were considered significant. All values reported are mean $\pm$ SE.

Results
All fourteen subjects completed the normocapnic studies without problems or discomfort. Two subjects did not attend the hypercapnic session for unknown reasons; three others failed to complete the hypercapnic studies because of nausea and vomiting (two subjects) or discomfort (one subject). There were no signs of airway irritation, such as coughing, from desflurane during the studies.

Normocapnic Studies
End-tidal carbon dioxide tension averaged $43 \pm 0.8$ mmHg in the control and desflurane studies. The mean end-tidal desflurane concentration was $0.71 \pm 0.01\%$ in the desflurane studies. In the control stud-

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ies, the CNS arousal state of all subjects was 0 (normal alertness), and in the desflurane studies, 4 subjects were at level 1 and 10 were at level 2.

The $V_t$-S$_O_2$ relation over the S$_O_2$ range tested by us (98 to $\sim$70%) was linear (fig. 2). The hypoxic sensitivities obtained from the linear regression of $V_t$ on (100 - S$_O_2$) did not differ significantly between control and desflurane studies: $0.45 \pm 0.07 \cdot 1 \cdot \text{min}^{-1} \cdot \%^{-1}$ (control) versus $0.43 \pm 0.09 \cdot 1 \cdot \text{min}^{-1} \cdot \%^{-1}$ (desflurane). Inspiratory minute ventilation averaged $11.8 \pm 0.6 \cdot 1 \cdot \text{min}^{-1}$ in the control studies and $10.8 \pm 0.8 \cdot 1 \cdot \text{min}^{-1}$ in the desflurane studies (not significant). In figure 3, the hypoxic sensitivities of all subjects are collected in a scatter diagram. The three subjects that had an increase of their hypoxic sensitivity with desflurane had an CNS arousal score of 2. The values of the estimated parameters are listed in table 1.

**Hypercapnic Studies**

The hypoxic experiments were performed at a mean P$_{1\text{a}}$CO$_2$ background of $49 \pm 1$ mmHg, approximately 8 mmHg above resting P$_{1\text{a}}$CO$_2$ and 6 mmHg above the P$_{1\text{a}}$CO$_2$ level of the normocapnic studies. The end-tidal desflurane concentration averaged 0.72 $\pm$ 0.01% in the desflurane studies. In the control studies, the CNS arousal state of all subjects was 0 (normal alertness); in the desflurane studies, 4 subjects were at level 1, and 5 subjects were at level 2.

The slopes of the linear regression of $V_t$ on (100 - S$_O_2$) decreased from $0.74 \pm 0.09 \cdot 1 \cdot \text{min}^{-1} \cdot \%^{-1}$ (control) to $0.53 \pm 0.06 \cdot 1 \cdot \text{min}^{-1} \cdot \%^{-1}$ (desflurane; $P = 0.04$). In figure 3, the individual hypoxic sensitivities are plotted. Inspiratory minute ventilation did not differ significantly between treatments: $20.7 \pm 1.7 \cdot 1 \cdot \text{min}^{-1}$ and $20.9 \pm 1.6 \cdot 1 \cdot \text{min}^{-1}$ in the control and desflurane studies, respectively. See table 1 for results of all estimates.

**Discussion**

In the current study, we observed that subanesthetic desflurane in a group of 14 healthy volunteers did not influence significantly the ventilatory response to isocapnic hypoxia over the range of 110 to 38 mmHg (S$_O_2$ 98 to $\sim$70%) when experiments were performed against a background of normocapnia. This indicates that desflurane at 0.1 MAC lacks the well described and pronounced effect on the carotid bodies that the other inhalational anesthetic agents (halothane, isoflurane, and enfurane) possess. Still, the carotid bodies did not remain unaffected by their exposure to 0.1 MAC desflurane, because the ventilatory response to the combination of hypoxia and hypercapnia (asphyxia) was reduced by 30%.

**Critique of Methods**

**Control of Exhaled Gas Concentrations.** To study the ventilatory response to acute hypoxia (i.e., hypoxia <5 min), we used the computer-driven dynamic end-tidal forcing technique. This allowed us to perform steps in P$_{1\text{a}}$O$_2$ while maintaining a constant P$_{1\text{a}}$CO$_2$ by manipulation of the inspired gas concentrations independently of the ventilatory response. The P$_{1\text{a}}$CO$_2$ was set at 2 mmHg above the resting values in the normocapnic studies and at 8 mmHg above resting in the hypercapnic studies. The reason for the increase in the normocapnic studies is twofold. First, a small increase in inspired carbon dioxide concentration is necessary to control the end-tidal carbon dioxide concentrations adequately. The precision of end-tidal PCO$_2$ control was 0.6 mmHg; that is, the standard deviation of the breath-to-breath P$_{1\text{a}}$CO$_2$ of single periods [A or B] was 0.6 mmHg or less. A similar precision of control was obtained for P$_{1\text{a}}$O$_2$ in periods A and B. Second, this procedure permits the control and drug baseline P$_{1\text{a}}$CO$_2$'s to be similar, despite differences in baseline $V_t$. Differences in P$_{1\text{a}}$CO$_2$ between control and drug studies make the interpretation of the results difficult, and sometimes impossible, because the additive or synergistic effects of separate stimuli (for example pH, arterial PCO$_2$ and PO$_2$, or circulating catecholamines) on the measured response differ between treatments and may offset a specific drug effect. Other noncomputer-driven systems also are able to control end-tidal gas concentrations adequately to achieve near steps in P$_{1\text{a}}$O$_2$ at constant P$_{1\text{a}}$CO$_2$ (for example, see reference 11).

**Mask Versus Mouthpiece.** The subjects were attached to the pneumotachograph through an oronasal mask. We prefer a mask above a mouthpiece-noseclip arrangement for two reasons. It allows normal movement of mouth and lips and is less disruptive to normal breathing. The fit of the mask was loose to prevent excessive pressure on the face. However, the combination of mask and pneumotachograph increased the dead space to approximately 200 ml. This, together with the increased P$_{1\text{a}}$CO$_2$ level, explains the higher baseline $V_t$ of the normocapnic studies compared with studies.
that do not use a mask and/or inspired carbon dioxide.1,7

Corrections for Changes in Inspired Oxygen Concentrations. Because of the changes in oxygen concentration of the inspired air, the viscosity of the inspired gas changes and, consequently, so does the flow measured through the pneumotachograph. As in previous studies, we performed an online correction for these changes in oxygen viscosity.2–6

Step Hypoxic Test. We performed 3-min hypoxic steps in this study. It is our experience that peak $V_t$ is reached in the first 3 min of hypoxia, when the drop in $P_{O_2}$ is achieved within 4–6 breaths and the control of $P_{CO_2}$ is strict. We tested four levels of hypoxia for two reasons: (1) It allows the study of the hypoxic response to a broad hypoxic range ($S_{O_2}$ down to ~70%); and (2) It reduces the intra-subject response variability. In previous studies, we determined the hypoxic response at a single $P_{O_2}$ level (~44 mmHg).2–6 Analysis of the single step test at $P_{O_2}$ ~44 mmHg in the current study showed, however, that similar conclusions are drawn from a single test in comparison to the multiple step test. In addition, because a single step test reduces study duration, this test may be preferable above multiple effects of drugs on the hypoxic response.

The obtained ventilatory responses of different factors that decrease the hypoxia: (1) the hypoxic effects; (2) the depressive effects; and (3) the hypoxic effects, and blood flow in the central part of the brain, which are involved in determining the hypoxic response. Our measured responses, the central (depressant) effect due to flow (BBF) that may not be involved in determining the hypoxic response. The complete recovery requires as long as 1 h of room breathing 100% $O_2$.14 When the brain is sustained hypoxia, a subclinical be smaller in magnitude compared to the chronic hypoxia.15 This is most probably caused by autonomic depression.14,15 A 3-min step hypoxia, which is performed in the central medulla, is unable to exclude an autonomic depression on a subclinical study. A bias due to the autonomic depression is responsible for the awake responses.

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Table 1. Effects of 0.1 MAC Desflurane on the Ventilatory Response to Hypoxia at a Background of Isonormocapnia and Isohypercapnia

<table>
<thead>
<tr>
<th>Normocapnia (n = 14)</th>
<th>Control</th>
<th>Desflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_0/0$ (L · min⁻¹)</td>
<td>11.8 ± 0.6</td>
<td>10.8 ± 0.8</td>
</tr>
<tr>
<td>$\Delta V_0/\Delta S_{O_2}$ (ml·%⁻¹)</td>
<td>23.9 ± 4.0</td>
<td>17.8 ± 4.6*</td>
</tr>
<tr>
<td>$V_0/0$ (ml)</td>
<td>788 ± 40</td>
<td>709 ± 46*</td>
</tr>
<tr>
<td>$\Delta R/R/\Delta S_{O_2}$ (min⁻¹·%⁻¹)</td>
<td>0.10 ± 0.04</td>
<td>0.10 ± 0.05</td>
</tr>
<tr>
<td>RR(0) (min⁻¹)</td>
<td>15.2 ± 0.8</td>
<td>16.1 ± 0.7*</td>
</tr>
</tbody>
</table>

| Hypercapnia (n = 9) | | |
|---------------------| | |
| $V_0/0$ (L · min⁻¹) | 20.7 ± 1.7 | 20.9 ± 1.6 |
| $\Delta V_0/\Delta S_{O_2}$ (ml·%⁻¹) | 31.2 ± 5.7 | 26.7 ± 3.9 |
| $V_0/0$ (ml) | 1,149 ± 90 | 1,174 ± 120 |
| $\Delta R/R/\Delta S_{O_2}$ (min⁻¹·%⁻¹) | 0.3 ± 0.05 | 0.04 ± 0.07 |
| RR(0) (min⁻¹) | 18.3 ± 1.5 | 19.1 ± 1.0 |

$S$ = ventilatory hypoxic sensitivity, $V_0/0$, $\Delta R/R$, and RR(0) are minute ventilation, tidal volume, and respiratory rate at normoxia ($S_{O_2} = 98$%), respectively.

* $P < 0.05$ versus control.

be preferable above multiple step tests to study the effects of drugs on the hypoxic response. The obtained ventilatory step responses are the sum of different factors that determine $V_0/0$ on exposure to hypoxia: (1) the hypoxic drive from the carotid bodies; (2) the depressive effects of “central” hypoxia; and (3) the hypoxic effect on the ventral mediullary blood flow that determines the carbon dioxide tension at the site of the central chemo-receptors. After 3 min of hypoxia specially, factors 1 and 3 are thought to be involved in determining the hypoxic response. Our measured responses, therefore, include some central (pressant) effect due to the increased brain blood flow (BBF) that may not have reached a steady state within 3 min.

The complete recovery from 20 min of hypoxia requires as long as 1 h of room air breathing or 7 min of breathing 100% $O_2$. When breathing room air after sustained hypoxia, a subsequent hypoxic response will be smaller in magnitude compared with the first one. This is mostly probably caused by non-BBF-related hypoxic depression. A 3-min hypoxic episode generates hypoxic depression, most of which is due to an increase in ventral mediullary blood flow. However, we are unable to exclude an effect of non-BBF-related hypoxic depression on a subsequent hypoxic response in our study. A bias due to this effect was not observed. We relate this to the weak potency of non-BBF-related hypoxic depression generated during 3 min of hypoxia.

the random order of the hypoxic levels, and the intra-subject response variability.

Analysis of $V_1$-O₂ Data. The relation between $V_1$ and $P_{1/2}O_2$ obtained is nonlinear and were described using either hyperbolic or exponential functions, whereas linear functions were found empirically to describe the $V_1$-S$_{O_2}$ relation. There is no pathologic reason to select one over the other. However, with a linear response, the sensitivity S should in principle be independent of the level of hypoxia at which it is determined, simplifying the method. In addition, when the number of data points is limited, the linear relation between $V_1$ and $S_{O_2}$, with only two parameters to estimate, is preferred. Using exponential, hyperbolic, or other nonlinear functions (see below) increases the number of parameters to estimate. With limited data, this reduces the reliability of estimation.

We observed that the isocapnic semi-steady-state relation between $V_1$ and $P_{1/2}O_2$ was curvilinear (fig. 2). It is of interest to discuss to some extent the linearity of the $V_1$-S$_{O_2}$ relation. To the best of our knowledge, there are no studies in which researchers investigated the linearity of the $V_1$-S$_{O_2}$ relation when $V_1$ data points are obtained under (semi-)steady-state conditions. In some of our subjects, we observed a convex relation between $V_1$ and $S_{O_2}$ (e. g., subject A of fig. 2). Although not designed for this purpose, we tested the $V_1$-S$_{O_2}$ relation for nonlinearity. The data of individual responses were fitted to a second-order polynomial function of the form:

$$V_1 = \beta H + \gamma H^2 + \epsilon$$

where $H = [100 - S_{O_2}]$, $\epsilon$ is a constant, $\beta$ is a first order parameter, and $\gamma$ is a second order parameter. If the data are adequately described by a linear model, the value of $\gamma$ is not different from zero. Analysis of all 46 hypoxic responses revealed that nonlinearity occurred in only six responses (fig. 4). Although this seems to indicate that a linear function adequately describes the (semi-) steady-state $V_1$-S$_{O_2}$ relation (in the $S_{O_2}$ range from 98% to ~70%), further studies, using multiple responses in individual subjects on one day—to increase the sensitivity of the method—are necessary to clarify this matter. The finding that some of the $V_1$-S$_{O_2}$ responses are nonlinear does not affect our main conclusions.

Desflurane Administration. As in previous studies, the drug studies were performed at a target concentration of 0.1 MAC (in the age group 18–50 yr, the MAC of desflurane is 7.2%). Hypoxic studies began after a
days, because day-to-day variability of the hypoxic responses is greater than within-day variability.\textsuperscript{22} A randomized crossover design on one day was not considered, because it leads to long sessions and subject discomfort, a possible influence of a drug experiment on a subsequent control experiment, and an increased run-to-run variability. Because of the structured nature of the study design, we were unable to exclude an order or time effect on the measured responses. However, such an effect favorably outweighs the influences of a randomized crossover design on single or separate days.

\textbf{Normocapnic Studies}

The individual desflurane hypoxic sensitivities as fraction of the control responses ranged between 0.02 and 2.0 (mean 0.91 ± 0.14; fig. 3). The coefficient of variation was 57\%, indicating the "large" intersubject variability. The difference in the outcome of the normocapnic studies compared with our previous findings with halothane and isoflurane is surprising, and may not be related to methodologic differences, because in this investigation, we used identical standards, as were used in previous studies regarding subject selection and preparation. Randomization of drug and control experiments, the step hypoxic test, the magnitude of the inspired carbon dioxide concentration during the studies, the CNS arousal state of the subjects, the MAC fraction studied, and the equilibration time for desflurane brain uptake (see Methods section and references 2, 3, 5, 6, and 24).

We cannot exclude the fact that our data underestimated the effects of desflurane somewhat (type II error). Eliminating the four outliers from the normocapnic data pool (the subjects with closed symbols in fig. 3; $S_{\text{des}}/S_{\text{CON}} = 0.02, 1.6, 1.6, \text{and } 2.0$) yielded a significant 13\% reduction of the hypoxic response. This reduction is still less than observed with isoflurane and halothane in our laboratory (50\% or more reduction of the hypoxic response at 0.1 MAC; fig. 5).\textsuperscript{20}

Three of the subjects had a normocapnic control response < 0.21 min\(^{-1}\%\(^{-1}\)) (fig. 3). The average control normocapnic hypoxic sensitivity (0.45 ± 1 min\(^{-1}\%\(^{-1}\)) is low in comparison to one of our earlier studies on subanesthetic halothane (5 = 0.91 min\(^{-1}\%\(^{-1}\)).\textsuperscript{2} It is possible that a group with a low hypoxic response makes a type II error more likely. For this reason, some investigators select subjects with high hypoxic responses.\textsuperscript{11} However, the control responses of the current population volunteers are of similar magnitude in comparison to those of two groups of volunteers in studies on subanesthetic iso- 

\textbf{Sequence of Studies.} The order of experiments was fixed to control before desflurane studies. We did not want to perform control and drug studies on separate

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AHR ± 95% c.i. (% of control)

Fig. 5. The influences of 0.1 minimum alveolar concentration halothane, isoflurane, and desflurane on the ventilatory response to isonormocapnic hypoxia as a percentage of control response. Values are mean ± the 95% confidence interval. Halothane data are from Dahan et al.,1 isoflurane data are from van den Elsen et al.,5 and desflurane data are from the current study. AHR = acute hypoxic response.

Studies on subanesthetic isoflurane (5 = 0.54 and 0.44 1·min⁻¹·%⁻¹)5,6 in these studies, 0.1 MAC isoflurane caused a reduction of ~50% of the hypoxic responses. Taking into account the above, a different effect of desflurane, compared to halothane and isoflurane, should be taken into consideration (for example, on the carotid bodies or on the CNS).

The ventilatory changes due to a sudden decrease in \( P_{\text{ETO}_2} \) (step hypoxic test) are caused by an increase in tidal volume and respiratory rate. Halothane and isoflurane at 0.1 MAC reduce these increases of both ventilatory components. Desflurane caused a reduction in \( \Delta V_T/\Delta S_{\text{ETO}_2} \) similar to that observed with isoflurane and halothane (table 1). This indicates that low-dose desflurane had a depressant effect on the carotid bodies with respect to tidal volume. Conversely, the somewhat higher levels of RR in periods A and B compared with control counteracted the depression of tidal volume such that their product was not significantly different in control and desflurane studies. The sustained or even increased RR in normoxia and hypoxia may be related to stimulation of specific airway, lung, or systemic (for example, at the carotid bodies or within the CNS) receptors. At high inspired concentrations, stimulation of these receptors causes transient increases in sympathetic activity. The integrity of the hypoxic \( V_T \) response with low-dose desflurane may be related to the stimulation of these receptors that trigger a central mechanism that counteracts depression of the peripheral chemoreceptors in terms of \( V_T \) (for instance, by affecting rythmogenesis or increasing sympathetic activity).

Hypercapnic Studies
During hypercapnia, desflurane inhalation reduced the hypoxic sensitivities of 8 of the 9 subjects (individual desflurane hypoxic sensitivities as fraction of the control responses ranged between 0.42 and 1.0; mean 0.77 ± 0.08; coefficient of variation 34%; fig. 3). Desflurane reduced the carbon dioxide-induced augmentation of the hypoxic ventilatory drive: increase of S from normocapnia to hypercapnia = 65% and 23% in the studies before and during desflurane inhalation, respectively. From our data, we were able to estimate the ventilatory carbon dioxide sensitivities in normoxia and hypoxia. Remember, however, that normocapnic and hypercapnic studies were performed on separate days. Performing experiments on different days increases the run-to-run variability.24,26 The ratio of the carbon dioxide sensitivity obtained during desflurane inhalation to the control carbon dioxide sensitivity decreased from 1.1 to 0.87 and 0.78 at an \( S_{\text{ETO}_2} \) of 97.5%, 80%, and 70%, respectively. Our findings suggest that desflurane affects the carbon dioxide-induced augmentation of the hypoxic response (which is mediated by the carotid bodies) more than either the hypoxic or hypercapnic responses. This may be clinically of interest because the combination of hypercapnia and hypoxia may occur more frequently in perioperative patients than does hypoxia or hypercapnia alone.

The discrepant findings in the normocapnic and hypercapnic studies suggest that the translation of the oxygen-carbon dioxide interaction into \( V_T \) at the carotid bodies involves a separate mechanism from the hypoxic response at normocapnia or mild hypercapnia. To the best of our knowledge, there are no studies to support this suggestion. Because we do not conceive the hypoxic response at high inspired carbon dioxide concentrations to involve a fundamentally different mechanism
from the hypoxic response at low or no inspired carbon dioxide concentrations, we relate the inability to find a significant effect of 0.1 MAC desflurane in the normocapnic studies to a type II error. Clearly, the number of volunteers was too small to detect a small effect of subanesthetic desflurane on the hypoxic response. Inflation of the hypoxic response by carbon dioxide unearths the depressant influence of desflurane.

In conclusion, we report that, in contrast with the results on subanesthetic halothane and isoflurane, subanesthetic desflurane has only a small effect on the normocapnic ventilatory response to hypoxia in healthy volunteers. In common with the other inhalational anesthetic agents, subanesthetic desflurane decreases the ventilatory response to asphyxia.

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References


