Anesthesiology
1997; 87:289–96

Influence of Acute Pain Induced by Activation of Cutaneous Nociceptors on Ventilatory Control

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

Background: **Although many studies show that pain increases breathing, they give little information on the mechanism by which pain interacts with ventilatory control. The authors quantified the effect of experimentally induced acute pain from activation of cutaneous nociceptors on the ventilatory control system.**

Methods: **In eight volunteers, the influence of pain on various stimuli was assessed: room air breathing, normoxia (end-tidal pressure of carbon dioxide ($P_{ET_{CO_2}}$) clamped, normoxic and hyperoxic hypercapnia, acute hypoxia, and sustained hypoxia (duration, 15–18 min; end-tidal pressure of oxygen, approximately 53 mmHg). Noxious stimulation was administered in the form of a 1-Hz electric current applied to the skin over the tibial bone.**

Results: **While volunteers breathed room air, pain increased ventilation ($\dot{V}_I$) from 10.9 ± 1.7 to 12.9 ± 2.5 l/min^{-1} ($P < 0.05$) and reduced $P_{ET_{CO_2}}$ from 38.3 ± 2.3 to 36.0 ± 2.3 mmHg ($P < 0.05$). The increase in $\dot{V}_I$ due to pain did not differ among the different stimuli. This resulted in a parallel leftward-shift of the $\dot{V}_I$–carbon dioxide response curve in normoxia and hyperoxia, and in a parallel shift to higher $\dot{V}_I$ levels in acute and sustained hypoxia.**

Conclusions: **These data indicate that acute cutaneous pain of moderate intensity interacted with the ventilatory control system without modifying the central and peripheral chemoreflex loop and the central modulation of the hypoxia-related output of the peripheral chemoreflex loop. Pain causes a chemoreflex-independent tonic ventilatory drive. (Key words: Measurement techniques: dynamic end-tidal forcing; isocapnia. Pain, acute: transcutaneous electric stimulation. Respiration: hypercapnic response; hyperoxia; hypoxic response; short-term potentiation of breathing.)**

ALTHOUGH several human and animal studies have shown that pain and surgical stimulation act as respiratory stimulants in the awake, sedated, and anesthetized states,[1–11] these studies give little information on the mechanism by which pain modulates ventilatory control. Observations that noxious stimulation reverses the respiratory depression of anesthetics and opioids should not be attributed automatically to an antagonistic effect of pain on the sites or mechanisms by which these agents cause respiratory depression (*e.g.*, sedation, depression of the bulbar respiratory centers, reduction of the ventilatory oxygen and carbon dioxide sensitivities of the peripheral and central chemoreceptors, upper airway obstruction, impairment of respiratory muscles, and so on). For example, the studies of Lam *et al.*[3] and Sarton *et al.*[10] in humans indicate that although pain increases breathing, depression of the hypoxic ventilatory response by the anesthetic was not restored by surgical stimulation and experimentally induced pain, respectively. This suggests that pain interacts with the ventilatory control system without modulating the peripheral chemoreflex loop. Data from Bourke[12] suggest that pain interacts with ventilatory control *via* the central chemoreflex loop. He observed a decrease of the hyperoxic ventilatory carbon dioxide sensitivity when pain was removed in four patients with injuries to the upper extremities.

To explore the possible sites of action of pain on ventilatory control, we quantified the effect of experimentally induced acute pain at various chemical stimuli (room air, normoxia with clamped end-tidal pressure of carbon dioxide [$P_{ET_{CO_2}}$], hyperoxia, hypercapnia, and acute and sustained hypoxia). In this study, acute pain was induced by activating cutaneous nociceptors using an electric current applied to the skin over the tibia (transcutaneous electric stimulation [TES]).[7,10]

* Resident, Department of Anesthesiology, Leiden University Hospital.

† Associate Professor of Anesthesiology, Department of Anesthesiology, Leiden University Hospital.

‡ Associate Professor of Physiology Department of Physiology, Leiden University.

§ Staff Anesthesiologist, Department of Anesthesiology, Leiden University Hospital.

‖ Professor of Anesthesiology and Chairman, Department of Anesthesiology, Leiden University Hospital.

Received from Leiden University Medical Center, Leiden, The Netherlands. Submitted for publication January 2, 1997. Accepted for publication March 24, 1997.

Address reprint requests to Dr. Dahan: Department of Anesthesiology, Leiden University Hospital (AZL P5), P.O. Box 9600, 2300 RC Leiden, The Netherlands. Address electronic mail to: dahan@rullf2.leidenuniv.nl

Materials and Methods

Participants and Apparatus

Eight healthy, nonsmoking volunteers (four women and four men, aged 24–34 yr) were recruited for in this study after approval by the Leiden University Committee on Medical Ethics. All had participated in previous studies on respiratory control and were familiar with the experimental procedures and apparatus. Five of these persons participated in an earlier study on acute pain and respiration. All gave informed consent. The volunteers were advised not to eat or drink for at least 6 h before the study.

After arriving in the laboratory (8:30 AM) all participants rested for 30 min before the experiments started. During the study, the volunteers were in a semirecumbent position (135° between the lower extremities and thorax) and had a view of a park. They were instructed to keep their eyes open throughout the session. An oronasal mask (Vital Signs, Totawa, NJ) 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, Andovar, MA) and electronically integrated to yield a volume signal. This signal was calibrated with a motor-driven piston pump. The pneumotachograph was connected to a T piece. One arm of the T piece received a gas mixture with a flow of 45 l/min from a gas-mixing system, consisting of four mass flow controllers (F201-F203; Bronkhorst High Tec, Veenendaal, The Netherlands) with which the flow of oxygen, carbon dioxide, and nitrogen could be set individually at a desired level. Flows were calibrated with flow-resistance standards (Godart, Bilthoven, The Netherlands). When desired, a PDP 11/23 microcomputer (Digital Equipment Corp., Maynard, MA) provided control signals to the mass flow controllers, so that the composition of the inspired gas mixture could be adjusted to force the end-tidal oxygen concentration ($P_{ET_{CO_2}}$) to follow a specific pattern in time while maintaining a constant $P_{ET_{CO_2}}$ and *vice versa*.[13]

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. A pulse oximeter (Datex Satellite Plus, Helsinki, Finland) continuously measured the arterial hemoglobin-oxygen saturation *via* a finger probe (S_pO_2). The hand from which the S_pO_2 was measured was warmed with a sheepskin glove. Throughout the study, the ECG of the heart was monitored. Inspiratory minute ventilation ($\dot{V}_I$), tidal volume, respiratory rate, inspiratory time, expiratory time, mean inspiratory flow, S_pO_2, $P_{ET_{CO_2}}$, and $P_{ET_{O_2}}$ were calculated and stored on a breath-to-breath basis on computer disk for further analysis. The experimental dead space was 250 ml.

Induction of Acute Pain

Experimental acute pain was induced by an electric current through two electrodes (Red Dot; 3M, London, Ontario, Canada) placed on the skin directly overlying the tibial bone of the right leg (TES). This location on the body was selected to minimize muscle stimulation. The electrodes were attached to an electrostimulator (Innervator NS 242; Fisher & Paykel, Auckland, New Zealand). When appropriate, noxious stimuli lasting 0.2 ms at 1 Hz for a fixed duration (3 min or 5 min) were applied. The intensity or amperage of the current was set for each volunteer separately such that his or her numeric rating (NR) of the painful sensation was between 4.5 and 5.5 (on a scale of 0 = no pain to 10 = very intense pain). This procedure generates a "pricking pain" sensation without causing restlessness of the leg.[10] To exclude habituation to the noxious stimulus in time, the NR was reassessed after each study and the current set appropriately.

Study Design

Room Air Breathing. Participants were breathing room air with no inspired carbon dioxide. After $\dot{V}_I$ had reached a steady state for 10 to 15 min, acute pain was induced for 3 min. Thereafter the respiratory pattern was followed for another 2 or 3 min.

Carbon Dioxide Studies. The steady-state ventilatory response to imposed hypercapnic levels was assessed at four to six different target $P_{ET_{CO_2}}$ levels (ranging from approximately[4] to 18 mmHg above resting values; minimal duration of hypercapnic stimulus, 8 min) without and with noxious stimulation (duration, 3 min). When respiratory responses were brisk, stimulation at $P_{ET_{CO_2}}$ levels greater than 50 mmHg was avoided. Hypercapnic responses were obtained at a background of normoxia ($P_{ET_{O_2}}$ = 110 mmHg) and hyperoxia ($P_{ET_{O_2}}$ = approximately 300 mmHg).

Hypoxic Studies. Two isocapnic hypoxic responses were obtained. Hypoxic study 1 was a response to a step from normoxia ($P_{ET_{O_2}}$ = 110 mmHg) into hypoxia (target end-tidal oxygen fraction [$F_{ET_{O_2}}$] = 0.07, $P_{ET_{O_2}}$ = approximately 53 mmHg). This low end-tidal level

was reached within four to six breaths and maintained for 18 min. Noxious stimulation was applied during the last 3 min of hypoxia. Hypoxic study 2 was a step from normoxia into hypoxia (target $F_{ET_{O_2}}$ = 0.07). Duration of hypoxia was 3 min. Noxious stimulation started 2 min before the hypoxic exposure (total duration of acute pain = 5 min). In both studies the $P_{ET_{CO_2}}$ was clamped at 2 to 3 mmHg above resting level. Both hypoxic studies were followed by 7 min of breathing a hyperoxic gas mixture ($F_{ET_{O_2}}$ was approximately 0.7) to avoid possible "on-going" influences of hypoxia on a next trial.

The five studies (room air, normoxic carbon dioxide, hyperoxic carbon dioxide, 18-min hypoxic and 3-min hypoxic studies) were performed in random order.

Data Analysis

Room Air Breathing. Mean values of the breath-to-breath data were obtained from the last ten breaths before noxious stimulation and from the last 10 breaths of the 3-min period of noxious stimulation.

Carbon Dioxide Studies. The steady-state breath-to-breath data were averaged over 10 breaths. Data points were collected just before the induction of acute pain and in the last minute of acute pain. Through this procedure we obtained four to six $\dot{V}_I$-$P_{ET_{CO_2}}$ data points in each of the four different treatments: normoxia-control *vs.* normoxia-pain and hyperoxia-control *vs.* hyperoxia-pain. We expressed $\dot{V}_I$ as a linear function of $P_{ET_{CO_2}}$

$$\dot{V}_I = S\,[P_{ET_{CO_2}} - B] \quad (1)$$

where S is the ventilatory carbon dioxide sensitivity and B is the extrapolated $P_{ET_{CO_2}}$ at which $\dot{V}_I$ = 0 l/min or apneic threshold. The parameters were obtained by linear regression of $\dot{V}_I$ on $P_{ET}CO_2$.

Hypoxic Studies. In figure 1, the two hypoxic responses of a single volunteer are plotted in a diagram to exemplify the data analysis of the hypoxic studies. The open circles denote the $\dot{V}_I$ data during painful stimulation, and the closed circles are the $\dot{V}_I$ data without stimulation. The breath-to-breath data were averaged over identical segments: the last ten breaths of normoxia ($\dot{V}_0$ in the control study and $\dot{V}_0^*$ in the acute pain study) (fig. 1), the last ten breaths of the third minute of hypoxia ($\dot{V}_1$ and $\dot{V}_1^*$), the last ten breaths of the 15th min of hypoxia ($\dot{V}_2$), and the last ten breaths of the 18th min of hypoxia ($\dot{V}_2^*$). This allowed us to calculate the acute hypoxic response ($\dot{V}_1 - \dot{V}_0$ *vs.* $\dot{V}_1^* - \dot{V}_0^*$) and the subsequent slow ventilatory decrease or hypoxic ventilatory decline ($\dot{V}_1 - \dot{V}_2$ *vs.* $\dot{V}_1^* - \dot{V}_2^*$) for the control and pain experiments. The $\dot{V}_I$ response to noxious stimulation in acute hypoxia was calculated as $\dot{V}_1^* - \dot{V}_1$ and in sustained hypoxia as $\dot{V}_2^* - \dot{V}_2$. Hypoxic ventilatory decline during noxious stimulation is calculated from the two separate hypoxic studies.

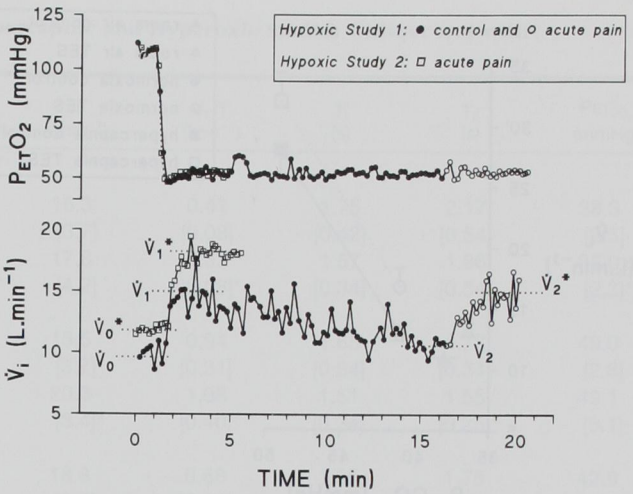

Fig. 1. The influence of nociceptive stimulation activated by transcutaneous electric stimulation (TES) on the ventilatory response to acute and sustained hypoxia of a single participant obtained from two separate studies. In study 1, the influence of pain on sustained hypoxia was tested (closed circles = control data, open circles = data obtained during nociceptive stimulation). In study 2, the influence of pain on acute hypoxia was studied (open squares = data obtained during nociceptive stimulation). (*Top*) The $P_{ET_{O_2}}$ waveform. (*Bottom*) Ventilatory responses. The following data points are defined: mean of ten breaths before the induction of hypoxia without ($\dot{V}_0$) and with nociceptive stimulation ($\dot{V}_0^*$); mean of the last ten breaths of the third min of hypoxia without ($\dot{V}_1$) and with noxious stimulation ($\dot{V}_1^*$); mean of the last ten breaths of the 15th min of hypoxia ($\dot{V}_2$) and the 18th min of hypoxia ($\dot{V}_2^*$). In this plot, each dot is the mean of three breaths. The acute hypoxic response (AHR) is defined as $\dot{V}_1 - \dot{V}_0$ for the control and as $\dot{V}_1^* - \dot{V}_0^*$ for the pain studies. The hypoxic ventilatory decline (HVD) is defined as $\dot{V}_1 - \dot{V}_2$ for the control and $\dot{V}_1^* - \dot{V}_2^*$ for the pain studies.

Statistical Analysis

A Student's paired *t* test was performed on the parameters of the hypercapnic and hypoxic ventilatory responses, and the variables of room air breathing, normoxia, hyperoxia, hypercapnia, and acute and sustained hypoxia in the control and in the acute pain states.

A two-way analysis of variance was performed (1) to determine an effect of time on the respiratory responses to acute pain and on the NR scores, (2) to determine an effect of the six stimuli (room air, normoxia, hyperoxia,

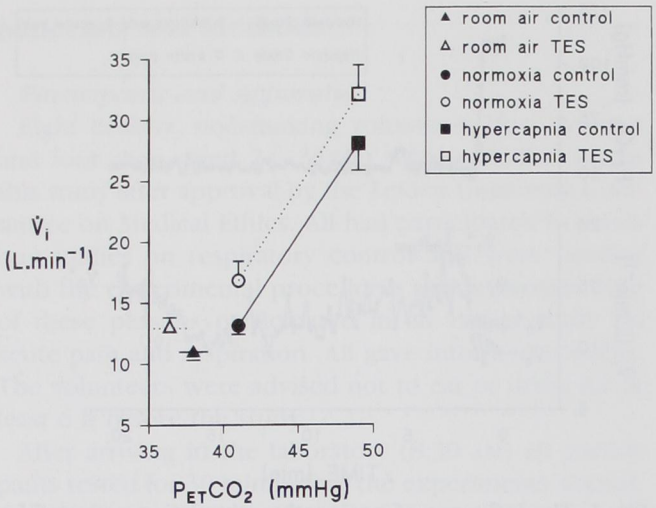

Fig. 2. The influence of transcutaneous electric stimulation (TES) on $\dot{V}_I$ at different $P_{ET}CO_2$ levels. The data points during air breathing were obtained without inspired carbon dioxide (*i.e.*, no $P_{ET}CO_2$ clamping). Despite a decrease of $P_{ET}CO_2$ by more than 2 mmHg, the increase in $\dot{V}_I$ during room air breathing is not different than that in normoxia ($P_{ET}CO_2$ = 41 mmHg) or hypercapnia ($P_{ET}CO_2$ = 49 mmHg). The two data points shown here at normoxia (low inspired carbon dioxide) and hypercapnia (high inspired carbon dioxide) were the only data points with identical absolute $P_{ET}CO_2$ levels among the eight participants. The ventilatory carbon dioxide sensitivities reported in the text were obtained from four or five data points in each person. Values are means ± SE.

hypercapnia, and acute and sustained hypoxia) on the magnitude of respiratory responses to acute pain, and (3) to compare the respiratory variables of the six data points of the hypoxic studies (data points are given in figure 1). When appropriate, differences between times, NR scores, stimuli, or hypoxic study data points were tested with the Student-Newman-Keuls test.

Probability values less than 0.05 were considered significant. All values are presented as means ± SD unless otherwise stated.

Results

All participants completed the studies without side effects. Most indicated an initial increase in the sensation of pain in the first 30–60 s of noxious stimulation. Thereafter the sensation remained constant. The participants typically described the sensation as a localized pricking or kicking. In three, the stimulus intensity had to be increased to obtain identical NR scores throughout the study. There was no significant difference in the NR scores over time. The mean NR scores for acute pain were 4.9 ± 0.8, and the mean current intensities were 43 ± 24 mA.

The effects of noxious stimulation on the respiratory variables with different chemoreflex stimuli are collected in tables 1 and 2. There was no significant difference among the increases in $\dot{V}_I$ by TES in any of the various chemoreflex stimuli ($P > 0.05$ by analysis of variance).

Room Air Breathing

The increase in ventilation was caused by an increase in mean inspiratory flow (V_T/T_I) without affecting any of the timing components or tidal volume (table 1). Transcutaneous electric stimulation caused a decrease of $P_{ET}CO_2$ from 38.3 ± 2.3 mmHg to 36.0 ± 2.3 mmHg ($P < 0.05$).

Carbon Dioxide Studies

Acute pain caused a leftward shift of the ventilatory carbon dioxide response curves (B normoxia: control = 31.5 ± 6.5 mmHg compared with B TES = 29.3 ± 4.2 mmHg, $P < 0.05$; B hyperoxia: control = 27.8 ± 4.2 mmHg compared with B TES = 22.5 ± 6.5 mmHg, $P < 0.05$) without affecting the magnitudes of the slopes (S normoxia: control = 1.60 ± 0.65 $l \cdot min^{-1} \cdot mmHg^{-1}$ compared with S TES = 1.62 ± 0.65 $l \cdot min^{-1} \cdot mmHg^{-1}$, NS; S hyperoxia: control = 1.32 ± 0.57 $l \cdot min^{-1} \cdot mmHg^{-1}$ compared with S TES = 1.29 ± 0.54 $l \cdot min^{-1} \cdot mmHg^{-1}$, NS) (fig. 2).

Hypoxic Studies

Table 2 summarizes the mean values of $P_{ET}CO_2$, $P_{ET}O_2$, and S_pO_2 of the different data points of the hypoxic studies. It shows the maintenance of isocapnia throughout the study despite sometimes brisk ventilatory changes. Figure 1 shows an example of the responses of one participant. The acute hypoxic response averaged 6.0 ± 2.5 l/min (0.60 ± 0.28 $l \cdot min^{-1} \cdot [\%\ desaturation]^{-1}$) and 6.6 ± 3.4 l/min (0.65 ± 0.31 $l \cdot min^{-1} \cdot [\%\ desaturation]^{-1}$) for the control and acute pain studies, respectively (NS). The hypoxic ventilatory decline was 3.7 ± 1.41 l/min in the control study and 4.5 ± 2.5 l/min in the pain study (NS). The hypoxic ventilatory sensitivities after 15–18 min of hypoxia averaged 0.20 ± 0.11 $l \cdot min \cdot^{-1} \cdot [\%\ desaturation]^{-1}$ for control and 0.20 ± 0.17 $l \cdot min \cdot^{-1} \cdot [\%\ desaturation]^{-1}$ for TES studies. The TES increased $\dot{V}_I$ by 3.6 ± 2.5 l/min in acute hypoxia compared with 4.5 ± 2.5 l.min in sustained hypoxia (NS).

Table 1. Respiratory Variables of the Room Air and Normoxic Hypercapnic and Hyperoxic Studies without and with Transcutaneous Electrical Stimulation (TES)

	$\dot{V}_I$ ($L \cdot min^{-1}$)	V_T (L)	f (min^{-1})	V_T/T_I ($L \cdot s^{-1}$)	T_I (s)	T_E (s)	$P_{ET_{CO_2}}$ (mmHg)
Room air breathing							
Control	10.9	0.72	16.3	0.41	1.75	2.17	38.3
	[1.7]	[0.2]	[3.7]	[0.08]	[0.42]	[0.54]	[2.5]
TES	12.9	0.81	17.8	0.52	1.57	1.96	36.0
	[2.5]*	[0.17]	[4.2]	[0.08]*	[0.34]	[0.54]	[2.3]*
Normoxic hypercapnia ($P_{ET_{CO_2}}$ clamped)							
Control	28.0	1.53	18.5	0.94	1.65	1.73	49.0
	[6.2]	[0.57]	[3.7]	[0.31]	[0.54]	[0.34]	[2.8]
TES	32.0	1.60	20.3	1.08	1.51	1.55	49.1
	[6.8]*	[0.56]	[3.4]*	[0.40]*	[0.34]	[0.25]*	[3.1]
Hyperoxia ($P_{ET_{CO_2}}$ clamped)							
Control	20.0	1.07	18.8	0.68	1.55	1.75	42.9
	[51]	[0.23]	[3.7]	[0.14]	[0.34]	[0.34]	[4.0]
TES	25.9	1.26	20.0	0.89	1.47	1.61	43.0
	[6.5]*	[0.42]*	[2.8]	[0.25]*	[0.25]	[0.25]	[4.2]

Values are mean [SD].

* $P < 0.05$ *versus* control (Student's paired *t* test).

Discussion

We observed that experimentally induced cutaneous pain of moderate intensity produces (1) an increase in ventilation in healthy volunteers of similar magnitude at different chemical stimuli, (2) a reduction of the apneic threshold, (3) no change in slopes of the $\dot{V}_I$-$P_{ET_{CO_2}}$ response curves in normoxia and hyperoxia, and (4) no influence on the development of hypoxic ventilatory decline.

The Pain Model

In this study, we investigated the influence of acute pain induced by activation of cutaneous nociceptors through TES. Transcutaneous electric stimulation provoked a pain sensation that was qualified by the participants as localized stinging or kicking. Comparable findings were made in previous studies using TES.[7,10] We assume that TES at the intensities we used activates Aδ-fibers, which results predominantly in a pricking or stinging sensation, whereas activation of C-fibers results in a predominantly burning sensation.[7,14]

Using electric stimulation of the vastus medial muscle in volunteers, Duranti *et al.*[15] studied the startle response to noxious stimulation. They determined the blink response by electromyograph (EMG) and observed at 1-Hz stimulation rapid habituation within the first 30 s of acute pain. Although we expected an overshoot in $\dot{V}_I$ due to the behaviorally related responses of pain or startle reaction, we observed in most instances an increase in $\dot{V}_I$ in the first 30–60 s of TES followed by steady-state $\dot{V}_I$. The participants reported the build up in pain sensation during the same time range. Taking into account our findings and those of Duranti *et al.*,[15] the data points we acquired were not influenced by the startle response to acute pain.

Hypercapnia elevates the pain threshold. In conscious rats, 5–10% inspired carbon dioxide depressed the withdrawal response to noxious stimuli by a mechanism involving the release of endogenous opioids.[16] This mechanism may also influence the ventilatory response to pain. In three participants, the current had to be increased by about 10 mA during the course of the study. Although this occurred in all three persons during hypercapnic testing, our design does not permit the discrimination between hypercapnia- and nonhypercapnia-related decreases in NR scores.

The experimental pain model that we used is unlike clinical pain, especially that of surgery. However, by controlling various factors (*e.g.*, anticipation of pain, anxiety, habituation, muscle movement, sympathetic activation, level of arousal, and activation of nociceptive afferents), we obtained a standard response to pain that enabled us to study the effects of acute pain on ventilatory control without problems in interpretation. Previous studies of noxious stimulation of respiration have

Table 2. Respiratory Variables, End-tidal Oxygen and Carbon Dioxide Concentrations, and Pulse Oximetry Values of the Hypoxic Studies without and with Transcutaneous Electrical Stimulation (TES)

	Control			TES		
	$\dot{V}_0$	$\dot{V}_1$	$\dot{V}_2$	$\dot{V}_0$*	$\dot{V}_1$*	$\dot{V}_2$*
$\dot{V}_I$ (L · min^{-1})	13.1	19.1	15.1	16.8	23.2	18.6
	[2.0]	[4.5]†	[3.4]	[4.5]†	[6.2]‡	[5.7]§
V_T (L)	0.81	1.11	0.95	0.93	1.27	1.00
	[0.25]	[0.37]†	[0.34]	[0.25]	[0.40]‡	[0.31]
f (min^{-1})	16.8	18.5	16.8	18.0	19.6	19.0
	[4.2]	[4.2]	[4.0]	[2.8]	[4.0]	[0.23]
$P_{ET_{CO_2}}$ (mmHg)	40.6	40.2	40.6	40.4	40.4	40.2
	[2.3]	[2.5]	[2.3]	[2.0]	[2.3]	[2.5]
$P_{ET_{O_2}}$ (mmHg)	109.0	52.6	52.6	112.5	53.0	52.6
	[2.3]	[0.8]‖	[0.8]‖	[5.7]	[1.1]‖	[0.8]‖
$S_{P_{O_2}}$ (%)	98	88	88	98	88	89
	[0.84]	[2.8]‖	[3.1]‖	[0.57]	[2.5]‖	[3.1]‖

$\dot{V}_0$ and $\dot{V}_0$* = normoxic data points without and with TES; $\dot{V}_1$ and $\dot{V}_1$* = acute hypoxic data points without and with TES; $\dot{V}_2$ and $\dot{V}_2$* = sustained hypoxic data points without and with TES.

Values are means [SD].

ANOVA: †$P < 0.05$ *versus* $\dot{V}_0$; ‡$P < 0.05$ *versus* all other data points; §$P < 0.05$ *versus* $\dot{V}_0$ and $\dot{V}_2$; ‖$P < 0.05$ *versus* $\dot{V}_0$ and $\dot{V}_0$*.

used the following stimuli: TES,[7,10] shining a bright light into the eyes,[6] electric stimulation of muscles,[7] limb ischemia,[7] pressure,[17] heating of the skin,[5] tail clamping,[8] and surgical stimulation.[1-4,9,11] Clinical studies using surgical stimulation as respiratory stimulus may be considered nonartificial and thus more useful. On the other hand, these studies may be hampered by the inability to control various factors (such as influence of anesthetics and opioids, $P_{ET_{CO_2}}$ level, site of surgery, degree of trauma, sympathetic stimulation, activation of inflammatory mediators, or stimulation by the endotracheal tube or laryngeal mask airway).

Acute Pain and Ventilatory Control

Duranti *et al.*[7] studied the influence of TES on respiration during air breathing. They used a more complex pattern of stimulation: 50-ms trains of 1-ms pulses at 200/s, repeated every 2 s, at an intensity of 4-6 mA. Similar to our findings, the predominant effect of pain was on mean inspiratory flow with no effect on V_T. We investigated the effects of TES on the peripheral chemoreflex loop, as reflected by the acute hypoxic response, and the central processing of the peripheral chemoreflex loop, during sustained hypoxia, into hypoxic ventilatory decline.[18] To obtain an estimate of the ventilatory carbon dioxide sensitivity of the central chemoreceptors, we determined the steady-state hyperoxic ventilatory response. We are aware of the inability of hyperoxia to completely silence the peripheral chemoreflex loop (approximately 10% of the total hyperoxic $\dot{V}_I$ response to carbon dioxide is still of peripheral origin).[13] We do not think that this small overestimation of the central carbon dioxide sensitivity will affect our conclusions. The finding of the reduced apneic threshold in hyperoxia corresponds with previous findings and indicates the stimulatory effect of hyperoxia at constant $P_{ET_{CO_2}}$ due to the reduced Haldane effect and the decrease of brain blood flow.[13,19-21]

We observed that TES had no effect on the normoxic and hyperoxic $\dot{V}_I$-carbon dioxide pressure sensitivities and the acute hypoxic response. Further, because the hypoxic ventilatory decline was similar in control and TES studies, the central processing of the hypoxia-related output of the peripheral chemoreflex loop into hypoxic ventilatory decline remained equally unaffected. This indicates that pain (TES at moderate intensities) did not modulate the normal translation of chemical stimuli into $\dot{V}_I$. We relate the increases in hypoxic $\dot{V}_I$ and the reduced apneic threshold during pain studies to a chemoreflex-independent tonic ventilatory drive (*i.e.*, the set point of the ventilatory controller was shifted).

The pathways by which acute pain increase ventilatory drive remain speculative. For reasons of simplicity, we restrict ourselves to the following three possibilities: spinal reflex pathways, activation of supra-pontine

structures provoking the modulation of respiratory centers in the central nervous system, and a direct effect of nociceptive afferents on the respiratory centers in the brain stem.

Waldrop *et al.*[5] showed that transection of the spinal cord in anesthetized cats (level C_7-T_1 or L_1-L_2) resulted in the absence of an increase in phrenic nerve activity with any intensity of thermal skin stimulation. This indicates the necessary involvement of central structures in the development of respiratory responses to acute pain.

In awake humans and animals, the perception of pain is accompanied by behavioral and emotional components. A recent study in mice showed the involvement of the enkephalin system in modulation of the behavioral responses to pain.[22] In humans, the anatomic substrates of pain perception were disclosed by Jones *et al.*[23] They showed the significant activation by painful thermal stimulation of the cingulate cortex, thalamus, and lentiform nucleus and a trend in the prefrontal cortex using positron emission tomography. The cingulate and prefrontal cortex are implicated in giving sensory stimuli their emotional significance. It is possible that acute pain triggered behavioral control of respiration *via* these cortical sites. When behavioral control is excited, breathing increases.[6,24,25] However, there is direct and indirect evidence that behavioral control of respiration is not the cause of the respiratory motor responses from pain. When behavioral control is actively suppressed by anesthesia, respiratory responses due to surgical stimulation are qualitatively identical to the responses observed in the awake state.[1-4,7,8,10,11] In cats, Waldrop *et al.*[5] showed that responses to thermal pain in decerebrate cats were similar to the responses in lightly anesthetized cerebrate animals. This suggests that afferent nociceptive inputs can relay directly to the bulbar respiratory centers without the need for higher hypothalamic/thalamic/cortical centers. Moreover, we showed previously that acute pain due to TES influences breathing in a manner that is functionally separate from the behavioral control system and designated the involved system as "pain-related control of breathing."[10,25]

A direct effect of nociceptive afferents on the respiratory centers in the central nervous system seems the most plausible mechanism of the increase in $\dot{V}_I$. The central neuronal network involved in the control of pain transmission is in close proximity to and overlaps neurons involved in respiratory control, especially in the rostral ventromedial and lateral medulla and pons.[26]

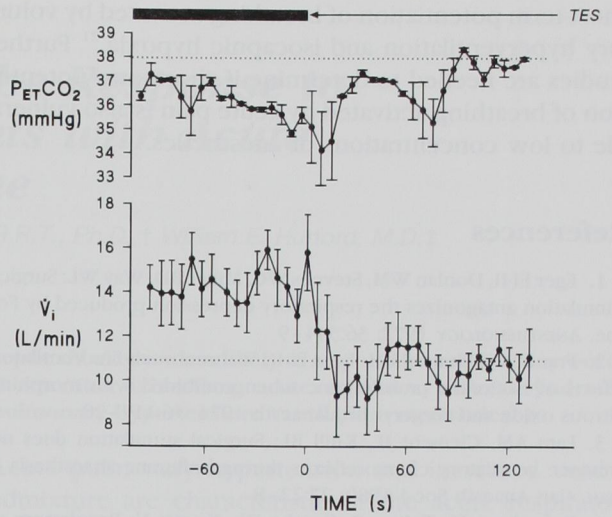

Fig. 3. Ensemble averages of $P_{ET_{CO_2}}$ (*top*) and $\dot{V}_I$ (*bottom*) of the last 90 s of transcutaneous electrical stimulation (TES) and the subsequent 2 min during air breathing of the eight participants. The averages were calculated with linear interpolation at 3-s time intervals between breaths of the individual responses. By indexing on the time of the last breath with TES (time $t = 0$), the first "nonpainful" breath was set at $t = 3$ s. We plotted the averages ± 2 SE, which constitutes an approximate 95% confidence interval. For presentation purposes, the averages are plotted at 6-s intervals. The dotted lines represent prestimulus baseline values.

Stimulation of neurons implicated in both respiratory functions and pain regulation or the spill-over of activity from neurons activated by nociceptive afferents to respiratory neurons may cause the increase in $\dot{V}_I$ by acute pain.

To obtain an impression of the dynamic ventilatory behavior at the termination of hyperventilation due to TES, we performed an ensemble average on the breath-to-breath $\dot{V}_I$ and $P_{ET_{CO_2}}$ data of air breathing of the eight participants (see the legend for figure 3 for the procedure). Despite the overt hypocapnia, $\dot{V}_I$ returned to baseline without undershooting below this level. This pattern (that is, sustained ventilatory activity despite a reduced chemical drive) is called short-term potentiation of breathing.[21,27-29] Short-term potentiation of breathing is activated by hyperventilation, either voluntary or in response to a respiratory stimulus (*e.g.*, hypoxia). It is thought that short-term potentiation of breathing exerts a stabilizing influence on $\dot{V}_I$.[30] Extrapolation of our data to the recovery period then suggests a stabilizing effect of pain-related hyperventilation. However, recent studies have shown that low concentrations of inhalational anesthetics in humans abolish

short-term potentiation of breathing activated by voluntary hyperventilation and isocapnic hypoxia.[21] Further studies are needed to determine if short-term potentiation of breathing activated by acute pain is also vulnerable to low concentrations of anesthetics.

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