

## Physiologic Responses to Mild Perianesthetic Hypothermia in Humans

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To evaluate physiologic responses to mild perianesthetic hypothermia, we measured tympanic membrane and skin-surface temperatures, peripheral vasoconstriction, thermal comfort, and muscular activity in nine healthy male volunteers. Each volunteer participated on three separate days: 1) normothermic isoflurane anesthesia; 2) hypothermic isoflurane anesthesia (1.5° C decrease in central temperature); and 3) hypothermia alone (1.5° C decrease in central temperature) induced by iced saline infusion. Involuntary postanesthetic muscular activity was considered thermoregulatory when preceded by central hypothermia and peripheral cutaneous vasoconstriction. Tremor was considered normal shivering when electromyographic patterns matched those produced by cold exposure in unanesthetized individuals. During postanesthetic recovery, central temperatures in hypothermic volunteers increased rapidly when residual end-tidal isoflurane concentrations were  $\leq 0.3\%$  but remained 0.5° C less than control values throughout 2 h of recovery. All volunteers were vasodilated during isoflurane administration. Peripheral vasoconstriction occurred only during recovery from hypothermic anesthesia, at end-tidal isoflurane concentrations of less than  $\approx 0.4\%$ . Spontaneous tremor was always preceded by central hypothermia and peripheral vasoconstriction, indicating that muscular activity was thermoregulatory. Maximum tremor intensity during recovery from hypothermic anesthesia occurred when residual end-tidal isoflurane concentrations were  $\leq 0.4\%$ . Three patterns of postanesthetic muscular activity were identified. The first was a tonic stiffening that occurred in some normothermic and hypothermic volunteers when end-tidal isoflurane concentrations were  $\approx 0.4$ – $0.2\%$ . This activity appeared to be largely a direct, non-temperature-dependent effect of isoflurane anesthesia. In conjunction with lower residual anesthetic concentrations, stiffening was followed by a synchronous, tonic waxing-and-waning pattern and spontaneous electromyographic clonus, both of which were thermoregulatory. Tonic waxing-and-waning was by far the most common pattern and resembled that produced by cold-induced shivering in unanesthetized volunteers; it appears to be thermoregulatory shivering triggered by hypothermia. Spontaneous clonus resembled flexion-induced clonus and pathologic clonus and did not occur during hypothermia alone; it may represent abnormal shivering or an anesthetic-induced modification of normal shivering. We conclude that among the three

patterns of muscular activity, only the synchronous, tonic waxing-and-waning pattern can be attributed to normal thermoregulatory shivering. (Key words: Anesthesia, volatile: isoflurane. Doppler. Hypothermia. Measurement techniques: electromyography; phlethysmography; laser. Reflexes, spinal, abnormal: clonus; spasticity; deep tendon. Temperature, measurement: skin; tympanic membrane. Thermoregulation: shivering; temperature; vasoconstriction.)

MILD HYPOTHERMIA is common during general and regional anesthesia and may be due to 1) exposure to a cold operating environment, 2) decreased metabolic heat production,<sup>1</sup> and 3) redistribution of heat within the body.<sup>2,3</sup> In addition, general anesthesia produces dose-dependent thermoregulatory inhibition that prevents peripheral vasoconstriction and shivering unless patients become sufficiently hypothermic (e.g., have central temperatures of  $\leq 35^\circ\text{C}$ ).<sup>4-7</sup> During recovery from general anesthesia, there is an initial period during which residual anesthesia suppresses thermoregulatory responses; this is followed by a period during which hypothermia triggers peripheral vasoconstriction and shivering. Between these two periods, partially suppressed thermoregulatory responses are likely.

Recovery from general anesthesia is frequently accompanied by involuntary muscular activity. Although much of this activity qualitatively resembles normal shivering, its etiology remains unclear: tremor has been reported in normothermic patients<sup>8</sup> but often is absent in those remaining distinctly hypothermic.<sup>9,10</sup> Consequently, postanesthetic tremor has been attributed to uninhibited spinal reflexes,<sup>11</sup> pain,<sup>12</sup> decreased sympathetic activity,<sup>13</sup> pyrogen release,<sup>14</sup> adrenal suppression,<sup>15</sup> respiratory alkalosis,<sup>§</sup> and most commonly, simple thermoregulatory shivering in response to intraoperative hypothermia.<sup>¶</sup>

Postanesthetic tremor (qualitatively resembling shivering) should not be automatically considered a thermoregulatory response; numerous tremors have been characterized, most of them not associated with thermal perturbations.<sup>16-20</sup> Consistent with multiple potential etiologies for postanesthetic muscular activity, we previously demonstrated two distinct electromyographic (EMG) patterns after isoflurane anesthesia.<sup>21</sup> The most frequent pattern was an irregular "tonic EMG activity" that some-

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times resembled normal shivering, but, on other occasions, lacked the typical synchronous "waxing-and-waning" pattern.<sup>22</sup> We speculated that some instances of tonic postanesthetic tremor were normal shivering, whereas others were not.

A second, much less common "spontaneous EMG clonus" pattern was observed after isoflurane anesthesia<sup>21</sup> and was characterized by a regular 5–7-Hz bursting pattern with signals virtually identical to those produced by flexion-induced clonus in postoperative patients<sup>23</sup> or by pathologic clonus in patients with spinal cord transections.<sup>20</sup> Based on the similarity among these three clonic signals and the additional observation that flexion-induced clonus was common at "intermediate" end-tidal isoflurane concentrations (*i.e.*, 0.2% isoflurane), we proposed that spontaneous EMG clonus was (in part) a spinal reflex facilitated by the presence of residual isoflurane. However, because all the patients in our previous study were hypothermic, it was impossible independently to evaluate thermoregulatory contributions to the observed tremor patterns.

In the present study, we evaluated postanesthetic recovery of thermoregulatory function by measuring central and mean skin temperatures, peripheral vasoconstriction, thermal comfort, and muscular activity in volunteers given isoflurane anesthesia. Specifically, we tested the hypothesis that postanesthetic tonic EMG activity is thermoregulatory but that spontaneous EMG clonus is not. Although any repetitive muscular contraction is *thermogenic*, involuntary postanesthetic muscular activity was considered *thermoregulatory* only when tremor was preceded by central hypothermia and peripheral cutaneous vasoconstriction.<sup>24,\*\*</sup> Thermoregulatory tremor was considered *normal shivering* when EMG patterns matched those produced by cold exposure in unanesthetized individuals.<sup>25–27</sup>

We used a triple-crossover design (normothermic isoflurane anesthesia, hypothermic anesthesia, and hypothermia alone) to permit independent evaluation of each variable. To eliminate the effects of surgery *per se* (*e.g.*, incisional pain, pharmacologic treatment of pain, large vascular volume shifts, and release of pyrogenic tissue factors), we studied volunteers who were not undergoing surgery.

### Materials and Methods

With approval from the University of California, San Francisco, Committee on Human Research and written informed consent from the volunteers, we evaluated thermoregulatory responses during and after isoflurane

anesthesia and cold-induced shivering in nine healthy young men. None was obese, was taking medication, or had a history of smoking, thyroid disease, dysautonomia, or Raynaud's syndrome.

Volunteers fasted during the 10 h preceding the study, which began at approximately 10:30 AM. All volunteers wore only short pants and lay on their backs on a standard operating room table, with the right arm exposed to room air.

### TREATMENT PROTOCOL

We evaluated thermoregulatory responses in each volunteer during hypothermia with and without isoflurane anesthesia and during normothermic isoflurane anesthesia. Studies were conducted on separate days and in random order. Each experiment was preceded by a 30-min control period; no preanesthetic medications were administered.

Hypothermia alone was studied by inserting a 16-G catheter into the superior vena cava *via* the internal jugular vein using a standard technique. After 30 min of control measurements, normal saline solution at  $\approx 3^\circ\text{C}$  was infused into the central catheter at  $1.8\text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  for 15 min and then at  $0.8\text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  for an additional 15 min. We have previously demonstrated that rapid intravenous infusion of iced fluid reduces central temperature by  $\approx 1.5^\circ\text{C}$  and provokes vigorous shivering.<sup>28</sup>

The effect of anesthesia with or without hypothermia was studied after inserting an 18-G catheter in a right antecubital vein and a 22-G arterial catheter in the left radial artery. Anesthesia was then induced by inhalation of 3–4% isoflurane and 70% nitrous oxide in oxygen, and tracheas were intubated without the use of a muscle relaxant. Thiopental, opioids, and other drugs were not administered. Anesthesia was maintained with isoflurane ( $\approx 1.1\%$  end-tidal concentration) in a mixture of 1 l/min oxygen and 4 l/min air, while the volunteers breathed spontaneously. Ventilation was assisted to maintain end-tidal carbon dioxide tension near 40 mmHg. At least 48 h elapsed after isoflurane administration before the next study began.

Respiratory gases were administered *via* a partially rebreathing circle system. Airway humidification was provided by placing a heat-and-moisture exchanger between the Y-piece of the circle system and the endotracheal tube. Approximately 1 l warmed lactated Ringer's solution was administered during each anesthetic study. Fluid administration was adjusted to maintain systolic blood pressure near 100 mmHg. Volunteers were lightly restrained during induction of general anesthesia and the initial portion of recovery so that they would not injure themselves during the "excitement phase."

\*\* Severe skin-surface cooling can provoke shivering despite normal or high central temperatures, but even many hours of exposure to a typical operating room environment rarely causes shivering.

During normothermic anesthesia, tympanic membrane temperatures were maintained near each volunteer's control temperature by adjusting the heater of a Bair Hugger<sup>®</sup> forced air warmer (Augustine Medical, Eden Prairie, MN).<sup>29</sup> The warming blanket was kept in place throughout the control, anesthetic, and recovery periods. During hypothermic anesthesia, central temperatures were allowed to decrease 1.5° C from control and then were maintained at that temperature by adjusting heat output from a Bair Hugger<sup>®</sup> warmer. The warmer was removed 30 min before the end of anesthesia, so nearly the entire skin surface was exposed to the ambient environment throughout the recovery phase.

After  $\approx 100$  min of anesthesia, the end-tidal isoflurane concentration was increased to  $\approx 2\%$  (to prevent bucking and laryngospasm) and the trachea extubated. The end-tidal concentration was then returned to  $\approx 1.1\%$ , at which it was maintained (*via* face mask) until total anesthetic administration time was 2 h. Isoflurane concentration in the fresh gas supply was then reduced to zero, and thermoregulatory responses evaluated for 2 h of recovery. Respiratory gases during recovery were administered and monitored using a clear plastic mask and fresh gas flows of 5 l/min.

Heart rate was continually monitored during each study using lead-two electrocardiography (ECG). During and after general anesthesia, blood pressure was continually monitored by a transducer attached to the radial arterial catheter. Blood pressure was evaluated oscillometrically (Dinamap<sup>®</sup> 1846 SX, Critikon, Tampa, FL) at 5-min intervals during intravenous infusion of iced saline.

#### TEMPERATURE AND RESPIRATORY GAS MEASUREMENTS

Measured thermoregulatory responses included tympanic membrane (central) and skin-surface temperature, peripheral vasoconstriction, and thermal comfort. Temperatures were monitored using Mon-a-Therm<sup>®</sup> (St. Louis, MO) thermocouple probes connected to Mallinckrodt Model 8700 (St. Louis, MO) two-channel electronic thermometers equipped with analog output.

Central temperatures were measured using a Mon-a-Therm<sup>®</sup> probe placed in contact with the tympanic membrane. Average skin-surface temperature was calculated by assigning the following regional percentages to ten thermocouple probes distributed on the left side of each volunteer: head 6%, upper arms 9%, forearms 6%, hands 4.5%, back 19%, chest 9.5%, abdomen 9.5%, thigh 19%, calves 11.5%, feet 6%.<sup>30</sup> Ambient temperatures were measured from a bare-wire probe placed near the volunteer and well away from any heat-generating electronic equipment. Temperature of infused fluids was evaluated using an 18-mm Mon-a-Therm<sup>®</sup> needle probe placed in

a "T extension" attached to the intravenous catheter. During general anesthesia, distal esophageal temperatures also were measured using a Mon-a-Therm<sup>®</sup> thermocouple incorporated into a stethoscope placed at the point of maximal breath sounds.

Respiratory gas concentrations were quantified using a Datex Capnomac<sup>®</sup> end-tidal gas analyzer (Datex Medical Instrumentation, Tewksbury, MA) equipped with analog output. The Capnomac<sup>®</sup> was calibrated using a known mixture of gases before each study. Arterial hemoglobin saturation was measured using a Nellcor (Hayward, CA) N200 pulse oximeter.

#### PERIPHERAL BLOOD FLOW DETERMINATIONS

Our primary measure of peripheral vasoconstriction was the skin-surface temperature gradient (forearm – fingertip) obtained from the exposed right arm.<sup>4</sup> We have previously demonstrated that the skin-temperature gradient correlates well with laser Doppler flowmetry<sup>5,7</sup> and volume plethysmography.<sup>31</sup> As in our previous studies, significant thermoregulatory vasoconstriction was prospectively defined as a skin-temperature gradient of  $\geq 4^{\circ}$  C. Additionally, the onset of vasoconstriction was indicated by a significant difference in the gradients for the normothermic and hypothermic anesthesia study conditions.

For comparison, absolute total fingertip blood flow (resulting primarily from arteriovenous shunt flow<sup>32,33</sup>) was quantified using venous-occlusion volume plethysmography at 5-min intervals. Volume plethysmography probably is the most reliable technique for evaluating peripheral blood flow,<sup>34</sup> and we have previously described the technique.<sup>31</sup> Fingertip vasoconstriction was further quantified using two types of laser Doppler flowmeter (Periflux<sup>®</sup> 3, Perimed, Piscataway, NJ, and BPM<sup>®</sup> 403, TSI, St. Paul, MN); in each case, the fiberoptic probe was positioned in the middle of one fingertip, opposite the nailbed. Laser Doppler flow indexes correlate well with other measures of cutaneous blood flow.<sup>5,35,36</sup> Finally, capillary flow was evaluated using reflectance photoelectric plethysmography (Textronix, Beaverton, OR).<sup>37</sup>

#### EMG ANALYSIS

After mild skin abrasion and degreasing, Red Dot<sup>®</sup> silver–silver chloride monitoring electrodes (3M, St. Paul, MN) were positioned to record the electrical activity of the pectoralis, trapezius, quadriceps, and anterior tibialis muscles on the right side of each volunteer. The electrodes were placed 4 cm apart and oriented in the direction of the muscle fibers. Signal acquisition epochs lasted 48 s. We have previously described our EMG acquisition and analysis system.<sup>3</sup>

Briefly, we used a modification of the EMG analysis technique developed by Stiles.<sup>19</sup> Fourier analysis of the EMG signals was preceded by amplitude demodulation<sup>17,19</sup> consisting of four steps: 1) digital full-wave rectification; 2) multiplication of the signal array by a Hanning window; 3) low-pass filtration to 20 Hz; and 4) decimation in time. Amplitude demodulation produces patterns well correlated with limb acceleration.<sup>17</sup>

To determine the intensity of each frequency in the 2–20-Hz “fast” band, we computed the power spectrum. This fast band includes broad-spectrum shivering (tonic) activity, usually peaking between 8–12 Hz,<sup>19</sup> and the regular 5–7-Hz bursting clonic tremor<sup>20</sup> sometimes observed after isoflurane anesthesia.<sup>21</sup> The transformed signals then were further filtered and decimated in time to 2 Hz to facilitate evaluation of the synchronous waxing-and-waning pattern characterizing normal thermoregulatory shivering.<sup>22</sup> From these data, a second power spectrum was calculated for frequencies in the 4–20-cyc/min “slow” band.

The EMG signals in each 48-s acquisition epoch were used to calculate the following characteristics: 1) root-mean square intensity (calculated from the 2-Hz data); 2) percentage of power between 4 and 10 cyc/min (inclusive) in the 4–20-cyc/min band (41% for a randomly distributed signal††); and 3) the Pearson product-moment correlation between the signals from each muscle (calculated from the 2-Hz data). Because tremor intensity varied with time, the EMG patterns in each study group were compared as a function of average total EMG intensity.

EMG pattern characteristics from each muscle and the correlation coefficients between the muscles were averaged. Because preliminary studies showed that spontaneous anterior tibialis tremor was rare, only signals from the pectoralis, trapezius, and quadriceps were averaged within each epoch. Signals from the anterior tibialis were used to evaluate intensity and patterns of induced spinal reflexes. EMG data are reported in relative intensity units because absolute EMG voltage is determined by factors such as electrode type and placement, skin impedance, and muscle size.

#### DATA ACQUISITION

Analog data from the thermometers, end-tidal gas monitor, pulse oximeter, laser Doppler flowmeters, and EMG amplifiers were acquired using an electrically isolated Macintosh® II computer (Apple, Cupertino, CA) equipped with three NB-MIO-16L® 16-channel, 12-bit,

analog–digital converters (National Instruments, Austin, TX). Data were digitized asynchronously and appropriately scaled. The results were averaged, displayed graphically on the computer screen, and recorded in spreadsheet format on a hard disk at 2- to 5-min intervals. This computer-program–emulating hardware was written using LabVIEW® graphic signal-processing software (National Instruments).

#### QUALITATIVE ASSESSMENTS

Overall thermal comfort was evaluated at 10-min intervals during hypothermia alone and when anesthetized volunteers were sufficiently recovered to respond to questioning. We used a 100-mm visual analog scale on which 0 mm was defined as worst imaginable cold, 50 mm as thermally neutral, and 100 mm as insufferably hot. A new, unmarked scale was used for each assessment.

Overt tremor intensity, quadriceps deep-tendon reflexes, and plantar flexion-induced clonus were evaluated qualitatively at 10- to 15-min intervals before and after anesthesia, once during isoflurane administration, and throughout iced saline administration. Responses were rated on a scale from zero to two (table 1). Reflexes were always tested by the same observer and on the same leg, which was supported with the knee bent at a 25° angle.

#### DATA ANALYSIS

A database program was used to sort and average data recorded from each volunteer at 2- to 5-min intervals using time (in 10- or 15-min epochs) and residual end-tidal isoflurane concentration (in 0.1% increments) as the sorting parameters. Because patterns of muscular activity during iced saline administration and after hypothermic anesthesia could not be directly compared using either residual isoflurane concentration or elapsed time, and because preliminary studies suggested that typical tremor characteristics may be apparent only during intense tremor, we also analyzed EMG patterns as a function of intensity. When performing these analyses, we gave equal statistical weight to data from the different volunteers within each time, end-tidal, or intensity range. The individual averages were used to calculate the means

TABLE 1. Scoring of Tremor Intensity and Spinal Cord Reflexes

	Zero	One	Two
Intensity	None	Mild	Severe
Deep tendon	None	Normal	Exaggerated
Clonus	None	<5 beats	≥5 beats

†† In a randomly distributed signal (with equal power at each frequency), the percentage of power between 4 and 10 cyc/min (inclusive) would be derived by dividing the difference between 4 and 10 cyc/min (7) by the difference between 4 and 20 cyc/min (17), i.e., 41%.

Overt tremor intensity, deep tendon reflexes, and plantar flexion-induced clonus were evaluated qualitatively at 10-min intervals, on a scale from 0–2.

( $\pm$  standard deviations) for the entire group in a given study condition.

The study periods during normothermic and hypothermic anesthesia were divided into a 30-min control period, 120-min isoflurane administration (from 31 to 150 min), and 120-min recovery period (from 151 to 270 min). The control period for study of hypothermia alone was 30 min and was followed by 30 min of iced saline infusion. (We did not evaluate recovery from hypothermia alone.) To compare and represent changes in measured variables in all three study conditions, we arbitrarily set the beginning of the iced saline infusion to coincide with the end of isoflurane administration. (In table 2 and figures 3 and 4, therefore, normal shivering and postanesthetic tremor coincide.)

Repeated-measures analysis of variance and Dunnett's tests were used to evaluate intragroup changes in central and average skin temperature, skin-temperature gradients, and thermal comfort during each study condition. Differences between groups at given times or end-tidal concentrations were analyzed using repeated-measures analysis of variance and Scheffé's *F* tests (or two-tailed, paired *t* tests when only two treatments were compared). The last 10- or 15-min acquisition epoch before iced infusion and induction of anesthesia or an end-tidal isoflurane concentration between 0 and 0.1% was considered the reference for intragroup comparisons.  $P < 0.05$  identified significant differences.

Nonparametric qualitative data were summed among volunteers during each study condition. Thus, the maximum possible score during any condition at any time (or end-tidal concentration) was 18. These data were analyzed using Wilcoxon signed-rank or Friedman's tests as appropriate. Spontaneous tremor preceded by central hypothermia and peripheral vasoconstriction was considered thermoregulatory.<sup>38</sup> Thermoregulatory tremor during recovery from isoflurane anesthesia was considered normal shivering only when EMG patterns were similar to those produced by hypothermia alone.

## Results

The mean age of our volunteers was  $27 \pm 4$  yr; mean weight was  $72 \pm 12$  kg; and mean height was  $171 \pm 11$  cm. Average ambient temperatures were not significantly different during hypothermia alone ( $20.3 \pm 0.7^\circ\text{C}$ ) and during hypothermic anesthesia ( $20.9 \pm 0.5^\circ\text{C}$ ); by design, environmental temperature was significantly higher during normothermic anesthesia ( $25.5 \pm 0.9^\circ\text{C}$ ).

Average end-tidal isoflurane concentration was  $1.1 \pm 0.2\%$  and decreased to  $\approx 0.2\%$  30 min after anesthesia was discontinued. End-tidal isoflurane concentrations were not clinically significantly different at any time during or after normothermic and hypothermic anesthesia

(table 2). No complications resulted from the study other than occasional postanesthetic nausea and vomiting, the incidence of each being similar after both anesthetic studies. All volunteers recovered from isoflurane anesthesia quickly, and were discharged home 1–2 h after completion of the study.

## HEMODYNAMIC RESPONSES

Mean blood pressure was higher (although the differences were not statistically significant) during the control period before hypothermic anesthesia and iced saline administration than before normothermic anesthesia. Blood pressures were similar during hypothermic and normothermic anesthesia. Pressures were about 10 mmHg higher after hypothermic anesthesia than in the control period and were significantly higher than after normothermic anesthesia.

Heart rates were lower during the control periods before iced saline and hypothermic anesthesia than before normothermic anesthesia. During and after hypothermic isoflurane anesthesia, heart rates were lower (although not significantly so) than in volunteers kept normothermic. Iced saline infusion increased heart rates significantly above the control values (table 2). Oxyhemoglobin remained well saturated (saturation  $\geq 97\%$ ) in all volunteers throughout the study.

## THERMOREGULATORY RESPONSES

Esophageal and tympanic membrane temperatures rarely differed by  $> 0.1^\circ\text{C}$ , indicating adequate aural probe placement. Tympanic membrane temperatures were slightly, but significantly, higher during the control period before normothermic anesthesia than before either hypothermic anesthesia or hypothermia alone. Central temperatures did not differ significantly during hypothermia alone and hypothermic anesthesia but were significantly lower after normothermic anesthesia. During the first 30 min of recovery from hypothermic anesthesia, central temperature increased by  $\approx 1^\circ\text{C}$  but remained  $\approx 0.5^\circ\text{C}$  less than control values until the end of the study (table 2). Central temperatures increased rapidly in volunteers recovering from hypothermic anesthesia when residual end-tidal isoflurane concentrations decreased to  $< 0.3\%$  (the time of maximum overt tremor intensity) (fig. 1).

Mean skin-surface temperature was not significantly different before hypothermia alone ( $31.6 \pm 0.6^\circ\text{C}$ ) than before hypothermic anesthesia ( $31.5 \pm 0.8^\circ\text{C}$ ); by design, skin temperature was significantly higher before normothermic anesthesia ( $34.9 \pm 0.7^\circ\text{C}$ ). Mean skin temperature was significantly lower after hypothermic anesthesia than after normothermic anesthesia at all times during recovery (fig. 1). Skin temperature was lower dur-

TABLE 2. Blood Pressure, Heart Rate, Tympanic Membrane Temperature, Skin-temperature Gradients, and End-Tidal Isoflurane Concentrations

	Time (min)									
	25	55	115	145	175	205	235	265		
Mean blood pressure (mmHg)	92 ± 8 84 ± 9	71 ± 11 71 ± 9	64 ± 7 65 ± 6	72 ± 9 69 ± 10†	99 ± 6 88 ± 8	98 ± 7* 84 ± 7	102 ± 9* 84 ± 8	101 ± 9* 84 ± 7		
Heart rate (beats per min)	56 ± 5 59 ± 8	69 ± 16 75 ± 17	62 ± 8* 70 ± 8	68 ± 9 73 ± 11†	71 ± 14 79 ± 20	63 ± 10 70 ± 16	60 ± 11 66 ± 13	56 ± 11 67 ± 13		
Tympanic temperature (°C)	36.6 ± 0.2* 36.9 ± 0.2	35.4 ± 0.3* 36.6 ± 0.3	35.4 ± 0.2* 37.0 ± 0.2	35.4 ± 0.2* 37.0 ± 0.3†	35.7 ± 0.3* 37.2 ± 0.2†	36.2 ± 0.5* 37.2 ± 0.3	36.2 ± 0.4* 37.2 ± 0.2	36.3 ± 0.3* 37.1 ± 0.3		
Gradient (°C)	6.2 ± 2.6* -1.4 ± 2.8	-2.8 ± 1.3* -1.7 ± 1.2	-1.2 ± 2.9 -1.6 ± 0.7	-1.5 ± 1.0 -1.6 ± 0.9†	3.8 ± 1.5* -0.7 ± 1.1†	6.7 ± 1.7* -0.5 ± 1.6	7.2 ± 1.5* 0.3 ± 2.5	6.9 ± 0.9* 0.2 ± 3.0		
Isoflurane concentration (%)	— —	1.1 ± 0.3 1.2 ± 0.3	0.9 ± 0.2 1.2 ± 0.3	1.4 ± 0.3 1.5 ± 0.5	0.2 ± 0.1 0.2 ± 0.0	0.1 ± 0.0 0.1 ± 0.0	0.1 ± 0.0 0.1 ± 0.0	0.1 ± 0.0 0.1 ± 0.0		

The study periods during normothermic and hypothermic anesthesia were divided into a 30-min control period, a 120-min isoflurane administration (from 31 to 150 min), and a 120-min recovery period (from 151 to 270 min). The control period for study of hypothermia alone was 30 min and was followed by 30 min of iced saline infusion. To compare changes in measured variables in all three study states, we arbitrarily set the beginning of the iced saline infusion to coincide with the end of isoflurane administration (so that normal shivering and postanesthetic tremor coincide). Mean blood pressure was higher during the control period preceding hypothermic anesthesia (GA-cold) and iced saline administration (Cold iv) than preceding normothermic anesthesia (GA-warm). Blood pressures were similar during hypothermic and normothermic anesthesia. Pressures were ≈10 mmHg higher after hypothermic anesthesia than in the control period and significantly higher than in volunteers recovering from normothermic anesthesia. Heart rates during the control periods preceding each treatment were similar. During and after hypothermic isoflurane anesthesia, heart rates were always lower than in volunteers kept normothermic. Iced saline infusion increased

heart rates significantly. Tympanic membrane temperatures during the control period were slightly, but significantly, higher before normothermic anesthesia than before hypothermic anesthesia or hypothermia alone. Volunteers were vasoconstricted (skin-temperature gradient ≥ 4° C) during the control period preceding hypothermic anesthesia, were vasodilated during isoflurane anesthesia, and then were vasoconstricted again during the recovery period. Volunteers were vasoconstricted before iced saline administration and remained so during the infusion. In contrast, volunteers remained vasodilated throughout normothermic anesthesia study. End-tidal isoflurane concentrations decreased at similar rates after normothermic and hypothermic anesthesia.

\* Significant differences between normothermic and hypothermic anesthesia data.

† Significant differences between iced saline and normothermic anesthesia data.

‡ Significant differences between iced saline and hypothermic anesthesia data.

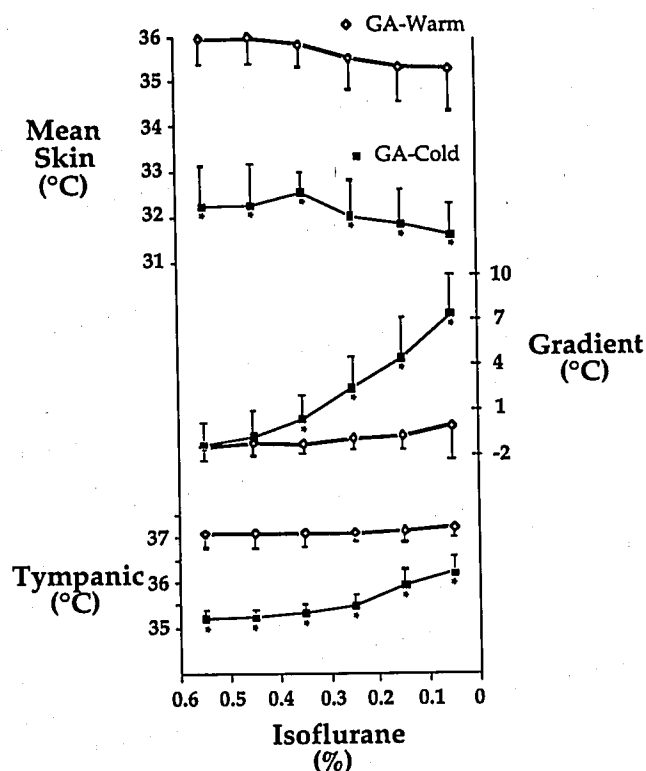


FIG. 1. Tympanic membrane temperatures increased rapidly in hypothermic volunteers when residual end-tidal isoflurane concentrations were below 0.3% (the time of maximum overt tremor intensity). During the last 30 min of the study (end-tidal concentrations below 0.1%), central temperatures in volunteers recovering from hypothermic anesthesia remained  $\approx 0.5^\circ\text{C}$  below control temperatures, and  $\approx 1^\circ\text{C}$  lower than during recovery from normothermic anesthesia. Mean skin-surface temperature (area-weighted average of ten sites) were significantly different throughout recovery from normothermic (GA-Warm) and hypothermic (GA-Cold) anesthesia. Skin temperatures in each group decreased slightly during the recovery period. The skin-surface temperature gradients (an index of peripheral blood flow) were similar during hypothermic (GA-Cold) and normothermic anesthesia (GA-Warm). The gradient in hypothermic volunteers rapidly increased to  $>4^\circ\text{C}$ , and was significantly lower than after normothermic anesthesia at all isoflurane concentrations below 0.4%. Significant vasoconstriction was never observed during normothermic anesthesia. Significant differences between the treatments are indicated by an asterisk (\*).

ing iced saline infusion than during the first 30 min of recovery from hypothermic anesthesia, but the temperatures differed by  $<1^\circ\text{C}$ .

Forearm – fingertip skin-surface temperature gradients were similar before hypothermic anesthesia and hypothermia alone but were significantly higher than before normothermic anesthesia. (Gradients  $\geq 4^\circ\text{C}$  indicate significant vasoconstriction). During anesthesia, gradients did not differ significantly when the volunteers were hypothermic and normothermic. During recovery, the gradient in hypothermic volunteers rapidly increased to  $>4^\circ\text{C}$  (table 2) and was statistically significantly higher

than after normothermic anesthesia at all isoflurane concentrations  $<0.4\%$ . The large decrease in finger blood flow during recovery from hypothermic anesthesia was easily detected using skin-temperature gradients, volume plethysmography, and both types of laser Doppler flowmeter. Absolute finger blood flow could not be predicted from photoelectric plethysmographic values, but changes in each individual over time did correlate with other measures of flow (fig. 2). Significant vasoconstriction never was observed during or after normothermic anesthesia.

Thermal comfort was significantly greater at all times on days of experiments with normothermic anesthesia than during hypothermia with and without anesthesia. During hypothermia alone, thermal comfort decreased significantly from control values (fig. 3). There was no significant decrease from control after hypothermic anesthesia, despite central temperatures  $\approx 1.5^\circ\text{C}$  lower than control values and similar to those after hypothermia alone. During postanesthetic recovery, hypothermic volunteers were significantly less comfortable ( $\approx 47$  mm on the 100-mm visual analog scale) than normothermic volunteers ( $\approx 55$  mm) at residual end-tidal isoflurane concentrations of  $\leq 0.2\%$ . Data at higher residual anesthetic concentration could not be evaluated because few volunteers were sufficiently alert to mark a visual analog scale.

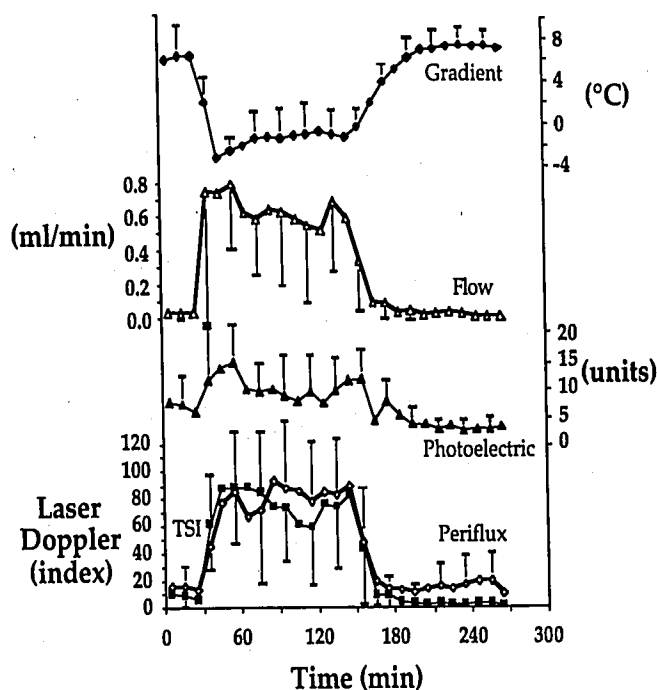


FIG. 2. Changes in fingertip blood flow on GA-Cold days were measured using skin-temperature gradients, volume plethysmography, two types of laser Doppler flowmeter, and photoelectric plethysmography. Absolute finger blood flow could not be predicted from photoelectric plethysmographic values, but changes in each individual over time did correlate with other measures of flow (data not shown).

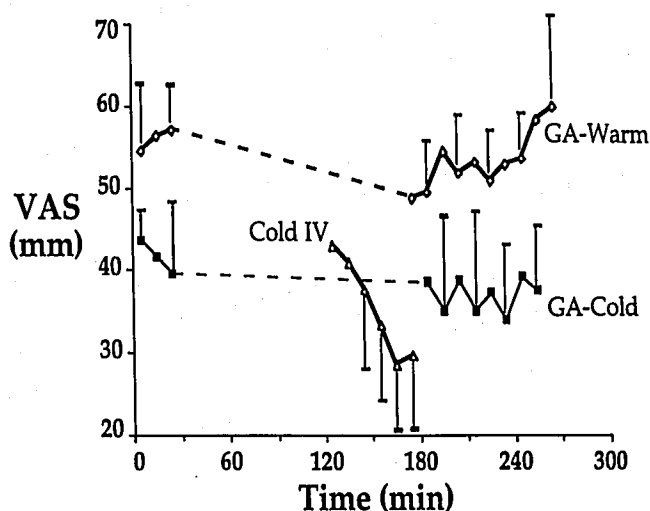


FIG. 3. Thermal comfort assessed with a visual analog scale (VAS) was significantly greater at all times during normothermic anesthesia (GA-Warm) than on the other two treatment days. Comfort decreased significantly from control during iced saline infusion (Cold IV) but not after hypothermic isoflurane anesthesia (GA-Cold). Isoflurane administration ( $\approx 1.1\%$ ) occurs between 30 and 150 elapsed min (dashed lines), and iced saline infusion between 150 and 180 elapsed min.

#### REFLEXES

Deep tendon reflexes were normal during exposure to a cold ambient environment (without central hypothermia) in the control periods before hypothermic anesthesia and iced saline administration but were decreased by cutaneous warming even before normothermic anesthesia. Tendon reflexes were essentially absent during general anesthesia but were significantly exaggerated by central hypothermia, and were similar after iced saline administration or hypothermic anesthesia (fig. 4).

There was an approximately linear increase in tendon reflex scores as end-tidal isoflurane concentration decreased from  $\approx 0.5\%$  to  $\approx 0.1\%$  during recovery from hypothermic anesthesia, and reflexes remained exaggerated at concentrations of  $\leq 0.1\%$ . Flexion-induced clonus was easily elicited when volunteers were recovering from hypothermic anesthesia and when residual end-tidal isoflurane concentrations were between 0.1 and 0.5% (fig. 5). Only brief periods of clonus could be elicited during recovery from normothermic anesthesia. None of our EMG analyses could distinguish flexion-induced from spontaneous clonus.

#### OVERT TREMOR

Overt tremor activity was not observed during any of the control periods or after normothermic anesthesia but was apparent in seven of nine volunteers after hypothermic anesthesia and in all volunteers during hypothermia

alone. Tremor activity stimulated by hypothermia alone was considerably more intense than that after hypothermic general anesthesia (fig. 4). In every case, tremor activity was preceded by significant peripheral vasoconstriction. Maximum tremor intensity scores coincided with residual end-tidal isoflurane concentrations  $< 0.3\%$  (fig. 5).

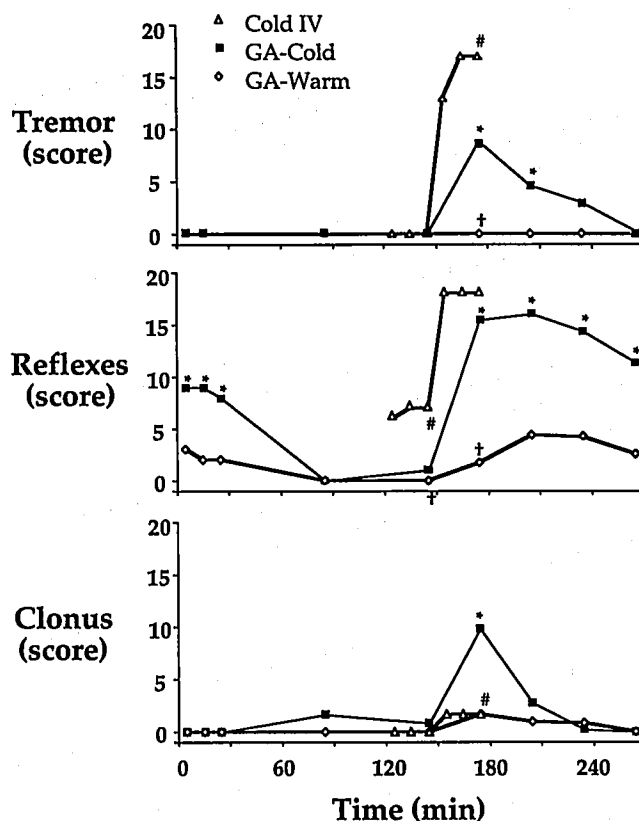


FIG. 4. Qualitative tremor scores were considerably higher during iced saline infusion (Cold IV) than during recovery from hypothermic anesthesia (GA-Cold), although central temperatures were similar ( $\approx 1.5^\circ\text{C}$  below control values). There was no apparent tremor after normothermic anesthesia (GA-Warm). Deep tendon reflexes were normal during exposure to a cold ambient environment (without central hypothermia) during the control periods preceding hypothermic anesthesia and iced saline administration, but were decreased by active warming before normothermic anesthesia. Tendon reflexes were essentially absent during general anesthesia but were markedly exaggerated by central hypothermia and were similar after iced saline administration or hypothermic anesthesia. Isoflurane administration ( $\approx 1.1\%$ ) occurred between 30 and 150 elapsed min, and iced saline infusion between 150 and 180 elapsed min. Flexion-induced clonus was significantly increased only when the volunteers were recovering from hypothermic anesthesia; clonus was not facilitated by hypothermia alone. Scores in each of the nine volunteers were summed; thus, the maximum possible score at any time was 18. Statistically significant differences between the groups were evaluated using Friedman's test; Significant differences between normothermic and hypothermic anesthesia data are indicated by asterisks (\*); differences between iced saline and hypothermic anesthesia data are indicated by number symbols (#); and significant differences between iced saline and normothermic anesthesia data are marked by daggers (†).



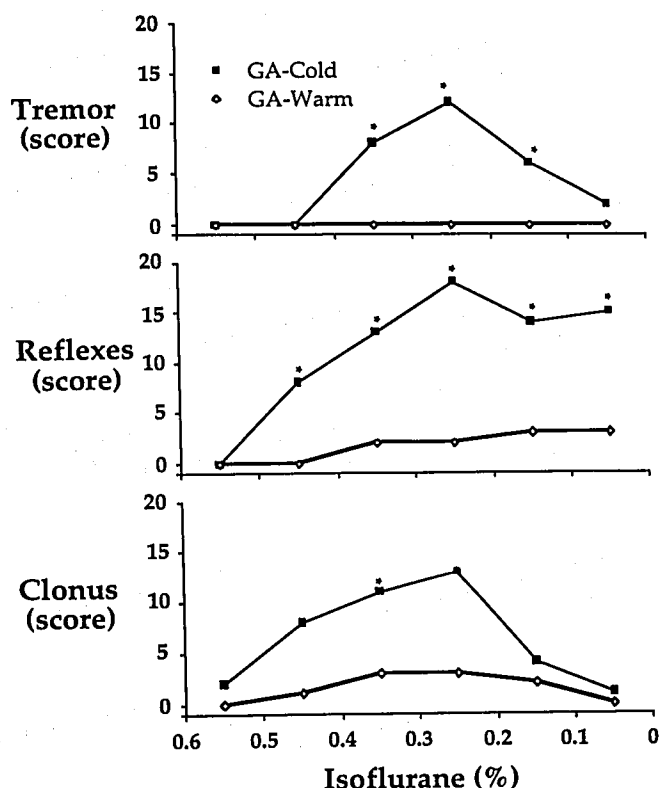


FIG. 5. Spontaneous tremor started when residual end-tidal isoflurane concentration decreased below 0.4% and continued until concentrations were below 0.1%. At this time, volunteers recovering from hypothermic anesthesia remained  $\approx 0.5^\circ\text{C}$  below control temperatures and  $\approx 1^\circ\text{C}$  lower than during recovery from normothermic anesthesia. Deep tendon reflexes were essentially absent during isoflurane administration and remained absent during recovery from normothermic anesthesia; in contrast, tendon reflexes were markedly exaggerated when volunteers were recovering from hypothermic anesthesia. There was an approximately linear increase in tendon reflex scores as end-tidal isoflurane concentration decreased from  $\approx 0.5$  to  $\approx 0.1\%$  during recovery from hypothermic anesthesia. Reflexes remained exaggerated in hypothermic volunteers, even when residual end-tidal isoflurane concentration was  $\leq 0.1\%$ . Clonus was easily elicited when volunteers were recovering from hypothermic anesthesia and when residual end-tidal isoflurane concentrations were between 0.1 and 0.5%. Only a small amount of clonus could be elicited during recovery from normothermic anesthesia. Tremor, tendon reflex, and clonus scores at each isoflurane concentration were scored on a scale from 0 to 2. The scores in each volunteer were summed; thus, maximum score during each treatment was 18. Statistically significant differences between the groups were evaluated using Wilcoxon signed-rank test; asterisks (\*) indicate  $P \leq 0.05$ .

Induced hypothermia alone produced the expected synchronous, waxing-and-waning EMG pattern characterizing normal shivering (fig. 6).<sup>22</sup> The peak power frequency in the 2–20-cyc/min band was  $\approx 13$  cyc/min during the control period but decreased significantly to  $\approx 7$  cyc/min during vigorous shivering. The percentage of EMG power between 4 and 10 cyc/min increased sig-

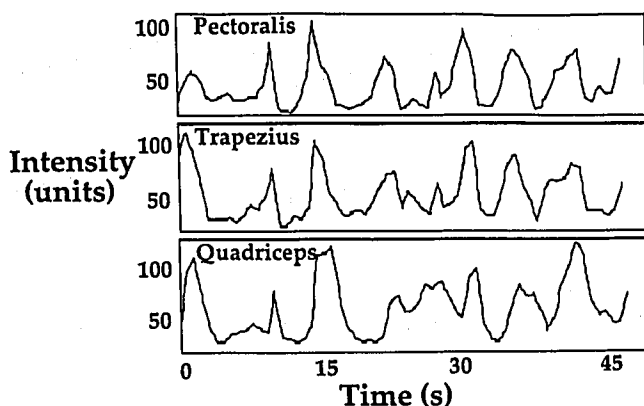


FIG. 6. Typical slow waxing-and-waning pattern of normal thermoregulatory shivering induced by rapid administration of cold intravenous fluids. Amplitude demodulated EMG intensity is in arbitrary units. Synchronous response of the three muscles is indicated by the high average correlation between the channels ( $r = 0.73$ ).

nificantly, from  $\approx 40\%$  during the control period to  $\approx 70\%$  during shivering. EMG intensity from the pectoralis, trapezius, and quadriceps muscles correlated well ( $r \approx 0.65$ ) during vigorous shivering (figs. 7 and 8).

Most postanesthetic tremor during recovery from hypothermic anesthesia had a synchronous waxing-and-waning pattern similar to that produced by normal shivering (fig. 9). EMG intensity in these volunteers was maximal when end-tidal isoflurane concentration was 0.2–0.3%. The peak power frequency in the 2–20-cyc/min

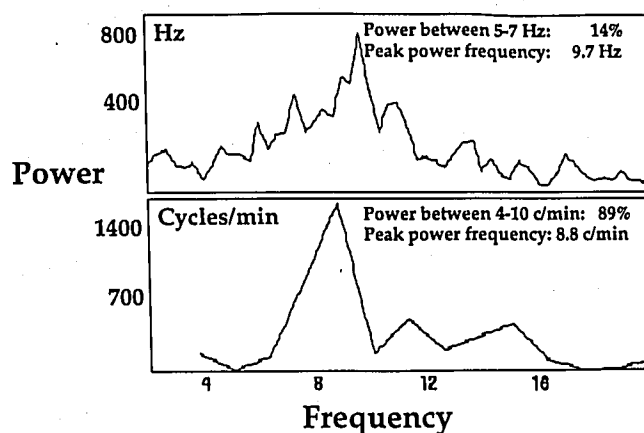


FIG. 7. Power spectral analysis of pectoralis EMG data in fig. 6. The top trace (analysis of high-speed activity) shows that the peak frequency is 9.7 Hz, with only 14% of the power (in arbitrary units) between 2 and 20 Hz in the 5–7-Hz clonic range. The spectrum is "broad," indicating that no single frequency is dominant. In contrast, analysis of the slow "waxing-and-waning" activity reveals that 89% of the power between 4 and 20 cyc/min was within the 4–10-cyc/min waxing-and-waning band. EMG power is in arbitrary units. Both the high- and low-frequency patterns are typical of normal shivering without clonic components.

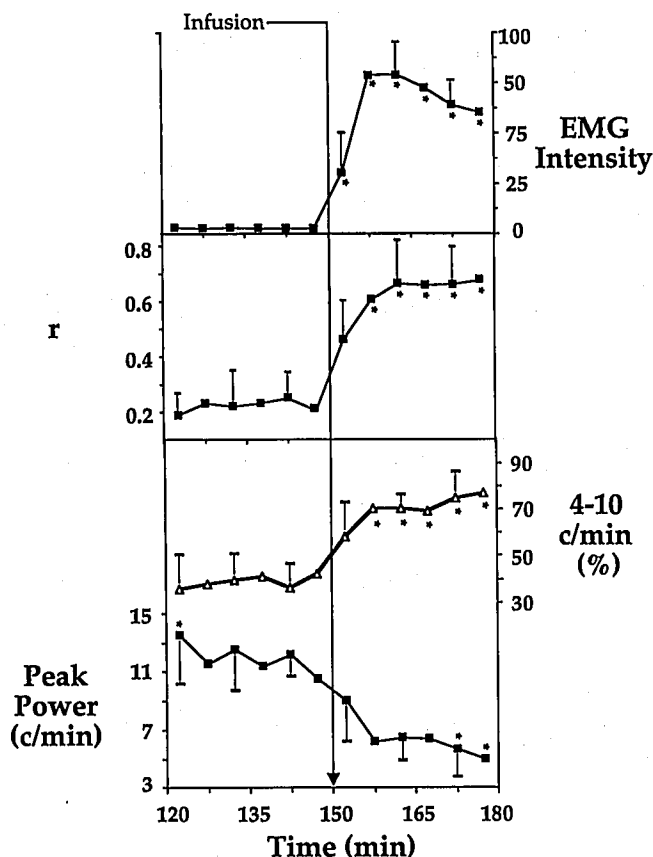


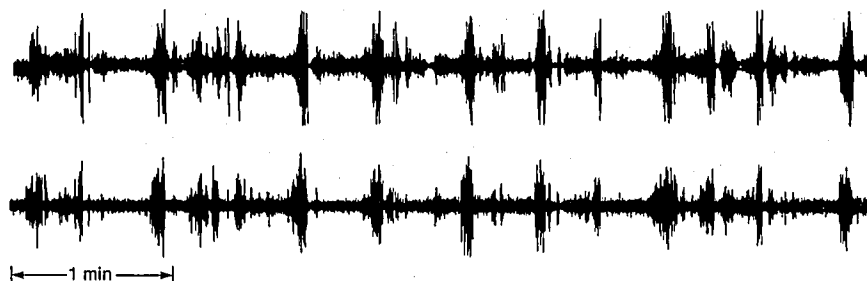
FIG. 8. Root-mean-square EMG intensity increased significantly during iced saline administration. The peak power frequency in the 2–20-cyc/min band in signals from the pectoralis, trapezius, and quadriceps was  $\approx 13$  cyc/min during the control period but decreased significantly, to  $\approx 7$  cyc/min during vigorous shivering induced by iced saline administration. The percentage of EMG power between 4 and 10 cyc/min increased significantly, from  $\approx 40\%$  during the control period to  $\approx 70\%$  during shivering. The average Pearson product-moment correlation coefficient between signals from the pectoralis, trapezius, and quadriceps in volunteers given iced saline was high (demonstrating synchrony among the muscles). This represents a statistical quantification of waxing-and-waning (e.g., shivering-like) tremor. The central venous infusion was started at 150 elapsed min. Asterisks (\*) indicate values significantly different from the 10-min epoch immediately preceding the saline infusion.

band was  $\approx 12$  when residual end-tidal isoflurane concentrations were  $\geq 0.3\%$ . When tremor intensity increased at end-tidal concentrations between 0.1 and 0.3%, the peak power frequency decreased significantly, to  $\approx 7$  cyc/min. The percentage of EMG power between 4 and 10 cyc/min increased significantly, from  $\approx 40\%$  at residual end-tidal isoflurane concentrations  $> 0.3\%$  to  $\approx 65\%$  when isoflurane concentrations were between 0.1 and 0.3%. EMG intensity from the pectoralis, trapezius, and quadriceps muscles were well correlated when tremor was most intense ( $r \approx 0.6$ ) (fig. 10). These figures represent a statistical quantification of synchronous waxing-and-waning (e.g., shivering-like) tremor.

Spontaneous EMG clonus occurred after hypothermic anesthesia and was most often observed when end-tidal isoflurane concentrations were between 0.4 and 0.2%. It was characterized by a regular, 5–7-Hz bursting pattern. Occasionally, clonus was observed from one muscle while tonic patterns were recorded simultaneously from others (fig. 11). Spontaneous EMG clonus dominated only a few complete 48-s epochs; a combination of clonus and waxing-and-waning was apparent in some epochs, but waxing-and-waning without clonic components was by far the most common tremor pattern. Clonus frequently evolved into tonic activity; conversely, tonic activity sometimes appeared to trigger a pure clonic signal (fig. 12).

There were no clinically important differences when signals from the pectoralis, trapezius and quadriceps muscles during hypothermia alone and recovery from hypothermic anesthesia were compared at different EMG intensities. During periods with little or no muscular activity,  $\approx 40\%$  of the signal power (the expected amount for a randomly distributed signal) was between 4 and 10 cyc/min. Approximately 70% of the power was between 4 and 10 cyc/min at EMG intensities of  $> 20$  units, but the percentage did not increase at still higher intensities. Maximum EMG intensity was greater during iced saline administration than after isoflurane anesthesia. During periods with little or no muscular activity, there was no correlation between the muscles. The correlation coefficient

FIG. 9. Most tremor during recovery from hypothermic anesthesia had a synchronous waxing-and-waning pattern resembling normal shivering. The top trace is from the pectoralis; the bottom trace was recorded simultaneously from the trapezius; the Y-axis is intensity in arbitrary units. In this example, the end-tidal isoflurane concentration was 0.14%; tympanic membrane temperature was  $35.8^\circ\text{C}$  (control temperature =  $36.5^\circ\text{C}$ ); mean skin temperature was  $31.2^\circ\text{C}$ ; and the skin-temperature gradient was  $6.1^\circ\text{C}$ . The Pearson product-moment correlation between signals from the pectoralis and trapezius was 0.87, indicating a high degree of synchrony between the muscles.



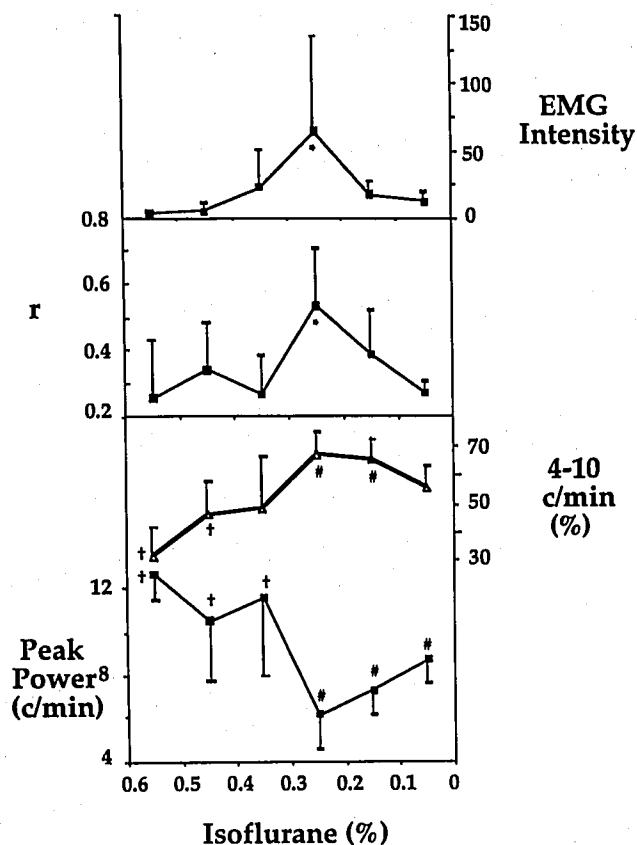


FIG. 10. During recovery from hypothermic anesthesia, root-mean-square EMG intensity was greatest when end-tidal isoflurane concentrations were between 0.2 and 0.3%. During recovery from hypothermic anesthesia, the peak power frequency was significantly lower at residual isoflurane concentrations  $\leq 0.3\%$  (number symbol [#]) than at concentrations above 0.3% (†). The percentage of EMG power between 4 and 10 cyc/min increased significantly, from  $\approx 40\%$  at residual end-tidal isoflurane concentrations  $> 0.4\%$  (†) to  $\approx 65\%$  at isoflurane concentrations between 0.1 and 0.3% (#). In volunteers recovering from hypothermic anesthesia, EMG intensities from the pectoralis, trapezius, and quadriceps were well correlated when tremor was most intense, at residual isoflurane concentrations between 0.2 and 0.3%. An asterisk (\*) indicates a significant difference from the intensity at end-tidal concentrations between 0 and 0.1%.

cient was  $\approx 0.6$  at EMG intensities of  $> 20$  units but did not increase further at higher intensities (fig. 13).

#### OTHER MUSCULAR ACTIVITY

During the early portion of recovery from anesthesia, a tonic "stiffening" (sustained muscular tone) resembling decerebrate posturing was apparent in many volunteers, usually at end-tidal isoflurane concentrations between 0.4 and 0.2%. We did not anticipate this pattern of muscular activity and so did not quantify its occurrence or intensity. (Acquisition epochs during which tonic stiffening was apparent were eliminated from all EMG analyses.) Comparable stiffening was rarely observed during hypothermia alone.

Coughing and bucking during anesthesia occurred at some time in most volunteers. In one volunteer, a particularly vigorous episode of coughing and bucking was associated with copious tracheal secretions and an isoflurane concentration that transiently decreased to  $\approx 0.9\%$ . EMG analysis of the movement revealed a pure clonic signal, nearly identical to that produced by flexion-induced clonus and pathologic clonus (fig. 14). Although this was the only observed episode of spontaneous clonus during isoflurane administration, we were able to induce ankle clonus in subsequent volunteers by transiently decreasing end-tidal isoflurane concentration to  $\approx 0.7\%$  and gently manipulating the endotracheal tube. (Deep tendon reflexes could not be elicited by this maneuver.) Clonus during anesthesia could be induced when volunteers were normothermic but seemed easier to elicit during hypothermia. Because clonus during anesthesia was not anticipated and required appropriate stimulation (which was only attempted in only five volunteers), these data were not included in the statistical analysis.

#### Discussion

Isoflurane washout rates were similar, probably because increased tissue isoflurane solubility in hypothermic vol-

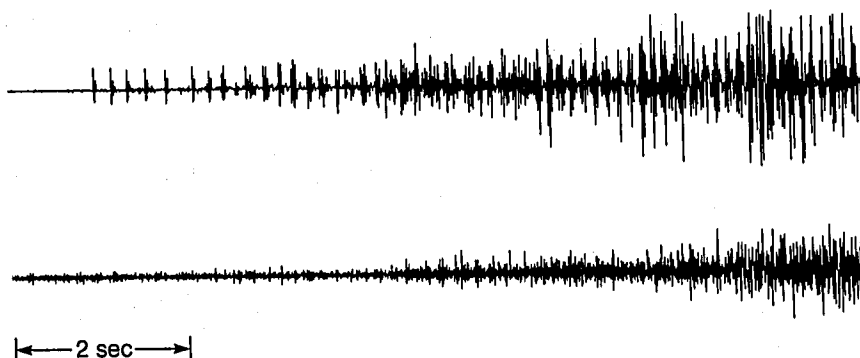
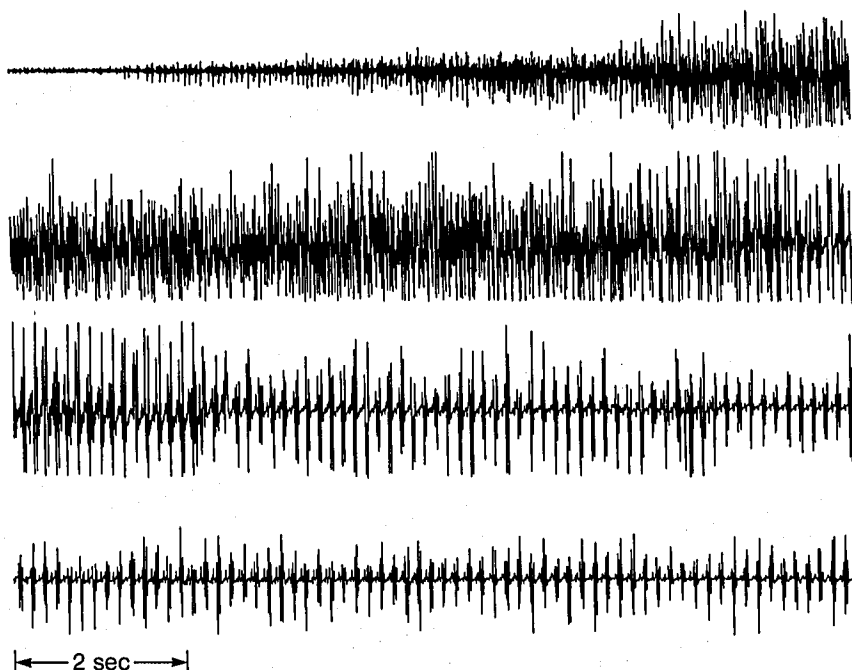


FIG. 11. Patterns of muscular activity after hypothermic anesthesia varied markedly. Spontaneous EMG clonus and waxing-and-waning tremors frequently occurred simultaneously. In this example, spontaneous clonus in the quadriceps muscle (top trace) was observed during recovery from hypothermic anesthesia, when the end-tidal isoflurane concentrations was 0.3%. After about 5 s, the clonus then "degenerated" into tonic (shivering-like) activity. Tonic tremor was simultaneously recorded from the anterior tibialis muscle (bottom trace). Tympanic membrane temperature was  $35.4^\circ\text{C}$  (control temperature =  $36.8^\circ\text{C}$ ) and mean skin-surface temperature was  $31.9^\circ\text{C}$ .

FIG. 12. During recovery from hypothermic anesthesia, tonic activity sometimes appeared to trigger a pure clonic signal. In this example, tonic (shivering-like) activity in the quadriceps appeared to trigger a nearly pure clonic tremor. The entire figure is a continuous recording made when the end-tidal isoflurane concentration was 0.28%, tympanic membrane temperature was 35.1° C (control temperature = 36.4° C), and mean skin-surface temperature 30.7° C. A similar pattern was simultaneously recorded from the anterior tibialis muscle.



unteers was offset by increased minute ventilation secondary to muscular activity. Peripheral vasoconstriction and tremor after hypothermic anesthesia raised central temperature by about 1° C in 1 h. Although we did not formally evaluate duration of recovery, mild hypothermia did not appear to delay recovery. Rapid recovery in our volunteers is consistent with clinical studies showing that even moderate hypothermia does not prolong recovery duration.<sup>39</sup> It is likely that hypothermia would last longer were postanesthetic tremor prevented by meperidine administration.<sup>40,41</sup>

#### THERMOREGULATORY AND HEMODYNAMIC RESPONSES

General anesthesia decreases the threshold temperatures triggering thermoregulatory responses to hypothermia.<sup>4-7</sup> Thermoregulatory inhibition in our volunteers was manifested by peripheral vasodilation (*i.e.*, skin-surface temperature gradients of  $\leq 0^\circ$  C) during hypothermic and normothermic anesthesia. After isoflurane administration was discontinued, volunteers remained vasodilated when normothermic but rapidly vasoconstricted when hypothermic. Vasoconstriction started when end-tidal isoflurane concentrations reached  $\approx 0.4\%$ , as expected from the thermoregulatory dose-response curve for isoflurane.<sup>6</sup> Once triggered, the intensity of peripheral vasoconstriction was similar after hypothermic anesthesia and during hypothermia alone. This is consistent with our previous report that, once triggered, vasoconstriction intensity is well preserved during isoflurane anesthesia.<sup>6</sup>

Mean skin-surface temperatures were similar before and after anesthesia. Thermal comfort also was similar before and after hypothermic isoflurane administration, despite postanesthetic central temperatures ranging from 1.5 to 0.5° C below control values. Similar thermal comfort before and after anesthesia is consistent with our previous observations (during epidural anesthesia) that behavioral thermal responses are determined primarily by skin-surface, and not central, temperature.<sup>38,42</sup>

Fingertip blood flow has both capillary and arteriovenous shunt components.<sup>43</sup> Both are under thermoregulatory control, but they respond differently to central warming and cooling and have varying degrees of local control.<sup>44</sup> We have previously demonstrated an excellent correlation between plethysmographic determinations of fingertip blood flow and skin-temperature gradients (both of which measure total flow) in unanesthetized volunteers.<sup>31</sup> Our current results indicate similar, excellent correlation during isoflurane anesthesia. We also have shown that there is a good correlation between skin-temperature gradients and laser Doppler flowmetry using the Periflux® 3 monitor.<sup>5,7</sup> In the current study, we demonstrate that Periflux® 3 and BPM® 403 laser indexes are similar. A specific test of the BPM® 403 monitor was required because different types of laser Doppler monitors detect varying ratios of capillary and shunt flow.<sup>45</sup> We found photoelectric plethysmography to be less reliable than the other measures of blood flow for detecting thermoregulatory vasodilation and vasoconstriction, perhaps in part because photoelectric plethysmography principally detects superficial capillary flow.

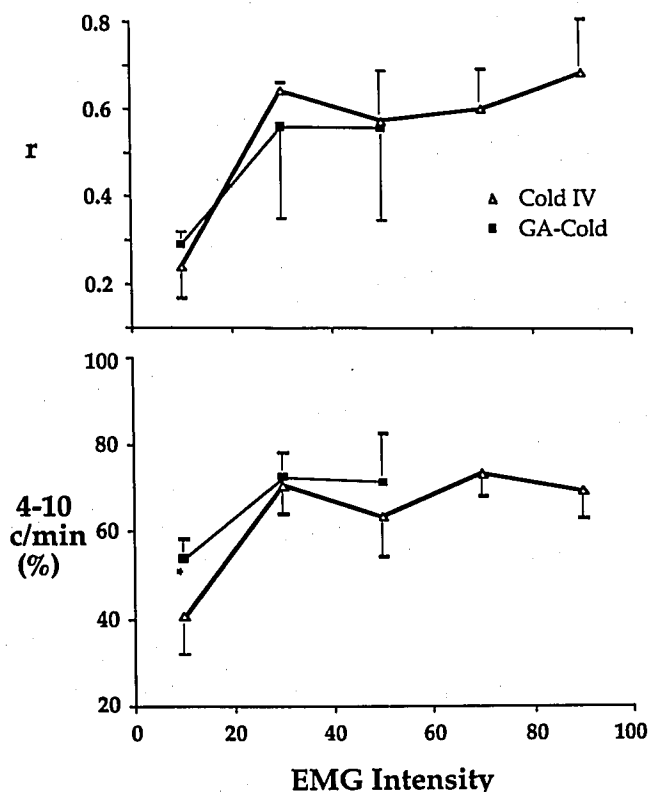


FIG. 13. The percentage of total power between 4 and 10 cyc/min in signals from the pectoralis, trapezius, and quadriceps at different EMG intensities (arbitrary units) in volunteers given iced saline and recovering from hypothermic isoflurane anesthesia. During periods with little or no muscular activity,  $\approx 40\%$  of the power (the expected amount for a randomly distributed signal) was between 4 and 10 cyc/min versus  $70\%$  at EMG intensities greater than 20 units. The percentage did not increase at higher intensities. Maximum EMG intensity was greater during iced saline administration than after hypothermic isoflurane anesthesia. The correlation coefficient between signals from the pectoralis, trapezius, and quadriceps at different EMG intensities (arbitrary units) in volunteers given iced saline and recovering from hypothermic isoflurane anesthesia were similar. During periods with little or no muscular activity, there was no correlation between the muscles. The correlation coefficient was  $\approx 0.6$  at EMG intensities greater than 20 units, but did not increase at higher intensities. An asterisk (\*) indicates that there was a statistically (but not clinically) significant difference between the groups only when there was little or no EMG activity.

Mean blood pressures were elevated and heart rates were lower during the control period and during recovery from isoflurane anesthesia in the hypothermic anesthesia group than in the normothermic group. In contrast, hemodynamic responses were similar in each group during isoflurane anesthesia. These data are consistent with increased systemic vascular resistance during cold exposure, presumably resulting from thermoregulatory vasoconstriction. At least in our young, healthy volunteers, cardiovascular stress produced by postanesthetic tremor appeared modest. It remains likely that the increased met-

abolic rate produced by tremor would not be tolerated so well by patients with limited cardiopulmonary reserves.

### OVERT TREMOR: BACKGROUND

The etiology of postanesthetic shivering-like tremor remains unclear despite numerous studies. Interpretation of previous investigations is difficult because none controlled the most important parameters: 1) specification and limitation of the number of anesthetic drugs (each may have different effects, and interact in unpredictable ways<sup>4-6,46-48</sup>); 2) choice of an accurate central temperature monitoring site (oral and axillary temperatures are not sufficiently reliable for thermoregulatory research<sup>49</sup>); 3) determination of central temperature before induction of anesthesia in each subject (population variability is great, so the difference from control in each individual is more important than absolute temperature<sup>27</sup>); 4) measurement of average skin-surface temperature (an important thermoregulatory input<sup>26,50</sup>); 5) assurance of adequate and uniform control of postoperative pain (pain may aggravate some types of tremor<sup>12</sup>); 6) evaluation of ancillary thermoregulatory responses such as peripheral cutaneous vasoconstriction (vasoconstriction usually precedes thermoregulatory shivering<sup>26</sup>); 7) measurement of residual anesthetic concentrations (some tremor appears to be aggravated by "intermediate" residual isoflurane concentrations<sup>21</sup>); 8) appropriate control groups, to isolate causal factors; and, 9) strict definition of "shivering" (not all tremor is normal shivering).<sup>16-20</sup> We were able to avoid most of these problems by studying volunteers who were not undergoing surgery, by using a triple cross-over de-

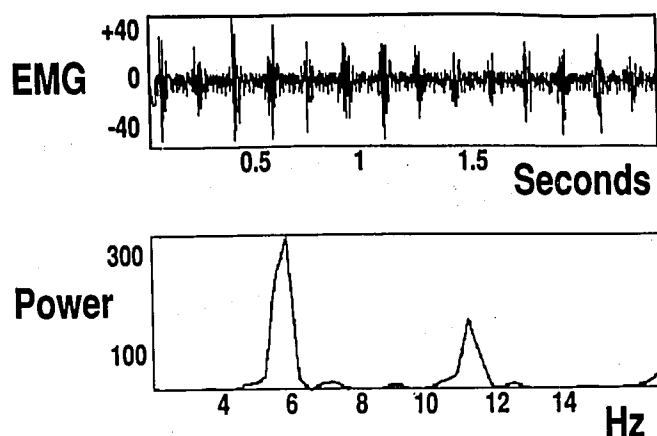


FIG. 14. EMG signals demonstrating typical flexion-induced clonus stimulated by light anesthesia and endotracheal tube manipulation (top trace, arbitrary units). The 5-7-Hz bursting pattern is evident and is confirmed by the power spectrum (bottom trace, arbitrary units), indicating that virtually all the power is near 6 Hz, with an apparent harmonic near 11 Hz.

sign, and by including appropriate physiologic measurements.

Although involuntary postanesthetic muscular activity is frequently referred to as "shivering," this term should be limited to thermoregulatory tremor in cold-stressed subjects. Thermoregulation is defined by *appropriate, coordinated, central responses to thermal perturbations*. Thus, muscular activity should be considered normal thermoregulatory shivering only when 1) mean body temperature<sup>24</sup> (a combination of central and skin temperature) is below the threshold for shivering; 2) tremor is preceded by peripheral cutaneous vasoconstriction; and 3) EMG patterns match those produced by cold-induced centrally mediated shivering in unanesthetized individuals.<sup>25-27</sup> Tremors that do not fulfill these criteria may be non-thermoregulatory (e.g., physiologic action tremor or pathologic clonus) or may result from abnormal thermoregulation (e.g., mediated by the brain stem<sup>51,52</sup> or spinal cord<sup>25,53</sup>) or from a modification of normal shivering (e.g., by residual anesthetic).<sup>54</sup> Naturally, analysis may be further complicated when a combination of tremor types is manifested simultaneously. The purpose of our study was to identify the postoperative tremors that were thermoregulatory responses.

#### OVERT TREMOR

Spontaneous tremor was observed in nearly all volunteers during recovery from hypothermic anesthesia but in none after normothermic anesthesia. In each case, muscular activity was preceded by significant peripheral vasoconstriction, one criterion by which tremor was considered to be thermoregulatory shivering.

The tonic waxing-and-waning postanesthetic tremor was thermoregulatory (i.e., always preceded by central hypothermia and peripheral vasoconstriction) and had a synchronous EMG pattern virtually identical to that of normal cold-induced shivering. Postanesthetic tremor was much less intense than cold-induced shivering; however, the similarity between the tremor patterns persisted even when their patterns were evaluated as a function of EMG intensity. Anesthetized patients who become sufficiently hypothermic (usually about 34.5° C) demonstrate thermoregulatory responses.<sup>4,5</sup> Anesthetic-induced thermoregulatory inhibition is dose-dependent.<sup>6</sup> Thus, when residual anesthetic concentration decreases during recovery in hypothermic individuals, thermoregulatory responses are expected. It is likely that the waxing-and-waning postanesthetic tremor is simply normal thermoregulatory shivering, resulting from a mean body temperature below the threshold that triggers shivering.

The shivering-like, synchronous waxing-and-waning pattern in the anesthetized hypothermic volunteers contributed most to total EMG intensity. Postanesthetic EMG

intensity peaked when end-tidal isoflurane concentration was near 0.3%; there was little spontaneous tremor at higher and lower concentrations. Thus, postanesthetic shivering in hypothermic volunteers started when residual isoflurane concentration decreased to  $\leq 0.4\%$  (the same concentration at which peripheral vasoconstriction was first observed). Tremor intensity increased as the thermoregulatory system was further disinhibited by decreasing isoflurane concentration. However, the tremor produced effective thermogenesis, rapidly increasing central temperature to within 0.5° C of control values. As a result, the initial increase in shivering intensity appears to have resulted from thermoregulatory disinhibition, but the subsequent decrease in intensity probably resulted because thermogenesis was no longer required.

As in our previous study, spontaneous EMG clonus was most common when residual end-tidal isoflurane concentration was near 0.2%, and frequently was accompanied by flexion-induced clonus. Spontaneous postanesthetic clonus was always preceded by central hypothermia and peripheral vasoconstriction, indicating that this tremor is thermoregulatory. However, spontaneous clonus is characterized by a regular, 5-7-Hz bursting EMG pattern that differs markedly from the slow, synchronous waxing-and-waning of normal shivering. Thus, this component of postanesthetic tremor is not *normal* thermoregulatory shivering. Whether it represents abnormal shivering or an anesthetic-induced modification of normal shivering remains to be determined.††

Israel and Pozos observed that normal thermoregulatory shivering produces a synchronous waxing-and-waning EMG pattern in volunteers in whom vigorous shivering was induced by skin cooling.<sup>22</sup> Skin-surface temperature is an important thermoregulatory afferent.<sup>50</sup> However, cutaneous thermal input does not necessarily produce regulatory responses proportional to central perturbations (i.e., thermal comfort is largely independent of central temperature in humans).<sup>38,42</sup> We therefore could not assume *a priori* that shivering induced by another mechanism (such as postanesthetic central hypothermia) would produce similar patterns. However, our data indicate that both peripheral and central cooling produces a synchronous waxing-and-waning EMG pattern. This pattern reflects the vigorous spasms of tremor interposed with periods of little muscular activity that can be observed clinically.

Postanesthetic tremor in our volunteers was considerably less vigorous than shivering induced by iced saline administration. We therefore analyzed EMG patterns

†† Studies in progress suggest that spontaneous EMG clonus and flexion-induced clonus are more common during recovery from enflurane than during recovery from isoflurane anesthesia but are virtually nonexistent after propofol anesthesia.

produced by postanesthetic tremor and cold-induced shivering as a function of intensity as well as of time. The results indicate that the synchronous waxing-and-waning pattern characterizing thermoregulatory shivering is readily apparent during both mild and vigorous activity.

In our previous study, we speculated that some tonic postanesthetic tremor was normal shivering, whereas other tremor was not.<sup>21</sup> It is likely that the previously observed tonic activity included both nonthermoregulatory tonic stiffening and the waxing-and-waning pattern identified here as normal shivering. Based on the similarity among spontaneous EMG clonus, flexion-induced clonus, and pathologic clonus, and the additional observation that clonus was most common at "intermediate" end-tidal isoflurane concentrations (*i.e.*, 0.2% isoflurane), we also proposed that spontaneous EMG clonus was (in part) a spinal reflex facilitated by the presence of residual isoflurane. However, all the patients in our previous study were hypothermic, making it impossible to independently evaluate thermoregulatory contributions to the observed tremor patterns. Our current data do not confirm our previous speculation and indicate that both spontaneous EMG clonus and tonic EMG activity are thermoregulatory (*e.g.*, preceded by hypothermia and peripheral vasoconstriction).

### REFLEXES

Postanesthetic spontaneous clonus was thermoregulatory and was observed only when residual isoflurane concentration was between 0.5 and 0.1%. In contrast, flexion-induced clonus could be induced during anesthesia by transiently decreasing end-tidal isoflurane concentration to 0.7% and manipulating the endotracheal tube when volunteers were both hypothermic and normothermic. These data suggest that the etiologies of spontaneous and flexion-induced clonus are multifactorial but may require both facilitation by anesthetic-induced spinal reflex disinhibition and a mechanical trigger.<sup>54,§§</sup> Clonus appears to be facilitated when end-tidal isoflurane concentration is near 0.3%, but facilitation may occur at higher concentrations (*e.g.*,  $\approx 0.7\%$ ) during sympathetic nervous system stimulation. The specific trigger may be mechanical flexion of the ankle or shivering-induced joint movement.

Deep tendon reflexes were facilitated by both cutaneous cold exposure and central hypothermia, a result consistent with previous reports. However, isoflurane *per se* produced no additional increase in the reflex amplitude.

§§ Anesthetic-induced facilitation may not be required when individuals are positioned differently. For example, clonus can be induced by "bouncing" the knee of a seated volunteer who is cold-exposed but not centrally hypothermic. (Pozos RS: Personal communication. Naval Research Laboratory, San Diego.)

Thus, tendon reflexes and flexion-induced clonus (both measured as an indexes of spinal cord disinhibition) did not change the same way. These data suggest that isoflurane specifically facilitates clonus without producing generalized spinal cord disinhibition.

### OTHER MUSCULAR ACTIVITY

Tonic stiffening was observed in some volunteers during the initial phase of recovery from both hypothermic and normothermic anesthesia. Because it occurred in normothermic and vasodilated volunteers, this posturing cannot be considered thermoregulatory. Furthermore, it lacked the synchronous waxing-and-waning pattern characterizing normal shivering. Similar muscular activity was rarely observed during cold-induced shivering in unanesthetized volunteers. Thus, tonic stiffening appears to be a direct, non-temperature-dependent effect of isoflurane anesthesia. Its specific etiology remains to be determined. Comparable nonthermoregulatory tonic activity has previously been described in cats recovering from halothane anesthesia.<sup>55</sup>

Coughing and bucking was observed in many volunteers at some point during isoflurane administration. As in previous studies, movement usually was not preceded by an increase in heart rate, blood pressure, or respiratory rate. Absence of sympathetic response is consistent with the frequent inability of lower esophageal contractility, electroencephalography, and other technologies to readily anticipate movement during anesthesia.<sup>56</sup>

### LIMITATIONS

Although central temperatures were similar after hypothermic anesthesia and induced hypothermia, these study conditions are not exactly analogous because hypothermia developed *via* different mechanisms and at different rates. Furthermore, to compare and represent changes in measured variables in all three study conditions, we arbitrarily set the beginning of the iced saline infusion to coincide with the end of isoflurane administration. Statistical comparisons between data with iced saline and those obtained during and after anesthesia would have produced different results had we chosen different reference times.

All our volunteers were young, healthy men. (We chose men because monthly hormonal and thermal cycles in women might have introduced additional variables into the study, which required participation on three separate days.) It is possible that our results would differ somewhat had we studied women and probable that they would differ in volunteers of extreme ages. By design, none of our volunteers experienced postoperative surgical pain and sympathetic stimulation. It is likely that both pain and stimulation contribute to the thermoregulatory responses

and tremor patterns in patients. Thus, results in patients may differ quantitatively and qualitatively from those observed in this study.

Mild hypothermia (*i.e.*, 1.5° C below control temperatures) is typical during recovery from surgery, but some patients are considerably colder. Those who are sufficiently hypothermic (*e.g.*, with central temperatures near 34.5° C) will trigger thermoregulatory responses while still anesthetized.<sup>4-7</sup> Presumably, thermoregulatory shivering during postanesthetic recovery will be particularly intense in these patients. It is likely that patterns of muscular activity in moderately hypothermic patients will differ from those with only mild hypothermia. Muscular activity also may differ significantly in surgical patients given ancillary anesthetic drugs such as opioids, barbiturates, benzodiazepines, and phenothiazines.

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