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Acute Pain and Central Nervous System Arousal Do Not Restore Impaired Hypoxic Ventilatory Response during Sevoflurane Sedation

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Background: **To quantify the effects of acute pain on ventilatory control in the awake and sedated human volunteer, the acute hypoxic ventilatory response was studied in the absence and presence of noxious stimulation before and during 0.1 minimum alveolar concentration sevoflurane inhalation.**

Methods: **Step decreases in end-tidal partial pressure of oxygen from normoxia into hypoxia (~50 mmHg) were performed in 11 healthy volunteers. Four acute hypoxic ventilatory responses were obtained per subject: one in the absence of pain and sevoflurane (C), one in the absence of sevoflurane with noxious stimulation in the form of a 1-Hz electrical current applied to the skin over the tibial bone (C + P), one in the absence of pain during the inhalation of 0.1 minimum alveolar concentration sevoflurane (S), and one during 0.1 minimum alveolar concentration sevoflurane with noxious stimulation (S + P). The end-tidal partial pressure of carbon dioxide was held constant at a value slightly greater than baseline (44 mmHg). To assess the central nervous system arousal state, the bispectral index of the electroencephalogram was monitored. Values are mean ± SE.**

Results: **Pain caused an increase in prehypoxic baseline ventilation before and during sevoflurane inhalation: C = 13.7 ± 0.9 l·min^{-1}, C + P = 16.0 ± 1.0 l·min^{-1} ($P < 0.05$ *vs.* C and S), S = 12.7 ± 1.2 l·min^{-1}, and S + P = 15.9 ± 1.1 l·min^{-1} ($P < 0.05$ *vs.* C and S). Sevoflurane decreased the acute hypoxic ventilatory response in the absence and presence of noxious stimulation: C = 0.69 ± 0.20 l·min^{-1} (% change in arterial hemoglobin-oxygen saturation derived from pulse oximetry [S_pO_2])$^{-1}$, C + P = 0.64 ± 0.13 l·min^{-1}·%$S_pO_2^{-1}$, S = 0.48 ± 0.15 l·min^{-1}·%$S_pO_2^{-1}$ ($P < 0.05$ *vs.* C and C + P) and S + P = 0.46 ± 0.12 l·min^{-1}·%$S_pO_2^{-1}$ ($P < 0.05$ *vs.* C and C + P). The bispectral indexes were C = 96.2 ± 0.7, C + P = 97.1 ± 0.4, S = 86.3 ± 1.3 ($P < 0.05$), and S + P = 95.0 ± 1.0.**

Conclusions: **The observation that acute pain caused an increase in baseline ventilation with no effect on the acute hypoxic ventilatory response indicates that acute pain interacted with ventilatory control without modifying the effect of low-dose sevoflurane on the peripheral chemoreflex loop. Acute pain increased the level of arousal significantly during sevoflurane inhalation but did not restore the ~30% depression of the acute hypoxic ventilatory response by sevoflurane. The central nervous system arousal state *per se* did not contribute to the impairment of the acute hypoxic ventilatory response by sevoflurane. (Key words: Anesthetics, volatile: sevoflurane. Central nervous system: arousal; state. Lungs: acute hypoxic response. Measurement techniques: bispectral index; dynamic end-tidal forcing; electroencephalogram; isocapnia. Monitoring: capnography. Pain: acute.)**

ALTHOUGH it is well known that surgical stimulation during anesthesia in a spontaneous breathing patient increases inspired minute ventilation ($\dot{V}_I$) and reduces the end-tidal carbon dioxide concentration ($P_{ET}CO_2$),[1–4] there are no controlled studies in humans that focus on the influences of acute pain on ventilatory control (that is, resting ventilation and the peripheral and central chemoreflexes) in the awake and sedated states. This was recently pointed out by Bourke.[5] In this study, we investigated the effects of noxious stimulation on resting $\dot{V}_I$ and the ventilatory response to isocapnic hypoxia during wakefulness and sedation by the inhalational anesthetic sevoflurane in healthy volunteers. Our main aims were to assess the influence of acute pain on normoxic and hypoxic ventilation and to determine the ability of acute pain to antagonize the depression of the hypoxic ventilatory response by 0.1

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minimum alveolar concentration (MAC) sevoflurane. Furthermore, we measured the electroencephalogram (EEG) to obtain information on the central nervous system (CNS) arousal states in the presence and absence of noxious stimulation.

Materials and Methods

Subjects and Apparatus

After approval by the Leiden University Committee on Medical Ethics, 11 healthy volunteers (aged 23–30 yr, 5 women, without history of medical or psychiatric illness, smoking, drug, or alcohol abuse) were recruited to participate in the study. All had participated in previous studies on respiratory control and were familiar with the experimental procedures and apparatus. They were all uninformed about respiratory physiology but did receive information on the nature and risks of the study. All gave informed consent. The subjects were advised not to eat or drink for at least 6 h before the study.

After arrival at the laboratory the subjects rested for 30 min. During the study the volunteers were in a semirecumbent position. An oronasal mask (Vital Signs) 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/min). 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 sevoflurane 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 (Digital Equipment Corporation, Maynard, IO) 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 concentration ($P_{ET}O_2$) to follow a specific pattern in time while the $P_{ET}CO_2$ is kept constant. Part of the nitrogen (5 l/min) passed through the sevoflurane vaporizer (Vapor 19.3, Dräger, Lubeck, Germany). 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. The sevoflurane concentration was measured at the mouth with a Datex monitor (Capnomac Ultima, Helsinki, Finland). A pulse oximeter (Datex Satellite Plus, Finland) continuously measured the arterial hemoglobin-oxygen saturation *via* a finger probe (S_PO_2). The hand from which S_PO_2 was measured was warmed with a sheepskin glove. Throughout the study, the ECG was monitored. Inspiratory minute ventilation, tidal volume, respiratory rate, heart rate, S_PO_2, $P_{ET}CO_2$ and $P_{ET}O_2$ were stored on a breath-to-breath basis. The experimental dead space was 250 ml.

Study Design

To study the ventilatory response to isocapnic hypoxia we used a computer-steered "dynamic end-tidal forcing" system.[6] With this system we are able to force the $P_{ET}CO_2$ and $P_{ET}O_2$ to follow a prescribed pattern in time by manipulation of the inspired gas concentrations independently of the ventilatory response. In this study, four hypoxic studies, against the background of a constant $P_{ET}CO_2$, were obtained in each volunteer. One study without pain or sevoflurane inhalation (control), one during experimentally induced acute pain without sevoflurane inhalation (control-pain), one during 0.1 MAC sevoflurane inhalation (sevoflurane), and one during 0.1 MAC sevoflurane inhalation and experimentally induced acute pain (sevoflurane-pain). The study started with the two studies without sevoflurane inhalation. Between studies there was a 20–30-min rest period.

Target End-tidal Carbon Dioxide Concentration, End-tidal Oxygen Concentration, and Sevoflurane Patterns. The study started with assessment of the resting $P_{ET}CO_2$ during 10–15 min of breathing a normoxic gas mixture without inspired carbon dioxide. Thereafter, the $P_{ET}CO_2$ was increased by ~2 mmHg above individual resting values. This value was maintained throughout the study. Hypoxic studies started after at least 5 min of steady-state ventilation.

Steps from normoxia (~110 mmHg) into hypoxia (target $P_{ET}O_2$ = 50 mmHg, obtained within 4–6 breaths) were applied. Hypoxia was maintained for 3 min after which normoxia was reintroduced.

When appropriate, we brought the end-tidal fraction of sevoflurane to 0.23% (~0.1 MAC)[7,**] within 1 min by means of an "overpressure" technique. Thereafter, a 15-min equilibration period preceded the hypoxic challenges.

Measurement of Central Nervous System Arousal State

At the start and end of the studies we recorded the CNS arousal state by a subjective six-point observers' assessment of alertness/sedation (OAA/S) scale (table 1). After assessment of the sedation score we instructed the volunteers to keep the eyes closed during the study.

The EEG and bispectral index were measured during the study. Electrodes (Zipprep, Aspect Medical Systems, Framingham, MA) were placed according to the international 10/20 system for electrode placement at A_1-C_4 and A_2-C_3 for bipolar recordings of the EEG. Electrode impedances were less than 2 KΩ. The EEG was recorded using an Aspect A-1000 EEG monitor (Framingham, MA). Data were acquired at 16,384 Hz and subsequently reduced to 128 Hz. High- and low-pass filters were set at 0.1 and 30 Hz, respectively. Electrical artifacts were automatically identified by the monitor and rejected. The Aspect monitor computed the bispectral index over 4-s epochs. The values of the bispectral index range between 0 and 100. We averaged the bispectral index over 15 epochs and used the values obtained during the 1-min period before hypoxia and the third min of hypoxia for further analysis.

Experimentally Induced Acute Pain

Two electrodes (Red dot, 3M, London, Ontario) were placed on the skin directly overlying the tibial bone. The electrodes were attached to an electrostimulator (Innervator NS 242, Fisher & Paykel, Auckland, New Zealand). When appropriate, noxious stimuli of 0.2-ms duration at 1-s intervals were applied. The stimuli consisted of a constant electrical current that could vary from 10 to 80 mA at 10-mA intervals. The amperage of the current was set for each volunteer separately such that his or her visual analog scale (VAS) for pain scoring was between 4.5 and 5.5 cm (on a scale from 0 cm = no pain to 10 cm = worst possible pain). After 1 min of stimulation, the VAS was reassessed and the current adjusted so that the VAS ranged again between 4.5 and 5.5 cm. Hereafter, the control-pain or sevoflurane-pain studies were performed. Sevoflurane was administered at 0.1 MAC for at least 15 min before the noxious stimuli were applied in the sevoflurane-pain studies. Immediately after the hypoxic episodes the VAS was determined a third time to exclude a drift of the VAS in time.

Table 1. The Leiden Observers' Assessment of Alertness/Sedation Scale (OAAS/S)

0 = normal alertness, eyes closed and opened on command
1 = drowsy with open eyes, closed and opened on command
2 = drowsy with closed eyes, opened in response to a light auditory stimulus
3 = eyes closed, opened in response to lightly rubbing the shoulder or a loud auditory stimulus
4 = closed eyes, eyes opened briefly in response to touching the subject
5 = closed eyes, unarousable

Data Analysis

The studies were evaluated by taking mean values of the breath-to-breath data over identical time segments: period A = 1 min before the introduction of hypoxia; period B = third min of hypoxia. We defined the difference of $\dot{V}_I$ between periods A and B as the acute hypoxic response.

To detect the significance of differences among the different studies (control, control-pain, sevoflurane, sevoflurane-pain), a two-way analysis of variance was performed on the bispectral index, heart rate, $\dot{V}_I$, tidal volume, respiratory rate, $P_{ET}CO_2$, and $P_{ET}O_2$ of period A. A similar procedure was performed on $P_{ET}O_2$ and S_pO_2 of period B. Furthermore, a two-way analysis of variance was performed on the difference of bispectral index, $\dot{V}_I$, tidal volume, respiratory rate, and $P_{ET}CO_2$ between periods B and A of the four studies. Differences among treatments were tested with the Student-Newman-Keuls test. The visual analog scales of the control-pain and sevoflurane-pain studies were compared using a paired Student's *t* test. A probability level of 0.05 was chosen for differences to be significant. All values are mean ± SE unless otherwise stated.

Results

All subjects finished the protocol without side effects. None of the individual studies had to be discarded.

The observers' assessment of alertness/sedation score averaged 2.4 ± 0.2 ($P < 0.05$ *vs.* all other treatments)

** Sevorane Compendium. Amstelveen, Abbott, 1995.

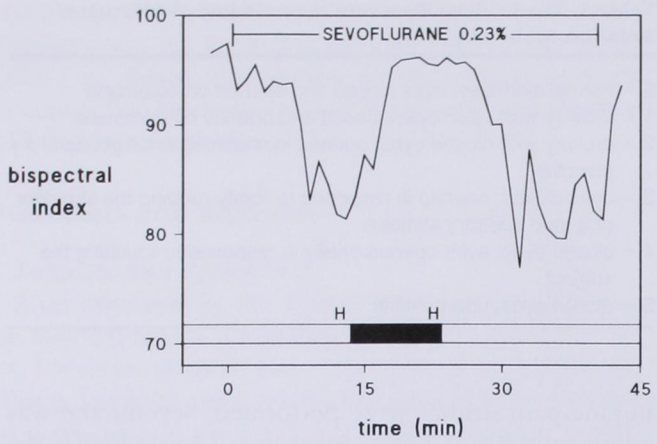

Fig. 1. The bispectral index during the inhalation of 0.23% end-tidal sevoflurane in one subject. Sevoflurane inhalation was started at time t = 0. The closed bar denotes the period during which noxious stimuli were administered (electrical current on the skin over the tibial bone); the open bar the pain-free periods. H denotes the 3-min exposure to isocapnic hypoxia.

15 min after the inhalation of sevoflurane was initiated. Noxious stimulation diminished the level of sedation in all subjects: observers' assessment of alertness/sedation score = 1.3 ± 0.1 ($P < 0.05$ *vs.* all other treatments). The bispectral index was 96.2 ± 0.7 and 97.1 ± 0.4 in the control and control-pain studies, respectively. In figure 1, the influence of 0.1 MAC sevoflurane on the bispectral index is shown for one subject. The index decreased slowly over 10 min; the lowest value measured was 82 after 13 min of sevoflurane inhalation. Noxious stimulation (black bar) increased the bispectral index within 3 min to a value of 95. Similar patterns in time were observed in all other subjects. The averaged bispectral index was 86.3 ± 1.3 in the sevoflurane studies ($P < 0.05$ *vs.* all other treatments). The bispectral index in the sevoflurane-pain studies did not differ from either of the awake states (95.0 ± 1.0; $P < 0.05$ *vs.* sevoflurane; fig. 2).

The VAS scores were similar for the control-pain (5.0 ± 0.1 cm) and sevoflurane-pain studies (5.2 ± 0.2 cm). The current needed to obtain a VAS between 4.5 and 5.5 cm was approximately 10 mA greater in the sevoflurane-pain compared to the control-pain studies. The values of the sedation score, bispectral index and VAS were not different obtained during the period before induction of hypoxia and at the period immediately after the 3-min hypoxic episode. The heart rate before the reduction of the $P_{ET}O_2$ was 70 ± 3, 71 ± 3, 66 ± 3, and 69 ± 2 beats/min for the control, control-pain, sevoflurane, and sevoflurane-pain studies, respectively (fig. 2).

The values of the $P_{ET}CO_2$, $P_{ET}O_2$, and S_PO_2 of period A and $P_{ET}O_2$ and S_PO_2 of period B did not differ among the four treatments (table 2). The mean difference of $P_{ET}CO_2$ between periods B and A ranged from −0.1 to 0.5 mmHg among treatments. The respective end-tidal concentrations of sevoflurane in the sevoflurane and sevoflurane-pain studies were 1.72 ± 0.02 mmHg (0.23%) and 1.68 ± 0.04 mmHg (0.22%).

Ventilatory parameters are collected in table 2 and figure 3. Baseline ventilation ($\dot{V}_I$ in period A) was similar in the control and sevoflurane studies. The administration of painful stimuli caused a significant increase

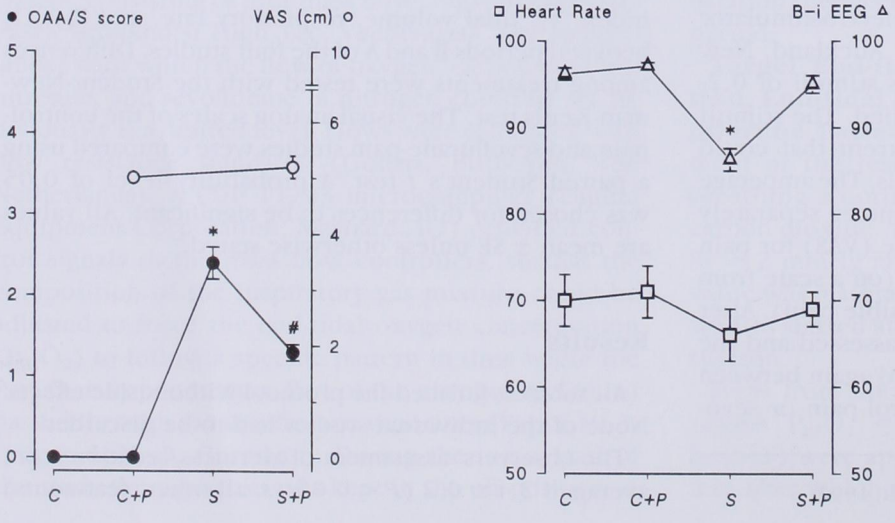

Fig. 2. Mean values of the observers' assessment of alertness/sedation score (left panel, ●), visual analog scale for pain scoring (*left*, ○), bispectral index of the electroencephalogram (B-i EEG) (*right*, △) and heart rate (*right*, □, units = beats/min) in the control (C), control-pain (C + P), sevoflurane (S), and sevoflurane-pain (S + P) studies. * and #$P < 0.05$ *versus* all other studies. The visual analog scale was assessed only during noxious stimulation.

Table 2. Influences of Acute Pain on the Ventilatory Response to Isocapnic Hypoxia in the Awake Subject and the Subject Sedated by 0.1 MAC Sevoflurane

		Control	Control Pain	Sevoflurane	Sevoflurone Pain
$\dot{V}_I$ (L/min)	A	13.7 ± 0.9	16.0 ± 1.0*	12.7 ± 1.2	15.9 ± 1.1*
	B	23.4 ± 3.4	25.1 ± 2.2	19.3 ± 2.8	22.3 ± 2.3
	Δ	9.6 ± 2.8	9.6 ± 1.9	6.7 ± 2.1†	6.5 ± 1.7†
V_T (ml)	A	930 ± 72	968 ± 95	850 ± 90	1,038 ± 105‡
	B	1,351 ± 153	1,414 ± 139	1,205 ± 174	1,318 ± 149
	Δ	421 ± 118	446 ± 98	345 ± 125†	281 ± 77†
RR (min^{-1})	A	15.2 ± 1.0	16.9 ± 1.1	15.2 ± 0.9	16.5 ± 1.4
	B	17.3 ± 1.0	18.7 ± 1.0	16.5 ± 0.6	17.6 ± 1.0
	Δ	2.0 ± 1.0	1.8 ± 1.0	1.3 ± 0.9	1.1 ± 0.7
PET_{CO_2} (mmHg)	A	44.6 ± 1.2	44.3 ± 1.3	44.4 ± 1.2	44.2 ± 1.4
	B	44.3 ± 1.2	44.0 ± 1.2	44.3 ± 1.2	44.2 ± 1.2
	Δ	0.5 ± 0.2	0.2 ± 0.2	0.1 ± 0.3	0.1 ± 0.3
PET_{O_2} (mmHg)	A	111.8 ± 0.4	111.0 ± 0.7	109.5 ± 0.4	111.7 ± 0.8
	B	49.5 ± 0.4	50.1 ± 0.5	49.7 ± 0.5	49.6 ± 0.4
Sp_{O_2} (%)	A	98 ± 0.2	98 ± 0.3	98 ± 0.3	98 ± 0.3
	B	84 ± 1.0	85 ± 0.2	84 ± 0.7	84 ± 0.5

Values are mean ± SE.

A = 1-min period before hypoxia; B = 3rd min of hypoxia; Δ = period B − period A.

* $P < 0.05$ *versus* Control and Sevoflurane.

† $P < 0.05$ *versus* Control and Control Pain.

‡ $P < 0.05$ *versus* Sevoflurane.

of baseline $\dot{V}_I$ of similar magnitude in the control-pain and sevoflurane-pain studies. In the control and sevoflurane studies pain had no effect on the increase in $\dot{V}_I$ due to hypoxia. The acute hypoxic ventilatory response averaged 0.69 ± 0.20 $l \cdot min^{-1} \cdot [\%$ change in $S_pO_2]-1$ (control) and 0.64 ± 0.13 $l \cdot min^{-1} \cdot \%S_pO_2^{-1}$ (control-pain). While sevoflurane *per se* had no effect on baseline $\dot{V}_I$ it significantly decreased the ventilatory response to acute hypoxia by 30% and 32% in the sevoflurane (0.48 ± 0.15 $l \cdot min^{-1} \cdot \%S_pO_2^{-1}$; $P < 0.05$ *vs.* control and control-pain) and sevoflurane-pain (0.46 ± 0.12 $l \cdot min^{-1} \cdot \%S_pO_2^{-1}$; $P < 0.05$ *vs.* control and control-pain) studies, respectively.

Discussion

Central Nervous System Arousal State

In the current study we employed two separate methods to obtain information on the CNS arousal states of the subjects. First, as in previous studies, we used a subjective six-point observers' assessment of alertness/sedation scale. All subjects in the sevoflurane study were sedated with a score of either 2 (eyes closed, opened by softly calling their name; $n = 7$) or 3 (a loud auditory stimulus necessary for eye opening; $n = 4$). We obtained similar scorings with 0.1 MAC halothane, isoflurane, and desflurane.[8–11] Pain caused an immediate arousal in all subjects (8 subjects had a score of 1 [eyes open, closed on command], 3 had a score of 2).

Second, we determined the bispectral index, a parameter derived from the bispectral analysis of the EEG, to objectify the level of sedation in the control and sevoflurane studies.[12–14] Bispectral analysis is a signal processing technique that quantifies the second-order interaction between components (*i.e.*, interfrequency phase coupling) that make up the signal generated from a nonlinear source (such as the CNS).[12] Studies have shown that the bispectral index is a more accurate predictor of patient movement during anesthesia compared to standard power spectrum parameters (95% spectral edge, median frequency, relative δ power) and the hemodynamic status.[13,14] Liu *et al.*[15] and Bloom *et al.*[16] used the bispectral index to assess the depth of sedation induced by midazolam and isoflurane, respectively. Both studies observed a progressive decrease of the bispectral index with increasing depth of sedation as determined by a subjective sedation scale similar to ours. Their data are in agreement with our findings of a bi-

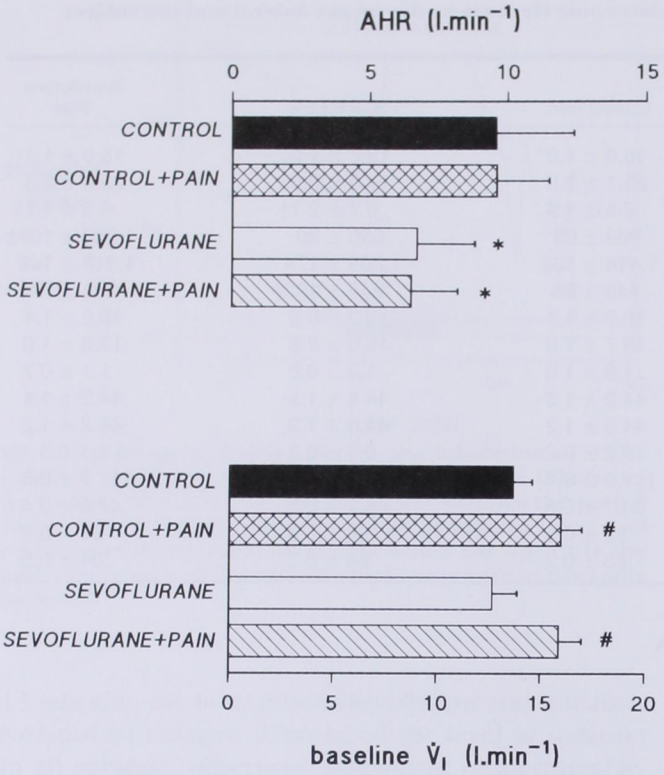

Fig. 3. Influences of pain and 0.1 minimum alveolar concentration sevoflurane on baseline ventilation and the ventilatory response to acute isocapnic hypoxia. *$P < 0.05$ *versus* control and control-pain; #$P < 0.05$ *versus* control and sevoflurane.

spectral index of 86 coupled to a sedation score of 2.4. We observed no effect of hypoxia on the bispectral index. Similar observations have been made at mild (S_pO_2 87%) and moderate (S_pO_2 77%) hypoxia.[17]

During sevoflurane inhalation the subjective sedation score and bispectral index indicated a significant decrease of the depth of sedation during the application of noxious stimuli (figs. 1 and 2). The increase in bispectral index is equivalent to the change seen after surgical incision during general anesthesia.[12] The values of the bispectral index indicate that the CNS arousal state during the sevoflurane-pain episodes was not significantly different from those during wakefulness (control and control-pain). On this basis as well as the subsequent analysis of the raw EEG data, we designate the CNS arousal state in the control, control-pain, and sevoflurane-pain studies as awake. In the sevoflurane studies, it did not differ from light nonrapid-eye-movement sleep. Similar observations have been made by Foo *et al.*[18] They defined the CNS arousal state during the inhalation of 0.1 MAC isoflurane as natural sleep stages 1 or 2 (*i.e.* light nonrapid-eye-movement sleep).

Acute Pain and Ventilatory Control

During wakefulness we observed that acute pain in the form of an electrical current applied to the skin augmented resting ventilation with no effect on the magnitude of the ventilatory response to mild isocapnic hypoxia (fig. 3). Furthermore, the depression of the hypoxic ventilatory response by a subanesthetic concentration of sevoflurane was not modified or restored by acute pain.

To the best of our knowledge, the only earlier study that investigated the effects of acute pain on ventilatory control in awake humans is that of Bourke.[5] He showed in four patients that the relief of acute pain from injuries to the upper extremities by an axillary brachial plexus block caused the reduction of the hyperoxic (inspired oxygen concentration = 40%) ventilatory carbon dioxide sensitivity by more than 20%. He did not determine the apneic threshold (extrapolated $P_{ET}CO_2$ at zero $\dot{V}_I$) but from his data a value of 36 mmHg and 35 mmHg can be calculated for the $\dot{V}_I$-CO_2 response curve before and after the axillary block. The VAS scores he measured were 7.1 before and 0.7 after the axillary block.

Lam *et al.*[3] and Rosenberg *et al.*[4] reported on the influences of surgical stimulation on the ventilatory chemoreflexes in patients during enflurane in oxygen anesthesia and enflurane in nitrous oxide/oxygen (50%/50%) anesthesia. The essential results of the two studies were the same: surgical stimulation caused a leftward shift of the hyperoxic $\dot{V}_I$-$P_{ET}CO_2$ response curve obtained during anesthesia alone with no change in slope. In addition, Lam *et al.* investigated the effects of stimulation on the ventilatory response to hypoxia during inhalation of 1.1 MAC enflurane. The response was absent during anesthesia; surgery did increase baseline $\dot{V}_I$ but did not restore the hypoxic response.[3]

The lack of effect of acute pain on the hypoxic ventilatory response in our study is consistent with the findings of Bourke,[5] Lam *et al.*[3] and Rosenberg *et al.*[4] Their observation that the hyperoxic $\dot{V}_I$-$P_{ET}CO_2$ response is shifted to the left or its slope steeper during acute pain or surgical stimulation suggests an effect on the central chemoreflex loop, because the contribution of the peripheral chemoreceptors to total ventilation is abolished or greatly reduced by hyperoxia.[6] Our results that baseline $\dot{V}_I$ at a slightly elevated $P_{ET}CO_2$ (44 mmHg, 2 mmHg above resting) is higher during acute pain, regardless of the CNS arousal state, also may be

explained by an effect of pain on the central chemoreflex loop. However, we are unable to exclude an effect on the chemoreflex-independent tonic ventilatory drive.

Central nociceptive mechanisms are poorly understood and the mechanisms by which acute pain modulates ventilatory control are unknown. With respect to an anatomic substrate in the CNS for an interaction between processing of pain stimuli and ventilatory control, data in cats and rats indicate the possibility of the nucleus paragigantocellularis lateralis (implicated in respiratory functions, pain regulation, analgesia, and cardiovascular control), raphe nuclei (implicated in ventilatory control and pain regulation), and locus coeruleus (implicated in the control of general alertness, receives input from the nucleus paragigantocellularis lateralis).[19–24,††]

Our subjects did not show an increase in heart rate during noxious stimulation. This may indicate the absence of sympathoexcitation. At higher intensities acute pain may cause activation of the sympathetic system. The circulating catecholamines may then influence ventilatory control in a different fashion compared to the neuronal pathways mentioned earlier.

What is the clinical importance of our findings? Our study indicates that acute pain, induced by electrical stimulation of the skin over the tibial bone, did not restore the blunted hypoxic ventilatory response during 0.1 MAC sevoflurane. However, the increase in baseline $\dot{V}_I$ by acute pain during sevoflurane inhalation caused the absolute value of hypoxic $\dot{V}_I$ to be similar to awake hypoxic $\dot{V}_I$ without pain (table 2). Because, from a clinical point of view, if all that matters is whether a patient maintains an adequate minute ventilation, the increase in baseline ventilation may be an important safety factor. With respect to this last remark two restrictions have to be made. First, at deeper levels of sedation, the noxious stimulation that we used may not at all be sufficient to increase baseline $\dot{V}_I$ such that hypoxic $\dot{V}_I$ equals awake hypoxic levels. Second, because we successfully opened the feedback loop with the dynamic end-tidal forcing technique the ventilatory response to acute pain may have been accentuated compared to a situation in which acute pain causes hypocapnia (*i.e.*, with an intact feedback loop).

Hypoxic Ventilatory Response and Central Nervous System Arousal State

Similar to that of most volatile anesthetics (halothane, isoflurane, and enflurane), a subanesthetic concentration of sevoflurane caused the impairment of the ventilatory response to a rapid decrease of $P_{ET}O_2$.[8–10,25] Quantitatively, the depression was less: the sevoflurane hypoxic response was 70% of the control response; the halothane, isoflurane, and enflurane hypoxic responses ranged between 30% and 50% of control (fig. 4). The impact of the CNS arousal state on the outcome of studies on the influence of inhalational anesthetics on ventilatory control is still the subject of controversy.[8–10,18,26–34] An interesting observation from our current study in this respect is that the arousal of the subjects to the level of wakefulness by noxious stimulation had no influence on the magnitude of the depressed hypoxic ventilatory response by sevoflurane. This indicates that the mechanism of the reduction of the hypoxic ventilatory response by low-dose inhalational anesthetic agents is not likely related to the CNS arousal state. Previously we showed that isoflurane at 0.1 MAC selectively affects the peripheral chemoreflex loop at the site of the carotid bodies.[10] Knill and Clement demonstrated a similar site of action for halothane at sedative concentrations.[35,36] For now, there is no reason to doubt that low-dose sevoflurane behaves any differently.

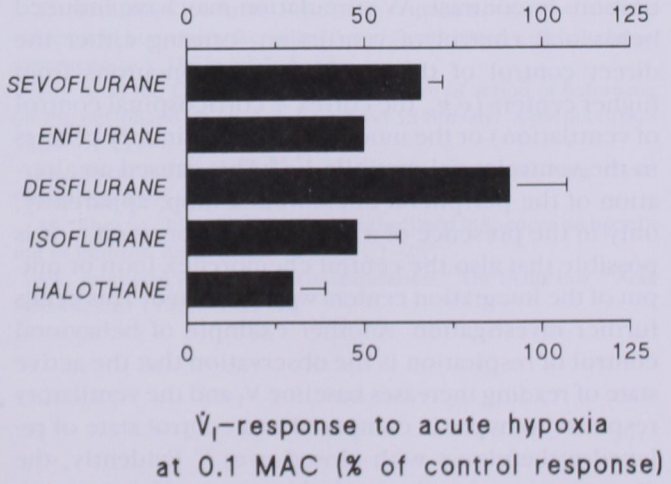

Fig. 4. Influence of 0.1 minimum alveolar concentration sevoflurane, enflurane, desflurane, isoflurane, and halothane on the ventilatory response to a step decrease in end-tidal oxygen concentration. Values are mean ± SD. Enflurane data are from Nagyova *et al.*[25] (obtained by interpolation), desflurane data from Dahan *et al.*,[11] isoflurane data from van den Elsen *et al.*,[10] and halothane data from two studies by Dahan *et al.*[8,9]

†† Connely CA, Bolser DC, Remmers JE: Respiratory modulation of sympathetic-related raphe neurons. Soc Neurosci Abstr 1987; 13: 280.

Our findings that the depression of the acute hypoxic response by sevoflurane at 0.1 MAC is independent of the CNS arousal state seems at variance with the results of two studies of Temp *et al.* on the effects of isoflurane at 0.1 MAC on the ventilatory response to isocapnic hypoxia.[28,29] To "minimize differences in level of consciousness between control and isoflurane experiments" they actively stimulated their subjects by touch, visual, and auditory input (AV-stimulation). Their results indicated no detectable depressant effect of 0.1 MAC isoflurane on the hypoxic ventilatory response. We confirmed their results and also observed an increase in baseline $\dot{V}_I$ by AV-stimulation during 0.1 MAC isoflurane inhalation.[27]

We attribute the contrast in studies to distinct modulatory effects that different methods of subject stimulation can have on ventilatory control. This modulation appears separate from the "nonspecific" CNS arousal that these different stimuli elicit.

In the current study, the painful stimulation may have activated specific neuronal structures to interact with ventilatory control (*e.g., via* the nucleus paragigantocellularis lateralis, see earlier). Whereas the central chemoreflex loop or the chemoreflex-independent ventilatory drive may have been modulated by acute pain, the peripheral chemoreflex remained unaffected (in the absence and presence of a respiratory depressant). We designate the system by which acute pain modulated ventilation as pain-related control of ventilation. In contrast, AV-stimulation may have induced behavioral control of ventilation, causing either the direct control of the respiratory motoneurons from higher centers (*e.g.*, the cortex = corticospinal control of ventilation) or the modulation of respiratory centers in the ventrolateral medulla.[37,38] This caused an alteration of the peripheral chemoreflex loop, apparently, only in the presence of a respiratory depressant.[27] It is possible that also the central chemoreflex loop or output of the integration centers were modified. This needs further investigation. Another example of behavioral control of respiration is the observation that the active state of reading increases baseline $\dot{V}_I$ and the ventilatory response to hypoxia compared to a control state of relaxed wakefulness with closed eyes.[39] Evidently, the aforementioned pathways linking a specific nonventilatory stimulus with ventilatory control are just some of many—most still unidentified—possible pathways.

Taken together, there is now ample evidence that the influences of low-dose halothane, isoflurane, enflurane, and sevoflurane on *metabolic* ventilatory control are (*i*) impairment of the peripheral chemoreflex loop, and (*ii*) no effect on baseline ventilation, despite a decrease in the level of CNS arousal state.[8–10,25,35,36] Whereas recent studies have shown that halothane and isoflurane at 0.1 MAC do not affect the central chemoreflex loop,[8,10] further studies are necessary to test the effects of low-dose sevoflurane on this pathway. An introduction of additional drives or modulatory inputs, respectively resulting from acute pain or AV-stimulation, precludes the assessment of pure metabolic or chemical control of breathing.

In conclusion, our data show that acute pain causes an increase in baseline ventilation with no effect on the isocapnic hypoxic ventilatory response in healthy volunteers. We contend that acute pain interacts with ventilatory control (the central chemoreflex loop or the chemoreflex-independent ventilatory drive) without modulating the peripheral chemoreflex loop. Second, we observed a depression of the hypoxic ventilatory response by subanesthetic sevoflurane, a property it shares with halothane, isoflurane, and enflurane. Third, we demonstrated that arousal by acute pain did not restore the hypoxic ventilatory response impaired by sevoflurane. This indicates that the CNS arousal state *per se* does not contribute to the depression of the hypoxic response by sevoflurane.

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