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Does Subanesthetic Isoflurane Affect the Ventilatory Response to Acute Isocapnic Hypoxia in Healthy Volunteers?

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Background: **Differences in results studying the effects of subanesthetic concentrations of volatile agents on the hypoxic ventilatory response may be related to the conditions under which the subjects were tested. In this study we investigated the effects of 0.1 minimum alveolar concentration (MAC) of isoflurane on the hypoxic ventilatory response without and with audiovisual stimulation.**

Methods: **Step decreases in arterial hemoglobin oxygen saturation from normoxia into hypoxia (arterial hemoglobin oxygen saturation 80% ± 2%; duration of hypoxia 5 min) were performed in ten healthy subjects. We obtained four responses per subject: one without isoflurane in a darkened, quiet room; one without isoflurane with audiovisual input (music videos); one in a darkened room at 0.1 MAC isoflurane; and one at 0.1 MAC isoflurane with audiovisual input (subjects were addressed to keep their eyes open). Experiments were performed against a background of isocapnia (end-tidal carbon dioxide tension 1–1.4 mmHg above initial resting values).**

Results: **The hypoxic responses averaged 0.54 ± 0.09 $l \cdot min^{-1} \cdot \%^{-1}$ (without isoflurane in a darkened, quiet room), 0.27 ± 0.06 $l \cdot min^{-1} \cdot \%^{-1}$ (in a darkened room at 0.1 MAC isoflurane; $P < 0.01$), 0.56 ± 0.13 $l \cdot min^{-1} \cdot \%^{-1}$ (without isoflurane with audiovisual input), and 0.47 ± 0.13 $l \cdot min^{-1} \cdot \%^{-1}$ (at 0.1 MAC isoflurane with audiovisual input). Values are means ± SE. During 0.1 MAC isoflurane administration, all subjects showed a depressed hypoxic response when not stimulated, while with stimulation two subjects had an increased response, four a decreased response and four an unchanged response compared to control.**

Conclusions: **We observed an important effect of the study conditions on the effects that 0.1 MAC isoflurane has on the hypoxic ventilatory response. A depressant effect of subanesthetic isoflurane was found only when external stimuli to the subjects were absent. With extraneous audiovisual stimuli the effect of isoflurane on the response to hypoxia was more variable. On the average, however, the response then was not depressed by isoflurane. (Key words: Anesthetics, volatile: isoflurane. Lung(s), ventilation: acute hypoxic response. Methods: dynamic end-tidal forcing; isocapnic hypoxia. Receptors: peripheral chemoreceptors. Stimulation: audiovisual input. Ventilatory control: behavioral control; metabolic control.)**

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KNILL and coworkers[1–6] studied the effects of several halogenated anesthetic agents on the chemical control of breathing in the late 1970s and early 1980s. Their conclusions were that subanesthetic concentrations of halothane, isoflurane, and enflurane selectively depress the peripheral chemoreceptors.[7] We recently confirmed the findings of Knill *et al.* regarding halothane.[8,9] We observed that subanesthetic halothane reduced the ventilatory response to acute isocapnic hypoxia[8,9] and the carbon dioxide sensitivity of the peripheral chemoreceptors appreciably, while the carbon dioxide sensitivity of the central chemoreceptors remained unaltered.[8]

The effects of *isoflurane* on the ventilatory response to acute isocapnic hypoxia were studied by Temp *et al.* in two recent studies.[10,11] In contrast to Knill *et al.*[5] they did not observe an effect of subanesthetic isoflurane on the hypoxic response. While Knill *et al.*[5] found a depression of the hypoxic response by more than 50%, Temp *et al.*[10,11] found control and 0.1 minimum alveolar concentration (MAC) isoflurane experiments to be not significantly different. An important difference

between these studies was the environment in which the subjects underwent the experiments. Knill *et al.* studied subjects in a quiet, darkened room during both control and 0.1 MAC isoflurane experiments.[5] Temp *et al.*, in contrast, required all subjects to watch a video documentary, and subjects were spoken to or touched when they closed their eyes[10,11] to "minimize differences in level of consciousness between control and isoflurane experiments." [11] Among the several possible reasons for the difference in outcome of the studies of Knill *et al.*[5] and Temp *et al.*[10,11] the most important may be the difference in subject arousal and hence the cortical influence on ventilatory control.[12,13]

The aim of the current study was to quantify the influence of 0.1 MAC isoflurane on the ventilatory response to hypoxia by applying a step hypoxic test with and without audiovisual input to the subjects.

Materials and Methods

Subjects and Apparatus

Ten subjects (eight men and two women, aged 20–35 yr) took part in a study approved by the Leiden University Committee on Medical Ethics. Excluded were subjects that were smokers, had evidence of cardiovascular, respiratory or liver disease, an abnormal electrocardiogram, or were on medication. Eight subjects had participated previously in a study on halothane.[8,9] The two subjects that had not participated in a previous study were familiarized with the experimental procedure and apparatus before the study started. All subjects were uninformed regarding respiratory physiology but did receive information on the nature and risks of the study. Before the study started all gave informed consent. The subjects were asked to refrain from stimulants and depressants for at least 12 h before the experiments.

Before data collection started all subjects rested for about 1 h. During an experiment (or trial) they were in a semirecumbent position. An oronasal mask was fitted before each study began. The mask allows normal movement of mouth and lips and is considered less disruptive to normal breathing than a mouthpiece–noseclip arrangement. To avoid excessive pressure on the face the fit of the mask was loose. Leakage was prevented by applying silicone putty between mask and face. 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 1,000 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 isoflurane 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 and oxygen tensions ($P_{ET_{CO_2}}$ and $P_{ET_{O_2}}$, respectively) to follow a specific pattern in time. Part of the nitrogen (5 l/min) passed through the isoflurane vaporizer. During control trials 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 concentrations isoflurane of in- and expired gas were 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 hemoglobin oxygen saturation through pulse oximetry *via* a finger probe (Sp_{O_2}). Throughout the study the electrocardiogram was monitored. The following parameters were stored on a breath-to-breath basis for further analysis: minute ventilation ($\dot{V}_E$), tidal volume, respiratory frequency, $P_{ET_{CO_2}}$, $P_{ET_{O_2}}$, and Sp_{O_2}.

Study Design

To force dynamically the $P_{ET_{CO_2}}$ and $P_{ET_{O_2}}$ to follow a prescribed pattern in time we used a computer-controlled "dynamic end-tidal forcing system." [14,15] By manipulating the inspired gas concentrations, $P_{ET_{O_2}}$ and $P_{ET_{CO_2}}$ were steered independently of the ventilatory response. At the start of the study resting $P_{ET_{CO_2}}$ levels were obtained after 15 min of steady-state $\dot{V}_E$ with no inspired carbon dioxide and no extraneous stimulation. Thereafter the $P_{ET_{CO_2}}$ was elevated 1–1.4 mmHg above the individual resting values and maintained constant

at this level in all four trials. To obtain the hypoxic stimulus we performed a step decrease in end-tidal oxygen concentration according to the following pattern: (1) kept at 110 mmHg for 20–25 min, (2) a rapid decrease to about 44 mmHg, to reach a target Sp_{O_2} of 80% ± 2%; this $P_{ET_{O_2}}$ was maintained for 5 min, and (3) a 10-min period of hyperoxia ($P_{ET_{O_2}} > 600$ mmHg). The step decrease in $P_{ET_{O_2}}$ was similar for single subjects among the four trials but differed between subjects.

For the isoflurane studies the end-tidal fraction of isoflurane was brought to 0.125% within 5 min by means of an "overpressure" technique. Thereafter a 20 min equilibration period preceded the hypoxic challenge. Throughout the isoflurane trial, the end-tidal fraction of isoflurane was kept constant at the target level (0.125%) by manipulation of the isoflurane vaporizer (by M.v.d.E. or A.D.).

All studies started with two trials without isoflurane inhalation. During one trial the subjects were in a darkened, silent room (no audiovisual stimulation–control [NAVS-C] trials). During the other the subjects were required to watch and listen to prerecorded music videos (audiovisual stimulation–control [AVS-C] trials). Between trials there was a 30 min rest period. The order of trials was chosen by the toss of a coin. Following the control trials and another 30 min rest period the isoflurane trials were obtained. One trial was performed in complete rest in a darkened room with the eyes closed (no audiovisual stimulation–isoflurane [NAVS-I] trials). During the other, the subjects were required to watch the aforementioned music videos (audiovisual stimulation–isoflurane [AVS-I] trials). Between isoflurane trials there was a 30-min rest period. The order of trials was determined by the toss of a coin.

Inclusion and Exclusion Criteria with Respect to Behavioral State

During all studies one investigator (M.J.L.J.v.E. or A.D.) continuously watched the subjects. During the NAVS-C studies, the subjects were instructed to keep their eyes closed. Data were included for analysis when this was achieved throughout the trial. During the AVS-C studies, data were included for analysis when subjects continuously watched the music videos (*i.e.,* had their eyes open). At the end of both trials (NAVS-C and AVS-C) the memory of the subjects as well as their awareness of time and space was determined through a short interview (Questions asked: Did you notice that your breathing increased during the experiment? Do you know where you are? Do you know what time it is?). Before data collection started in the individual trials of the NAVS-I studies, we called the name of the subjects. Only when they were able to open their eyes we continued the experiment. We then instructed the subjects to keep the eyes closed. Also at the end of that trial we called the name of the subjects. If again they were able to open their eyes and, furthermore, had not spontaneously opened them during the trial, the data were included in the analysis. This procedure was similar to that performed in our previous study during inhalation of 0.1 MAC halothane.[8] During the AVS-I studies, the subjects were instructed to keep their eyes open and watch the videos. If eye closure occurred the subjects name was called and they were encouraged to keep their eyes open. After both trials (NAVS-I and AVS-I) the aforementioned questions were repeated.

Data Analysis

The trials were evaluated by taking mean values of the breath-to-breath $\dot{V}_E$ over identical time segments: period A = the final two min of normoxic $\dot{V}_E$ before induction of hypoxia, and period B = minutes 4 and 5 after exposure to hypoxia. We defined the difference in $\dot{V}_E$ between periods B and A as the acute hypoxic response.

With respect to stimulus control trials were included for analysis if the following criteria were met: (1) a difference in mean $P_{ET_{CO_2}}$ between periods A and B less than 1.5 mmHg, (2) a difference in mean $P_{ET_{CO_2}}$ between periods A of the isoflurane and control studies less than 1.5 mmHg, (3) a standard deviation of the breath-to-breath $P_{ET_{CO_2}}$ in all the periods less than 1.5 mmHg, and (4) an Sp_{O_2} of 80% ± 2% within 1 min after the start of hypoxic stimulation. Inclusion criteria regarding the behavioral state of the subjects are mentioned above.

Statistical Analysis

A two-way analysis of variance was performed on the acute hypoxic response, the changes in tidal volume, respiratory frequency, Sp_{O_2}, $P_{ET_{CO_2}}$ and $P_{ET_{O_2}}$ between periods B and A, and $\dot{V}_E$ of periods A and B, of the four treatment groups (NAVS-C, NAVS-I, AVS-C, and AVS-I). Differences between treatments were tested with the Student-Newman-Keuls test.

Probability levels < 0.05 were taken as significant. All values are mean ± SE unless otherwise mentioned.

Results

None of the trials had to be discarded. In the NAVS studies all subjects had their eyes closed. During the NAVS-I studies they maintained their ability to respond to command (eye opening after name calling before and after the trial). At the end of these trials subjects indicated awareness of time and space but could not remember an increase of breathing activity. In contrast, all AVS experiments were performed with open eyes and all subjects had awareness of time and space and no memory defects. It was never necessary to touch the subjects.

The mean differences of the $P_{ET_{CO_2}}$ between periods A and B ranged between −0.6 and 0.2 mmHg, similar differences were observed among the mean concentrations of $P_{ET_{CO_2}}$ of periods A of the different studies (table 1). The control of the $P_{ET_{CO_2}}$ was within 0.4 mmHg (*i.e.*, the standard deviation of the breath-to-breath $P_{ET_{CO_2}}$ of single periods [A or B] was 0.4 mmHg or less). The step decreases in $P_{ET_{O_2}}$ and Sp_{O_2} and their values in period B were not significantly different among treatments. The standard errors of the $P_{ET_{O_2}}$ in table 1 indicate intersubject variability; in a single subject the $P_{ET_{O_2}}$ (and also the Sp_{O_2}) of periods B was similar among the four studies. The control of the $P_{ET_{O_2}}$ was within 0.4 mmHg (*i.e.*, the standard deviation of the breath-to-breath $P_{ET_{O_2}}$ of single periods [A or B] was 0.4 mmHg or less). The end-tidal fractions of isoflurane were 0.123% ± 0.002% in NAVS-I trials and 0.124% ± 0.002% in AVS-I trials.

Baseline ventilation ($\dot{V}_E$ of period A) was largest in the AVS studies (AVS-I $P < 0.05$ *vs.* NAVS-C and *vs.* NAVS-I; AVS-C $P < 0.05$ *vs.* NAVS-I). The ventilatory responses of one subject are shown in figure 1. It shows a large depression of the ventilatory response to acute hypoxia by 0.1 MAC isoflurane only when there was no audiovisual stimulation. The AVS-C and AVS-I trials were not different. His hypoxic responses of all subjects averaged 0.54 ± 0.09 $l \cdot min^{-1} \cdot \%^{-1}$ (NAVS-C), 0.27 ± 0.06 $l \cdot min^{-1} \cdot \%^{-1}$ (NAVS-I; $P < 0.01$), 0.56 ± 0.13 $l \cdot min^{-1} \cdot \%^{-1}$ (AVS-C), and 0.47 ± 0.13

Table 1. The Effect of 0.1 MAC Isoflurane on the Ventilatory Response to Isocapnic Hypoxia without and with Extraneous Input to the Subjects

		NAVS-C	NAVS-I	AVS-C	AVS-I
$\dot{V}_E$ (l/min)	A	13.3 ± 0.8	11.4 ± 0.7	15.1 ± 0.8‡	17.5 ± 1.3§
	B	23.0 ± 2.1	16.4 ± 1.3*	25.2 ± 2.6	26.5 ± 3.2
	Δ	9.7 ± 1.9	5.0 ± 1.3†	10.1 ± 2.0	9.0 ± 2.3
V_T (ml/breath)	A	886 ± 53	783 ± 90	884 ± 43	938 ± 61
	B	1311 ± 106	1070 ± 113	1311 ± 96	1248 ± 102
	Δ	424 ± 92	287 ± 70*	426 ± 109	310 ± 85
f (breaths/min)	A	15.9 ± 1.4	16.1 ± 1.3	17.4 ± 1.4	19.1 ± 1.3
	B	18.0 ± 1.3	16.3 ± 1.3	19.5 ± 1.3	21.0 ± 1.3
	Δ	2.1 ± 1.3	0.1 ± 0.6*	2.1 ± 0.7	1.9 ± 0.6
$P_{ET_{CO_2}}$ (mmHg)	A	44 ± 0.7	44 ± 0.7	44 ± 0.7	44 ± 0.7
	B	44 ± 0.7	44 ± 0.7	44 ± 0.7	44 ± 0.7
	Δ	0.1 ± 0.2	−0.6 ± 0.1	0.2 ± 0.1	0.0 ± 0.2
$P_{ET_{O_2}}$ (mmHg)	A	110 ± 0.5	109 ± 0.7	110 ± 0.5	110 ± 0.2
	B	43 ± 1.2	44 ± 0.9	43 ± 0.9	43 ± 0.7
Sp_{O_2} (%)	A	99 ± 0.3	99 ± 0.3	99 ± 0.3	99 ± 0.3
	B	81 ± 0.4	80 ± 0.4	81 ± 0.4	80 ± 0.4

A = final 2 min of normoxic ventilation before induction of hypoxia; B = min 4 and 5 of hypoxia; Δ = differences between periods B and A; $\dot{V}_E$ = minute ventilation; $\dot{V}_T$ = tidal volume; *f* = breathing frequency; Sp_{O_2} = hemoglobin oxygen saturation derived from pulse oximetry via a finger probe; NAVS-C = hypoxic challenges without isoflurane and without auditory and visual stimulation; NAVS-I = hypoxic challenges at 0.1 MAC isoflurane without auditory and visual stimulation; AVS-C = hypoxic challenges without isoflurane with auditory and visual stimulation; AVS-I = hypoxic challenges at 0.1 MAC isoflurane with auditory and visual stimulation; n = 10.

Values are mean ± SE.

* $P < 0.05$ *versus* all other treatments.

† $P < 0.01$ *versus* all other treatments.

‡ $P < 0.05$ *versus* NAVS-I.

§ $P < 0.05$ *versus* NAVS-C and NAVS-I.

$l \cdot min^{-1} \cdot \%^{-1}$ (AVS-I). The depression of the acute hypoxic response in the NAVS-I studies occurred through changes in breathing frequency as well as tidal volume (table 1). In figure 2 we plotted the individual values of acute hypoxic response of all four treatment groups. During 0.1 MAC isoflurane administration, all subjects showed a depressed hypoxic response when not stimulated, while with stimulation two subjects had an increased response, four subjects a decreased response, and the remainder an unchanged response compared to control. We did not observe an effect of the order of stimulation on the hypoxic response in the trials both before and during isoflurane inhalation.

Discussion

Critique of Methods

Study Design. We performed control and drug experiments on 1 day within a 3.5-h period. To avoid the effect of residual isoflurane control experiments always preceded drug experiments. Therefore, only the order of audiovisual stimulation was randomly chosen. A randomized crossover study could have been performed on 1 day or on separate days. Performing such a study on 1 day would have resulted in long sessions and discomfort of the subjects. Also an influence of a drug trial on a subsequent control trial could not have been excluded. Performing trials on separate days would have increased the trial-to-trial variability, since day-to-day variability is more significant than within-day variability.[16,17] Since control trials always preceded drug trials we are not able to exclude an effect of the order of drug administration on the measured response. However, an effect of the order of stimulation was not observed in control or isoflurane studies.

All hypoxic trials were performed within a short time span. To warrant no effect of a previous hypoxic challenge on a subsequent one[18,19] we introduced a 10-min hyperoxic period (F_I oxygen > 0.8) after exposure to hypoxia. This prevents an ongoing "depressant" effect of hypoxia to influence a next hypoxic trial.[18]

Subjects. To prevent an effect of anxiety of the subjects on the hypoxic response, which is normally present during the first few hypoxic exposures, we performed experiments in subjects that had participated in previous protocols or "trained" our subjects by performing several test trials. The magnitude of the control acute hypoxic responses and the level of control baseline $\dot{V}_E$ were consistent with our findings in previous studies.[8,9,19-21]

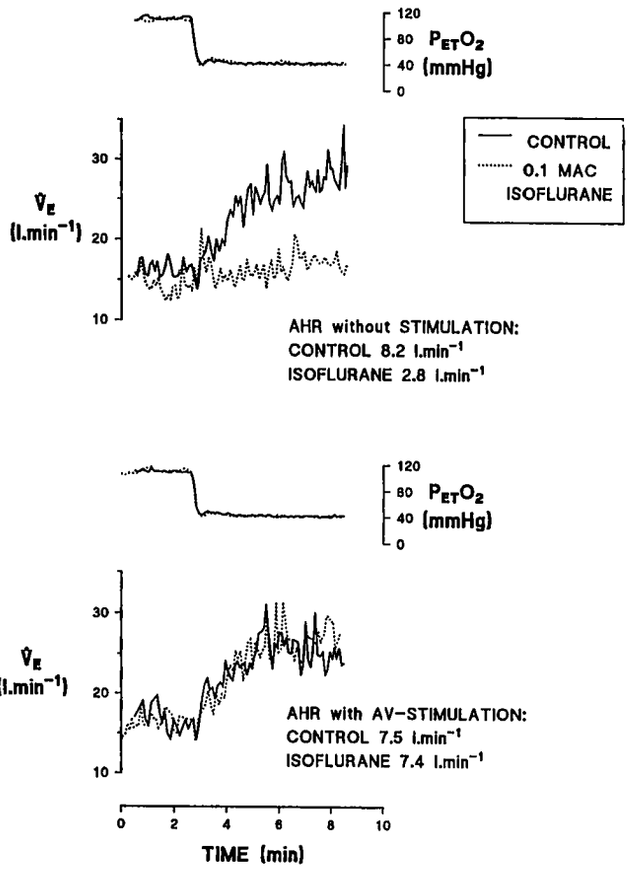

Fig. 1. Effect of 0.1 minimum alveolar concentration isoflurane on the acute hypoxic response (AHR) of a subject without (*top*) and with (*bottom*) audiovisual (AV) stimulation.

Control of Inhaled and Exhaled Gas Concentrations. Within 5 min we obtained our target end-tidal isoflurane concentration (0.125%). Thereafter a 20-min period preceded the hypoxic challenge. Throughout the experiment the end-tidal isoflurane concentration was kept constant by manipulation of the vaporizer. The target level of 0.125% represents 0.1 MAC in our subject group[22]; the 20-min period represents five time constants for brain uptake and equilibration.[23] This strategy is similar to that of Knill *et al.*[5] and Temp *et al.*[10,11]

To study the effects of isoflurane we used the "dynamic end-tidal forcing" technique.[14,15] We performed steps in Sp_{O_2} while maintaining constant $P_{ET_{CO_2}}$ by manipulating the inspired gas concentrations independently of the ventilatory response. The $P_{ET_{CO_2}}$ was set at 1–1.4 mmHg above resting values at the start of the

study and maintained at this level in all four trials. The mean differences in $P_{ET_{CO_2}}$ of periods B and A are similar to results in other studies (table 1).[8,9,14,18–21] The fluctuations of the breath-to-breath $P_{ET_{CO_2}}$ in the different periods (*i.e.*, the control of $P_{ET_{CO_2}}$) were small and comparable to other studies.[8,9] The magnitude of baseline ventilation in the NAVS studies is comparable to other studies using $P_{ET_{CO_2}}$ control.[8,9,14,19–21] We attribute the larger ventilation in period A of the AVS studies to the extraneous stimuli (see below), the increase of inspired carbon dioxide concentration (1–1.5%), and in the AVS-I studies also to the taste or smell of isoflurane, now apparent due to the inability to fall "asleep".

Arousal State of the Central Nervous System. We included data of the trials in our analysis if simple criteria were met: in the AVS trials subjects had to keep their eyes open and were addressed if they closed them; in the NAVS trials the room was darkened and subjects had to close their eyes and keep them closed. This approach was chosen to compare our results to those of Knill *et al.*[5] (NAVS trials) and those of Temp *et al.*[10,11] (AVS trials). Although we did not obtain electrographic data (electroencephalogram, electrooculogram, electromyogram), the ability of the subjects to respond to command before and after data collection of the NAVS-I studies as well as no significant effect in the NAVS trials on resting ventilation, pattern of breathing or $P_{ET_{CO_2}}$ indicates that none of the subjects had behavioral characteristics of "sleep." Similar findings were obtained by Newton *et al.*[24] with 0.1 MAC isoflurane, Dahan *et al.*[8] with 0.1 MAC halothane and Knill *et al.*[5] with 0.1 MAC isoflurane. Newton *et al.*[25] observed the loss of memory after 0.1 MAC isoflurane administration despite the ability to react normally to command during exposure to isoflurane. This is in agreement with our findings.

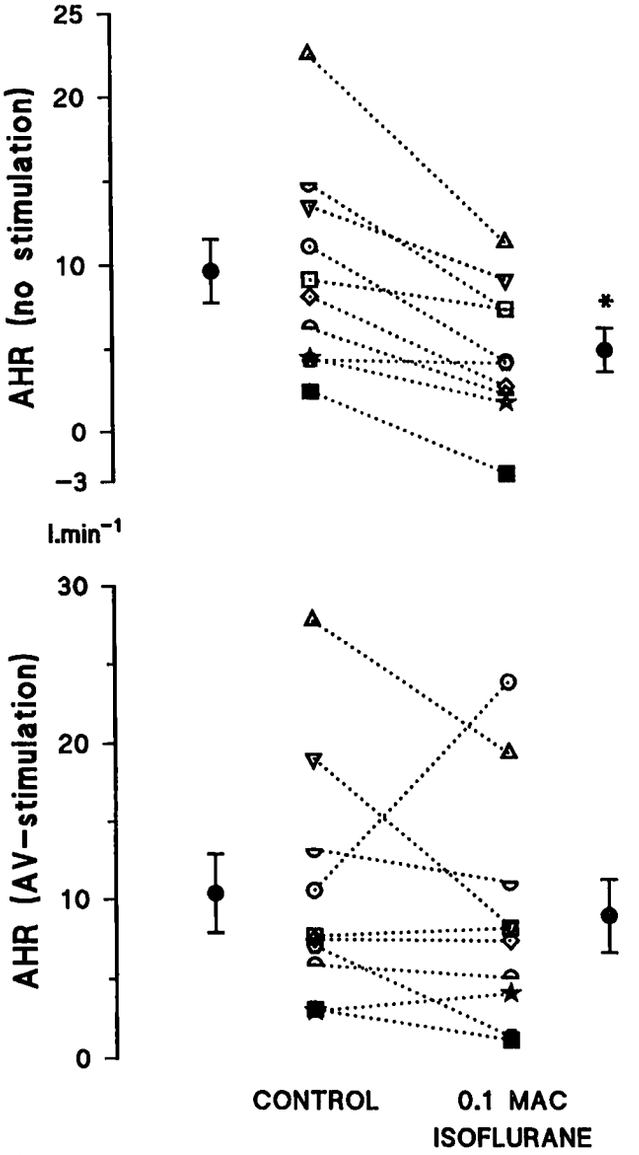

Fig. 2. The acute hypoxic response during 0 and 0.1 minimum alveolar concentration isoflurane inhalation without (*top*) and with (*bottom*) audiovisual (AV) stimulation. Each subject is represented by the same symbol in all diagrams. *$P < 0.01$ *versus* all other treatments. Mean values are ± SE.

Comparison with the Literature

Knill *et al.*[5] studied the effects of 0.1 MAC isoflurane on the hypoxic ventilatory response in 5 subjects. All subjects were in a darkened room and were never addressed or touched during an experiment. To obtain the hypoxic stimulus, these investigators decreased the $P_{ET_{O_2}}$ to 6% over 8–10 min[5] (ramp hypoxic test). The hypoxic response was represented by the "the measured increment of instantaneous ventilation between $P_{ET_{O_2}}$ values of 400 mmHg and 45 mmHg." [5] This increment was 9.7 l/min in control experiments and 4.1 l/min in isoflurane experiments (depression of hypoxic response 58%). This is similar to our findings in 10 subjects with a step hypoxic test in the NAVS trials (depression of hypoxic response 50%) (fig. 3).

Temp *et al.*[10,11] determined the effects of 0.1 MAC isoflurane on the response to hypoxia by using a step hypoxic test. In both studies subjects were required to watch a video documentary and addressed or touched when they closed their eyes. In their first study[10] (eight

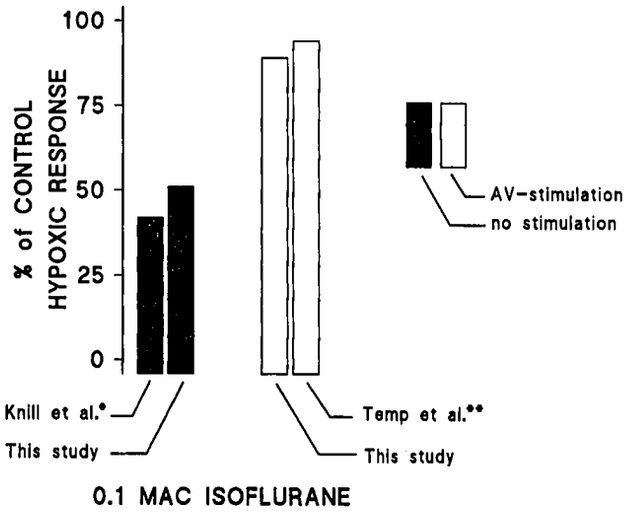

Fig. 3. The effect of 0.1 minimum alveolar concentration isoflurane on the ventilatory response to hypoxia. *Knill *et al.*[5] **Temp *et al.*[9]

subjects) they observed an increase of $\dot{V}_E$ of 10.3 l/min in control experiments and 9.7 l/min with 0.1 MAC isoflurane (depression of response 6%). In that study, using the end-tidal forcing technique, the $P_{ET_{O_2}}$ was decreased from 113 to 45 mmHg within four or five breaths and subsequently kept constant at this level. In a subsequent study[11] (eight subjects) the $P_{ET_{O_2}}$ was rapidly decreased from 300 to 45 mmHg and maintained at this low level. The increase in $\dot{V}_E$ was 11.0 l/min in control and 9.4 l/min in isoflurane experiments (depression of response 15%). These findings are similar to ours with a step hypoxic test in the AVS trials (depression of response 11%) (fig. 3).

Site of Action of Isoflurane and Interaction of the Behavioral State with the Hypoxic Response. The regulation of breathing is determined by two control systems: the metabolic control system (determined by stimuli to the chemoreceptors, *i.e.,* oxygen tension, carbon dioxide tension, and *p*H) and the behavioral control system.[26] It is possible for one system to override the influences of the other. For instance, during emotional states the output of the ventilatory system is to a large extent determined by the behavioral control system. When the behavioral control system is excited it usually leads to an increased but irregular and unstable breathing which is variable from individual to individual.[26,27]

In the NAVS studies we observed depression of the hypoxic response by 0.1 MAC isoflurane in all subjects and consider these responses primarily derived from the metabolic control system. The depression by 0.1 MAC isoflurane of the hypoxic ventilatory response may then be attributed to an effect at the site of any of the components involved in this control system (peripheral chemoreceptors, central chemoreceptors, integrating center in the central nervous system, neuromechanical link between brain stem and $\dot{V}_E$). In a previous study[8] we performed step increases in $P_{ET_{CO_2}}$ during 0.1 MAC halothane inhalation. From the hypercapnic responses we derived 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. These results indicate a selective effect of subanesthetic halothane on the peripheral chemoreceptors *per se.* Similar conclusions may be drawn from the studies of Knill and Clement.[3,6] In one study they observed a rapid decrease of hypoxia-driven $\dot{V}_E$ on exposure to halothane (inspired fraction 0.15–0.30%),[6] in another the large decrease by halothane of the ventilatory response to isocapnic metabolic acidosis.[3] Studies on the effects of 0.1 MAC isoflurane on the ventilatory response to step changes of $P_{ET_{CO_2}}$ are necessary to determine its site of action during metabolic control of ventilation. However, our results suggest that the peripheral chemoreflex loop is affected by both halothane and isoflurane in a similar fashion. Furthermore, they suggest that an effect of sedation or "sleep" is not probable at the concentrations we have used, since subanesthetic halothane did not affect the central chemoreflex loop or the integrating centers in the central nervous system.

In the AVS studies, the findings of a higher and more variable baseline ventilation ($\dot{V}_E$ in period A; table 1), especially during isoflurane administration, as well as the variable effects of isoflurane on the response to hypoxia compared to control among subjects, indicates that the behavioral control of ventilation was evoked by the extraneous input to the subjects. The results of the AVS-C studies are in agreement with the findings of Shea *et al.*[27] and Gallego and Perruchet.[28] Shea *et al.* showed that adding audiovisual input to baseline conditions of rest and low sensory input increased resting $\dot{V}_E$ (through an increase in respiratory frequency), especially when there was visual stimulation.[27] Gallego and Perruchet showed that combining an auditory stimulus with hypoxia did not cause a larger ventilatory response compared to hypoxia alone,[28] as noticed by

us. Similar to our findings in the AVS-I studies, Temp *et al.*[11] observed that the effects of isoflurane varied among subjects (less than 50% of control in three, greater than control in four subjects), resulting in an average response similar to control. Our observations together with those of Temp *et al.*[10,11] show that extraneous input to the subjects precludes the proper assessment of *metabolic control* due to the resultant additional cortical drives on $\dot{V}_E$.

Our results indicate that the different results of Knill *et al.*[5] and Temp *et al.*[10,11] should be attributed to the difference in behavioral state of the subjects. Other differences between the protocols of Knill *et al.*[5] and Temp *et al.*[9,10] (addition of inspired carbon dioxide[9,10]; a step decrease in $P_{ET_{CO_2}}$ *versus* a ramp decrease[5]; randomization of control and drug experiments[9,10]) are therefore of only minor importance. The results of the NAVS studies should lead to a more vigilant approach toward hypoxia, hypercapnia and acidosis when patients (in the anesthesia care unit) still have low concentrations of volatile anesthetics in their body.

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