Influence of a Subanesthetic Concentration of Halothane on the Ventilatory Response to Step Changes into and out of Sustained Isocapnic Hypoxia in Healthy Volunteers

Albert Dahan, M.D.,* Maarten J. L. J. van den Elsen, M.D.,* Aad Berkenbosch, Ph.D.,† Jacob DeGoede, Ph.D., † Ida C. W. Ollevier,‡ Anton G. L. Burm, M.Sc., Ph.D., § Jack W. van Kleef, M.D., Ph.D. ||

Background: In humans the ventilatory response to isocapnic hypoxia is biphasic: an initial increase in minute ventilation (V̇ₐ) from baseline, the acute hypoxic response, is followed after 3–5 min by a slow ventilatory decay, the hypoxic ventilatory decline, and a new steady state, 25–40% greater than baseline V̇ₐ, is reached in about 15–20 min. The transition from 20 min of isocapnic hypoxia into normoxia results in a rapid decrease in V̇ₐ, the off-response. In humans, halothane, at subanesthetic concentrations, is known to decrease the acute hypoxic response. In order to investigate the effects of halothane on sustained hypoxia we quantified the effects of 0.15 minimum alveolar concentration halothane on the ventilatory response at the onset of 20 min of hypoxia and at the termination of 20 min of hypoxia by normoxia in healthy volunteers.

Methods: Step changes in end-tidal oxygen tension were performed against a background of constant mild hypocapnia (end-tidal carbon dioxide tension about 1 mMHg above individual resting values) in fourteen male subjects. The end-tidal oxygen tension was forced as follows: 5–10 min at 110 mmHg, 20 min at 44 mmHg, and 10 min at 110 mmHg. In each subject we performed one trial before and one during 0.15 minimum alveolar concentration halothane administration.

Results: Ten responses into hypoxia and nine out of hypoxia were considered for analysis. All control trials were performed during wakefulness. Using behavioral characteristics, the central nervous system arousal state of the subjects during halothane inhalation was defined as “anesthesia-induced hypoxia.” The acute hypoxic response averaged 10.4 ± 4.7 1/min for control versus 3.7 ± 2.4 1/min for halothane trials (P < 0.01). The hypoxic ventilatory decline was 4.8 ± 2.5 1/min versus 3.9 ± 2.1 1/min (NS), the off-response was 6.7 ± 3.2 1/min versus 3.7 ± 3.0 1/min (P < 0.05) for control versus halothane, respectively. All values are mean ± SD.

Conclusions: Our results indicate that halothane caused V̇ₐ to be less than control levels during acute and sustained hypoxia as well as when sustained hypoxia is replaced by normoxia. It is argued that the depression of V̇ₐ during acute hypoxia is attributed to an effect of halothane on the peripheral chemoreceptors. During sustained hypoxia halothane had no effect on the magnitude of the hypoxic ventilatory decrease, which is probably related to an increase by halothane of inhibitory neuromodulators within the central nervous system. With halothane, the ventilatory decrease when sustained hypoxia is replaced by normoxia is related to the removal of the hypoxic drive at the site of the peripheral chemoreceptors. (Key words: Anesthetics, volatile; halothane. Central nervous system, arousal state; anesthesia-induced hypoxia; wakefulness. Lung(s), ventilation; acute hypoxia; sustained hypoxia. Methods: dynamic end-tidal forcing; isocapnic hypoxia. Receptors: peripheral chemoreceptors.)

HALOTHANE, at subanesthetic concentrations, depresses the peripheral chemoreflex loop in humans. Knill and colleagues observed that 0.1 minimum alveolar concentration (MAC) reduced the hypoxic ventilatory response by 70%,1 and the response to acute isocapnic metabolic acidosis by 58%.2 In a recent study, we confirmed the observations of Knill's group.3 With 0.1 MAC halothane, we observed a 68% depression of the acute hypoxic ventilatory response, while the portion of the ventilatory carbon dioxide sensitivity at-
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tributable to the peripheral chemoreceptors was reduced by 61%. To obtain the hypoxic ventilatory response Knill and colleagues used a different method of inducing hypoxia than we did. Knill’s group used a progressive decrease in oxygen concentration over 8–10 min (ramp hypoxic test), whereas we used a rapid decrease in end-tidal oxygen tension (P\textsubscript{ETO\textsubscript{2}}) within three or four breaths and subsequently maintained hypoxia at this level (step hypoxic test). When hypoxia is induced as a step and sustained longer than 3–5 min, the ventilatory response is biphasic.\textsuperscript{4,5} Initially (<3 min), there is an increase in ventilation due to carotid body stimulation by hypoxia. Thereafter, due to the “central” depressant effects of hypoxia ventilation decreases. A new steady-state ventilation, about 30–40% greater than baseline level, is reached after 15–20 min.\textsuperscript{6} A recent study by Temp et al.\textsuperscript{7} has shown that a ramp hypoxic test is not able to separate in time the initial hyperventilatory response from the subsequent decline. Therefore, this latter test is unsuitable to investigate the influences of a drug on the ventilatory decline of sustained hypoxia.

In our previous study we determined the ventilatory response to the initiation of only 5 min of hypoxia with a step hypoxic test and therefore did not obtain information on the influences of subanesthetic halothane on the development and magnitude of the ventilatory decline.\textsuperscript{3} In this study we quantified the influences of a subanesthetic concentration of halothane (inspired fraction 0.22%) on the ventilatory response to the initiation of sustained (20-min) isocapnic hypoxia. Furthermore, we examined the effects of halothane on the ventilatory pattern when sustained hypoxia was terminated by normoxia. We did so by applying the “dynamic end-tidal forcing technique”\textsuperscript{8,9} to perform square wave changes in P\textsubscript{ETO\textsubscript{2}} against a background of mild hypercapnia. 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 decline. When normoxia followed sustained hypoxia we determined the initial change in ventilation, the off-response, as well as the nadir of ventilation compared with baseline, the undershoot (fig. 1).

Materials and Methods

Subjects and Apparatus

Fourteen men (aged 26–32 yr) took part in an experimental protocol approved by the Leiden University Committee on Medical Ethics. Only healthy, nonsmoking subjects who were not receiving medication were included in the study. Any subject who had received anesthesia in the 6 months prior to this study was excluded. None of the subjects had participated previously in other drug studies. They were all naïve to respiratory physiology but received 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 stimulants and depressants for at least 12 h before the experiments.

During an experiment (or trial) 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 3, Switzerland) connected to a differential pressure transducer (model 270, Hewlett-Packard, Andover, MA) and electronically integrated to yield a volume signal.\textsuperscript{10} This signal was calibrated with a motor-driven piston pump (stroke volume 1,000 ml at 20 strokes/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-F203, Bronkhorst High Tec, Veenendaal, 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, Bilthoven, The Netherlands). A PDP 11/23 microcomputer 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 carbon dioxide tension (PetCO2) and PetO2 to follow a specified pattern in time. Part of the nitrogen (5 l/min) passed through the halothane vaporizer. During control runs 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 concentrations. The halothane concentration was measured in the outflow limb of the vaporizer with an infrared absorption monitor (LB-2, Beckman). This monitor was calibrated with a gas mixture of halothane (in air) of known concentration. A pulse oximeter (Satellite Plus, Datex, Finland) continuously measured the arterial oxygen saturation via a finger probe. Throughout the study the electrocardiogram was monitored. Minute ventilation (Ve), tidal volume, respiratory frequency, PetCO2, and PetO2 were calculated and the data were stored on a breath-to-breath basis.

Study Design

After arrival at the laboratory the subjects rested for 60 min. To study the responses to initiation and termination of hypoxia, we applied the dynamic end-tidal forcing technique. With this technique we are able to force dynamically PetCO2 and PetO2 to follow a prescribed pattern in time by manipulating the inspired gas concentrations independently of the ventilatory response. Resting PetCO2 levels were obtained after 10–15 min of steady-state Ve with no inspired carbon dioxide. Thereafter, PetCO2 was elevated 0.8–1.4 mmHg above the individual resting values and maintained constant throughout the control and drug trials at this level.

The PetO2 was forced according to the following pattern (fig. 1): (1) 5–10 min at 110 mmHg, (2) a rapid decrease to 44 mmHg (fraction of inspired oxygen ~ 0.08) within three or four breaths, (3) maintenance at 44 mmHg for 20 min, (4) a rapid increase to 110 mmHg within three or four breaths, (5) maintenance at 110 mmHg for 10 min, and (6) a 10-min period of hyperoxia (fraction of inspired oxygen > 0.8). This protocol was once performed before and once during inhalation of halothane (see below). In one subject, transitions from hypoxia to normoxia could not be analyzed. To avoid the effect of residual halothane, control trials were performed before halothane trials. Between trials there was a 60-min rest period. The 10-min period of hyperoxia was introduced to avoid a possible influence of “on-going” hypoxic ventilatory decline on a next trial. Before a halothane trial the subject started inhaling halothane at twice the desired inspired concentration for 5 min, after which it was set at 0.22%. After another 15 min, data collection started.

Data Analysis

The trials were evaluated by taking mean values of the breath-to-breath Ve over identical time segments (fig. 1): period A = the final 2 min of normoxic Ve before induction of sustained hypoxia; period B = minutes 3 and 4 after exposure to hypoxia; period C = the last 2 min of sustained hypoxia (i.e., min 19 and 20 of hypoxia); period D = the minute following the first 15 s after the return to normoxia (i.e., min 0.25–1.25 of normoxia after hypoxia); and period E = the last 2 min of normoxia (i.e., min 9 and 10 of normoxia after hypoxia). We defined the difference in Ve between periods B and A as the acute hypoxic response, between periods B and C as the hypoxic ventilatory decline, between periods C and D as the off-response, and between periods A and D as the undershoot (fig. 1).

Inclusion and Exclusion Criteria

During each trial subjects were continuously watched by one investigator (A.D. or M.v.d.E.). Before data collection and at regular intervals during a trial the response of the subjects to calling their name (at normal loudness of voice) was tested. After each trial information on the awareness of time and space, as well as on the memory of the name calling during the experiment was obtained through a short interview.

Trials were included for analysis if criteria were met with respect to stimulus control and central nervous system (CNS) arousal state. The criteria with respect to stimulus control were (1) a difference in PetCO2 be-
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Table 1. The Ventilatory Response to Sustained Hypoxia before and during Halothane Inhalation (F$_i$ 0.22%)

<table>
<thead>
<tr>
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<th>A'</th>
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<th>C'</th>
<th>D†</th>
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<tr>
<td>$V_{e}$ (l/min)</td>
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<tr>
<td>Control</td>
<td>14.7 ± 2.2</td>
<td>25.1 ± 5.4</td>
<td>20.3 ± 4.3</td>
<td>13.5 ± 3.4</td>
<td>13.9 ± 3.2</td>
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<tr>
<td>Halothane</td>
<td>13.1 ± 2.7</td>
<td>16.7 ± 4.6</td>
<td>12.9 ± 3.6</td>
<td>9.0 ± 2.0</td>
<td>12.5 ± 3.3</td>
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<td>$V_{e}$ (% of baseline $V_{e}$)</td>
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<tr>
<td>Control</td>
<td>100</td>
<td>171.0 ± 34.6</td>
<td>138.0 ± 20.5</td>
<td>93.4 ± 17.6</td>
<td>95.4 ± 14.3</td>
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<tr>
<td>Halothane</td>
<td>100</td>
<td>126.6 ± 16.0</td>
<td>97.0 ± 14.4</td>
<td>69.0 ± 17.0</td>
<td>96.0 ± 7.0</td>
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<td>$V_{t}$ (ml/breath)</td>
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<td>Control</td>
<td>913 ± 133</td>
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<td>1179 ± 242</td>
<td>939 ± 90</td>
<td>974 ± 124</td>
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<tr>
<td>Halothane</td>
<td>795 ± 195</td>
<td>935 ± 212</td>
<td>769 ± 176</td>
<td>583 ± 109</td>
<td>723 ± 191</td>
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<td>$f$ (breaths/min)</td>
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<tr>
<td>Control</td>
<td>16.7 ± 3.7</td>
<td>18.6 ± 4.6</td>
<td>17.9 ± 3.0</td>
<td>16.8 ± 4.9</td>
<td>16.2 ± 4.3</td>
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<tr>
<td>Halothane</td>
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<td>17.8 ± 3.7</td>
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<td>$P_{ETC_{O2}}$ (mmHg)</td>
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<tr>
<td>Control</td>
<td>44.3 ± 2.3</td>
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<td>44.3 ± 2.9</td>
<td>44.3 ± 2.3</td>
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<tr>
<td>Halothane</td>
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<td>44.3 ± 2.3</td>
<td>44.3 ± 1.5</td>
<td>45.0 ± 2.3</td>
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<td>$P_{ETC_{O2}}$ (mmHg)</td>
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<tr>
<td>Control</td>
<td>110.3 ± 1.5</td>
<td>44.3 ± 2.3</td>
<td>44.3 ± 2.3</td>
<td>108.0 ± 5.3</td>
<td>111.0 ± 3.0</td>
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<tr>
<td>Halothane</td>
<td>108.5 ± 1.5</td>
<td>45.0 ± 1.5</td>
<td>45.8 ± 2.3</td>
<td>106.5 ± 3.8</td>
<td>111.0 ± 1.5</td>
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Values are means ± SD.

Period A = the final 2 min of normoxia before hypoxia; Period B = minutes 3 and 4 of hypoxia; Period C = last 2 min of sustained hypoxia (i.e., minutes 19 and 20 of hypoxia); Period D = the minute following the first 15 s after return to normoxia (i.e., minutes 14–15) of normoxia after hypoxia; Period E = the last 2 min of normoxia after hypoxia (i.e., minutes 9 and 10 of normoxia); $V_{e}$ = minute ventilation; $V_{t}$ = tidal volume; $f$ = breathing frequency; Baseline $V_{e}$ = ventilation of period A; $F_i$ = inspired fraction.

* n = 10.
† n = 9.

between period A and periods B, C, D, and E of less than 1.5 mmHg; (2) a difference in $P_{ETC_{O2}}$ between periods A of the halothane and control studies of less than 1.5 mmHg; and (3) a standard deviation of the $P_{ETC_{O2}}$ in all of the periods of less than 1.5 mmHg.

The inclusion criteria with respect to the CNS arousal were based on the behavioral state of the subjects: (4) the state of wakefulness during a control trial; (5) no occurrence of obstructive apnea; (6) the loss of consciousness while breathing an inspired halothane concentration of 0.22%; (7) and no apparent changes in state of CNS arousal during a halothane experiment. We considered subjects in the state of wakefulness (i.e., an actively maintained state dependent on tonic excitation from the reticular activating system) only when they had open eyes, responded to verbal communication (i.e., name calling) and had no memory defects or loss of awareness of time and space after a control experiment. Because the electroencephalogram, electromyogram, or electrooculogram was not monitored, loss of consciousness was assumed when subjects had their eyes closed, did not respond to verbal communication by eye-opening or movement of body or limbs, and had no memory of any name calling during the halothane trial at the end of the experiment. For example, if during a halothane trial a subject opened his eyes spontaneously or was able to remember afterward that his name was called during a trial, albeit not able to respond at that time, data from that trial would have been discarded.

**Statistical Analysis**

To detect a significance of differences between the two treatment groups we performed Student's paired $t$-test on the acute hypoxic response, hypoxic ventilatory decline, off-response, and undershoot. A probability level of 0.05 was chosen for differences to be significant. All values presented are means ± standard deviation unless otherwise stated.

**Results**

The inspired carbon dioxide fraction necessary to increase $P_{ETC_{O2}}$ by about 1 mmHg was between 0.5 and 1.5% (3.8–11.3 mmHg) among subjects. The $P_{ETC_{O2}}$ was controlled within 0.6 mmHg (standard deviation).

The trials of four subjects were eliminated from the analysis because one or more of the inclusion criteria were not met. In two of these subjects several periods of central apnea occurred with the return to normoxia following sustained hypoxia during halothane administration. This caused the standard deviation of the $P_{ETC_{O2}}$ to exceed 1.5 mmHg in periods D and E. All inclusion criteria were met during the trials of the re-
Fig. 2. Typical ventilatory responses of two subjects to a step into sustained isocapnic hypoxia before and during halothane inhalation (Inspired fraction 0.22%). $V_e$ = minute ventilation. Solid line = control; dotted line = halothane.

remaining subjects ($n = 10$). The mean values of the different parameters of periods A to E are collected in table 1.

The ventilatory responses at the onset of 20 min of isocapnic acute hypoxia of two subjects are shown in figure 2. All subjects showed biphasic responses to sustained hypoxia in both the control and the halothane trials. For all trials the acute hypoxic response averaged to $10.4 \pm 4.7$ l/min (71.0 ± 34.0% of baseline $V_e$) in the control and $3.7 \pm 2.4$ 1/min (26.6 ± 16.0% of baseline $V_e$) in the halothane trials ($n = 10; P < 0.01$). The hypoxic ventilatory decline did not differ between treatments: $4.8 \pm 2.5$ 1/min (33.3 ± 19.0% of baseline $V_e$) in the control and $3.9 \pm 2.9$ 1/min (29.0 ± 13.5% of baseline $V_e$) in the halothane trials ($n = 10; P = 0.7$). In figure 3 the individual values are shown.

In figure 4 the off-responses of one subject are plotted. Overall, ventilation decreased to just less than prehypoxic baseline level after return to normoxia in the control trials. In the halothane trials there was a decrease in $V_e$ to 70% of baseline $V_e$. The off-response was $6.7 \pm 3.2$ l/min (46.0 ± 20.9% of baseline $V_e$) for the control and $3.7 \pm 3.0$ 1/min (29.9 ± 28.0% of baseline $V_e$) for the halothane trials ($n = 9; P < 0.05$). The undershoot (i.e., the drop below baseline ventilation after return to normoxia) was $0.8 \pm 1.9$ 1/min (5.5 ± 13.2% of baseline $V_e$) for control and $4.0 \pm 2.8$ 1/min (29.0 ± 16.0% of baseline $V_e$) for halothane trials ($n = 9; P < 0.01$). For individual values see figure 3.

In contrast to control, with halothane the average acute hypoxic and off-responses were similar in amplitude (acute hypoxic response versus off-response: control $P < 0.05$; halothane NS; paired-t-test).

Discussion

Critique of Methods

We used an oronasal mask to connect the subject to the pneumotachograph. The mask allows normal movements of mouth and lips and is considered less disruptive to normal breathing than is a mouthpiece-noseclip arrangement. To avoid excessive pressure on the face (in particular on the trigeminal nerve) the fit of the mask was loose. Leakage was prevented by applying silicone putty between mask and face.

Control of Inhaled and Exhaled Gas Concentrations. We used the dynamic end-tidal forcing technique\textsuperscript{6,9} to perform square wave changes in $P_E O_2$ against a background of mild hypercapnia. The $P_{ET CO_2}$ were increased by about 1 mmHg above resting $P_{ET CO_2}$ values. The reason for this increase is two-fold.

Fig. 3. Individual values of the acute hypoxic response (AHR), hypoxic ventilatory decline (HVD), off-response, and undershoot before and during halothane inhalation (Inspired fraction 0.22%). Each subject is represented by the same symbol in all diagrams. * $P < 0.01$; ** $P < 0.05$. Values are means ± SE.
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Fig. 4. Minute ventilation (V̇\textsubscript{E}) at the termination of 20 min of isocapnic hypoxia by normoxia before halothane (circles) and during halothane inhalation (inspired fraction 0.22%) (squares) of one subject. At t = 0 the step into normoxia occurred. Dotted line = control baseline V̇\textsubscript{E}; solid line = halothane baseline V̇\textsubscript{E}.

First, a small increase in inspired carbon dioxide concentration is necessary to adequately control the PET\textsubscript{CO\textsubscript{2}}. The mean differences in PET\textsubscript{CO\textsubscript{2}} between the different periods were extremely small (table 1) and also the fluctuations in PET\textsubscript{CO\textsubscript{2}} in the different periods (precision of PET\textsubscript{CO\textsubscript{2}} control 0.6 mmHg) were small and comparable to those in our previous study.\textsuperscript{3} Second, because an appreciable depression of the V̇\textsubscript{E} during sustained hypoxia and especially at the termination of sustained hypoxia by normoxia was anticipated, an initial elevated PET\textsubscript{CO\textsubscript{2}} is essential to avoid an increase in PET\textsubscript{CO\textsubscript{2}} above baseline levels. The small increase in PET\textsubscript{CO\textsubscript{2}} will result in a increase in resting V̇\textsubscript{E} by about 1–3 l/min.\textsuperscript{8} Our baseline V̇\textsubscript{E} (period A; table 1) is higher than observed in studies in which no inspired carbon dioxide was added, but is consistent with other studies using dynamic end-tidal forcing.\textsuperscript{7–9,14–17}

Because there is a positive interaction of oxygen and carbon dioxide at the carotid bodies the hypoxic response will be somewhat augmented when performing hypoxic studies under mild hypercapnic conditions.\textsuperscript{18} On the other hand, our control hypoxic response is similar to what others have found when inducing a step decrease in PET\textsubscript{CO\textsubscript{2}} (see reference 19 and references cited therein).

The subjects started inhaling 0.45% halothane for 5 min, followed by 0.22%. Twenty minutes after the subjects first started inhaling halothane data collection started. Twenty minutes of halothane breathing will result in an alveolar-to-inspired halothane fraction of 0.55.\textsuperscript{20} The MAC of our young group of subjects is approximately 0.84%.\textsuperscript{21} Because we performed our studies in the flat part of the alveolar-to-inspired halothane fraction–time curve (after 55 min of a constant inspired concentration, the alveolar-to-inspired halothane fraction is 0.6),\textsuperscript{21} it is reasonable to assume an alveolar halothane concentration of approximately 0.15 MAC during the halothane trials.

Central Nervous System Arousal State. We refrained from using objective means to determine the state of CNS arousal of our subjects, but used instead, comparable to other studies,\textsuperscript{1–3,14–16,22–24} simple subjective means (i.e., observation of subject behavior). During halothane administration, data were included in the analysis when the subjects had closed eyes, did not respond to verbal communication during a trial, and had no memory of name calling after a trial. For the want of a term, we designated this arousal state “anesthesia-induced hypnosis.” Although there are several characteristics this state shares with natural sleep (both rapid eye movement [REM] sleep and nonREM sleep),\textsuperscript{25–28} a comparison of anesthesia-induced hypnosis with natural sleep, with respect to ventilatory control seems not fruitful in our study, because electrographic data were not collected to determine the CNS arousal state of our subjects. Furthermore, a large variability of the ventilatory responses to hypoxia is observed during both REM and non-REM sleep.\textsuperscript{29–33}

Acute Hypoxic Response

Dose–Response Data. The observation that a subanesthetic concentration of halothane (0.15 MAC) depressed the ventilatory response to acute hypoxia appreciably was no surprise.\textsuperscript{1,5,25} The mean ventilation was about 25% greater than baseline V̇\textsubscript{E} when acute hypoxia was induced (V̇\textsubscript{E} in period B; table 1). Previously, we observed at 0.05 and 0.1 MAC halothane that V̇\textsubscript{E} increased during acute hypoxia to 180% and 135% of baseline, respectively.\textsuperscript{3} This indicates a steep dose-response curve for the effects of subanesthetic concentrations of halothane on the hypoxic drive (fig. 5).

Site of Action of Halothane and Interaction of Central Nervous System Arousal State with Hypoxic Response. It is of interest to consider the location of the depression of the acute hypoxic response with
subanesthetic halothane. Halothane may exert its effect on the peripheral chemoreceptors, integrating centers within the CNS or on the neuromechanical link between brainstem and \( \bar{V}_e \) (i.e., motor neuron, neuromuscular junction, intercostal muscles, diaphragm, lung tissue, airway resistance). An effect of halothane on the integrating centers or the neuromechanical link between brainstem and \( \bar{V}_e \) would presumably result in an effect on both the peripheral and central chemoreflex loops. In a previous study\(^9\) we performed step increases in \( \text{PETCO}_2 \) and step decreases in \( \text{PETO}_2 \) (duration of hypoxia 5 min) during subanesthetic halothane administration (0.05 and 0.1 MAC). From the hypercapnic responses we determined the portions of the carbon dioxide sensitivities of the central and peripheral chemoreflex loops. We found a significant decrease of the carbon dioxide sensitivity of the peripheral chemoreflex loop, while the carbon dioxide sensitivity of the central chemoreflex loop showed no significant change. The acute hypoxic response showed a depression in magnitude proportional to that of the peripheral carbon dioxide sensitivity. These results suggest a selective effect of subanesthetic halothane on the peripheral chemoreceptors per se. Because effects of subanesthetic halothane, with respect to steady-state characteristics, were absent on the central chemoreflex loop or the integrating centers within the CNS, the altered CNS arousal state induced by halothane appeared of minor importance on the study outcome. We believe that this also holds good in our present study, although the alveolar concentration of halothane was somewhat higher. As mentioned before\(^7\) electrographic data (electroencephalogram, electromyogram, or electro-oculogram) will be necessary to answer the question whether drug induced ventilatory depression is related to the drug itself, to the alteration of the CNS arousal state the drug produces, or to both.

**Influence of Extraneous Input on Hypoxic Response.** Temp et al. tested the influence of subanesthetic **isoflurane** on the ventilatory response to hypoxia.\(^7,16\) Using dynamic end-tidal forcing equipment, similar to ours, they performed step decreases in \( \text{PETO}_2 \) during 0.1 MAC isoflurane inhalation and found no significant effect on the acute hypoxic response\(^5,16\) or the hypoxic ventilatory decline.\(^16\) This is in sharp contrast with the findings of Knill et al.\(^22\) with isoflurane and our observations with halothane.\(^3\) However, in contrast to our subjects, those of Temp et al. were required to watch a video-tape, and furthermore were regularly touched or spoken to during the isoflurane trials, to “minimize differences in level of consciousness between control and isoflurane experiments.”\(^16\)

Both Robotham\(^23\) and Knill\(^24\) discussed some possible causes of the large differences in outcome of the studies of Temp et al.\(^7,16\) and those of Knill et al.\(^1,23,24\) and ours.\(^3\) Factors Robotham considered were the addition of inspired carbon dioxide for \( \text{PETCO}_2 \) control (see above); the rate at which hypoxia was induced (a step decrease in \( \text{PETO}_2 \) within three or four breaths in our studies and those of Temp et al. versus a ramp hypoxic test in the studies by Knill et al.\(^1,23,24\); see above); randomization of control and drug experiments (see also reference 3); and the effects of the “anesthesia-induced sleep state.”\(^25\) Knill\(^24\) remarks on the extraneous stimuli to the subjects. These stimuli may have caused added behavioral drives on breathing,\(^35,36\) causing a net response similar to control during isoflurane administration. Due to these additional drives on \( \bar{V}_e \), the effects of isoflurane on the hypoxic responses showed a large intersubject variability. In one study\(^7\) (n = 8 subjects) Temp et al. observed the hypoxic response during isoflurane administration to be greater than control in four subjects, but less than 50% of control in three others. In our previous study the hypoxic responses of all subjects were depressed by 0.1 MAC halothane.\(^3\) This suggests that it is inappropriate to draw conclusions from averaged data when the inter-subject variability of the drug effect is increased due to additional drives. A study

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on the ventilatory response to a step into hypoxia without and with extraneous input, and without and with isoflurane administration in a single group of subjects is necessary to clarify this matter.37

We prefer performing experiments without extraneous stimulation of the subjects to the level of consciousness for various reasons: (1) the occurrence of hypnosis is an inherent property of halothane; (2) we want to avoid changes in level of CNS arousal during a trial; (3) we opt for a protocol with minimal trial-to-trial variability; and (4) extraneous input affects the proper assessment of the chemical regulation of breathing.34-36

Hypoxic Ventilatory Decline

A significant effect of halothane on the magnitude of the hypoxic ventilatory decline was not found in our study. With halothane, despite a decrease of \( \mathrm{PETCO}_2 \) from 110 to 45 mmHg, ventilation was not different from baseline after 20 min of hypoxia. The early small increase in \( V_E \) was completely abolished by the hypoxic ventilatory decline. This contrasts sharply with the control trials, in which \( V_E \) remained 40% above baseline after 20 min of hypoxia.

The mechanism of hypoxic ventilatory decline remains unclear. Studies in awake humans and animals suggest that the decline in \( V_E \) during sustained hypoxia is caused by the accumulation of inhibitory neuromodulators (\( \gamma \)-aminobutyric acid, adenosine, or dopamine).34-36,41,42,43,44,45,46 Furthermore, it has been shown in awake humans that the afferent input from the carotid bodies influences the magnitude of ventilatory decline. Increasing the drive from the peripheral chemoreceptors with almitrine causes an increase in magnitude of the hypoxic ventilatory decline,46 the reverse is true with dopamine and somatostatin.47,48 Georgopoulos et al. suggest that the relation between the acute hypoxic response and ventilatory decline is caused by the "central routing of peripheral chemoreceptor afferents to brain structures with inhibitory effects on ventilation."49 Our observation with halothane, that despite a 65% reduction of the acute hypoxic response, the absolute and relative (% of baseline \( V_E \)) magnitude of the hypoxic ventilatory decline remained unaltered, is in contrast with this concept. Knill and Gelb1 observed at 1.1 MAC halothane that in 13 of 15 subjects the ventilatory response to a ramp hypoxic test did not show an increase in \( V_E \) but a decrease, especially at high arterial carbon dioxide tension values (their fig. 2). We interpret this as the occurrence of hypoxic venti-
latory decline despite no apparent acute hypoxic response. These findings may be related to the specific ability of halothane to (further) increase the concentration of inhibitory neuromodulators within the CNS (for instance, \( \gamma \)-aminobutyric acid).43

Our results seem at variance with those of Young et al.44 They studied the effects of halothane (end-tidal fraction 0.06%) on the ventilatory response to sustained hypoxia in humans. With halothane they observed that \( V_E \) during early hypoxia was 70% of control but not different from control after 14-17 min of hypoxia, so that a reduction of the hypoxic ventilatory decline occurred. This discrepancy may be explained by at least four differences in experimental approach. Young et al. tested their subjects at a lower MAC fraction than we did (about 0.05 MAC in their study versus 0.15 in our study). They did not keep the \( \mathrm{PETCO}_2 \) within narrow limits (\( \mathrm{PETCO}_2 \) held within 2.3 mmHg in their study versus 0.6 mmHg in ours) and there was a persistent rise of \( \mathrm{PETCO}_2 \) during sustained hypoxia, especially in their halothane experiments (their fig. 1), presumably leading to an increased ventilation. Furthermore, they selected subjects with a brisk response to hypoxia.

Off-response and Undershoot

Imposing isocapnic normoxia after 20 min of hypoxia yielded a small ventilatory undershoot in control trials (\( V_E \) at period D 97% of baseline \( V_E \)). This finding is consistent with that of other studies in which prolonged hypoxia is followed by normoxia.45,46 With halothane, we observed a larger undershoot (\( V_E \) at period D 69% of baseline \( V_E \)). Furthermore, we noticed in two subjects (data not included in the analysis; see Results) that the return to normoxia after sustained hypoxia caused an unstable pattern of breathing due to central apnea. The response out of sustained hypoxia is complex, because several physiologic processes take place simultaneously. (1) The hypoxic drive from the carotid bodies is suddenly removed. (2) The transition from hypoxia to normoxia causes a 30% decrease of brain blood flow.47 This causes an increase of central stimulation of ventilation through accumulation of acid metabolites.48 (3) The inhibitory influences from sustained hypoxia on ventilatory control persist beyond the hypoxic period. Several studies showed a reduction of the ventilatory response to acute hypoxia after sustained hypoxia.11,17,49 (4) Also the "wakeup drive to breathe" may be involved in the off-response. Badr et al.50 have shown that termination of 5 min of isocapnic hypoxia by hyperoxia was associated with cen-
eral apnea in several subjects during non-REM sleep. This is in contrast to findings in awake subjects that central apnea does not occur at the termination of even 20 min of isocapnic hypoxia by hyperoxia. The increase of ventilatory undershoot with halothane may have involved any of these factors. However, the finding that the average acute hypoxic response and the off-response are eventually the same with halothane strengthens the view that the neural output of the carotid bodies does not adapt during sustained hypoxia. Furthermore, the marked undershoot supports the concept that a substantial hypoxic drive remained present with halothane, even after 20 min of hypoxia.

In summary, we performed step decreases into and out of sustained isocapnic hypoxia before and during 0.15 MAC halothane administration in healthy volunteers. Halothane caused $V_e$ below control levels during acute and sustained hypoxia, as well as after return to normoxia. We argued that these effects were generated by specific (inter)-actions of halothane at the peripheral chemoreceptors and within the CNS.

Extrapolation of our results to the patients in the post-anesthesia care unit is somewhat speculative. We restricted ourselves to healthy volunteers, used strict control of $PrCO_2$, observed appreciable inter-subject variability, and excluded data from analysis when the CNS arousal state of our subjects did not appear constant. Moreover, $V_e$ in the postanesthesia period is influenced by factors such as lung function, posture, surgical incision, and analgesic agents. However, as stated by Robotham, the study by Knill and colleagues as well as our study suggest that a patient may be at risk with a depressed ventilatory response to acute hypoxia with even 0.1 MAC halothane, especially in those that are resting comfortably in the recovery room without extraneous input. The current study shows that this is also true when hypoxia persists for a period longer than 5 min.

References
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