Isoflurane Alters Shivering Patterns and Reduces Maximum Shivering Intensity

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Background: Shivering can be characterized by its threshold (triggering core temperature), gain (incremental intensity increase with further core hypothermia), and maximum response intensity. Isoflurane produces a clonic muscular activity that is not a component of normal shivering. To the extent that clonic activity is superimposed on normal thermoregulatory shivering, the gain of shivering might be increased during isoflurane anesthesia. Conversely, volatile anesthetics decrease systemic oxygen consumption and peripherally inhibit skeletal muscle strength, which might limit maximum intensity despite central activation. The purpose of the present study was, therefore, to evaluate the effect of isoflurane shivering patterns and the gain and maximum intensity of shivering.

Methods: Ten volunteers were each studied in two separate protocols: (1) control (no drug) and (2) 0.7% end-tidal isoflurane. On each day, the mean skin temperature was maintained at 31°C. Core temperature was then reduced by infusion of cold fluid until shivering intensity no longer increased. The core temperature triggering the initial increase in oxygen consumption defined the shivering threshold. The gain of shivering was defined by the slope of the core temperature *versus* oxygen consumption regression. Pectoralis and quadriceps electromyography was used to evaluate anesthetic-induced facilitation of clonic (5–7 Hz) muscular activity.

Results: Isoflurane significantly decreased the shivering threshold from 36.4 ± 0.3 to 34.2 ± 0.8°C. The increase in oxygen consumption was linear on the control day and was followed by sustained high-intensity activity. During isoflurane administration, shivering was characterized by bursts of intense shivering separated by quiescent periods. Isoflurane significantly increased the gain of shivering (as calculated from the initial increase), from −684 ± 266 to −1483 ± 752 ml · min^{-1} · °C^{-1}. However, isoflurane significantly decreased the maximum intensity of shivering, from 706 ± 144 to 489 ± 80 ml/min. Relative electromyographic power in frequencies associated with clonus increased significantly when the volunteers were given isoflurane.

Conclusions: These data indicate that isoflurane anesthesia markedly changes the overall pattern of shivering during progressive hypothermia from a linear increase to an unusual saw-tooth pattern. They further suggest that clonic muscular activity combines with shivering to increase the initial gain of shivering during isoflurane anesthesia, but that isoflurane peripherally inhibits the maximum expression of shivering. (Key words: Anesthesia; hypothermia; temperature; thermoregulation; volatile anesthetics.)

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SHIVERING can be characterized by its threshold (triggering core temperature), gain (incremental intensity increase with further core temperature deviation), and maximum response intensity.[1] Isoflurane markedly reduces the shivering threshold,[2] which is one reason why shivering is rare during anesthesia. However, sufficient reductions in the gain or maximum intensity would also reduce the manifestation of intraoperative shivering.

The effect of volatile anesthetics on the gain of shivering has yet to be evaluated. Isoflurane administration, unlike intravenous anesthetics and opioids, is associated with a clonic muscular activity that is not a component

of normal shivering. This activity appears to be thermoregulatory (*i.e.*, associated with core hypothermia and vasoconstriction) but facilitated by isoflurane.[3] To the extent that clonic activity is superimposed on normal thermoregulatory shivering, the gain of shivering might be increased during isoflurane anesthesia. In addition, shivering patterns may be altered.

The effect of volatile anesthetics on the maximum intensity of shivering also remains unknown. However, volatile anesthetics decrease systemic oxygen consumption[4,5] and peripherally inhibit skeletal muscle strength,[6] which might limit maximum intensity, despite central activation. The purpose of the present study was, therefore, to evaluate the effect of isoflurane on the gain and maximum intensity of shivering.

Methods

With approval from the Committee on Human Research at the University of California, San Francisco, and written informed consent, we studied 10 healthy men. None was obese, was taking medication, or had a history of thyroid disease, dysautonomia, or Raynaud's syndrome. The volunteers' morphometric characteristics included age 28 ± 5 yr, height 174 ± 10 cm, and weight 73 ± 8 kg. The volunteers fasted for 8 h before each study day and rested in the supine position on a standard operating room table. During the studies, they were minimally clothed and ambient temperature was maintained near $21\text{--}22^\circ C$.

Protocol

Volunteers were each evaluated on two study days, once without anesthesia (control) and once during 0.7% end-tidal isoflurane anesthesia. The treatment order was randomly assigned. To avoid circadian fluctuations, studies were scheduled so that shivering was triggered at similar times on each study day. The effects of isoflurane and administered fluid volume were minimized by allowing at least 48 h to elapsed between the study days. On the first study day, a 16-gauge internal jugular catheter was inserted for subsequent administration of cold fluid. Between study days, a small amount of heparin sodium was injected into the tubing, and the catheter was sealed.

On the isoflurane anesthesia day, a 20-gauge intravenous catheter was inserted in the left forearm. Anesthesia was induced by administration of 3 mg/kg propofol and incremental concentrations of isoflurane to $\approx 2\%$.

The volunteers' tracheas were then intubated without muscle relaxant, and anesthesia was maintained by spontaneous ventilation of 0.7% end-tidal isoflurane in 30% oxygen and 70% nitrogen. A catheter was inserted into the urinary bladder.

Throughout the study period, mean skin temperature measurement was kept constant near $31^\circ C$ using a forced-air cover (Augustine Medical, Eden Prairie, MN) and circulating-water mattress (Cincinnati Sub-Zero Products, Cincinnati, OH). Core cooling started 1 h after induction of anesthesia on the isoflurane day or after 15 min of baseline measurements on the control day. As in previous studies,[7] the core was cooled by central-venous administration of lactated Ringer's solution at $\approx 3^\circ C$. The cooling rate was restricted to $\leq 2^\circ C/h$, because such rates are unlikely to trigger dynamic thermoregulatory responses. Cooling ceased when shivering intensity no longer increased, despite a continued decrease in core temperature.

Measurements

Heart rate was measured continuously using an electrocardiogram, and blood pressure was determined oscillometrically at 5-min intervals at the left ankle. End-tidal isoflurane and carbon dioxide pressure were measured using an Ultima monitor (Datex; Helsinki, Finland); exhaust gas from this monitor was returned to a DeltaTrac oxygen consumption monitor (SensorMedics Corp., Yorba Linda, CA). Core and mean skin temperatures were recorded at 1-min intervals, as previously described.[8]

Oxygen consumption, as measured by a DeltaTrac metabolic monitor, quantified shivering; the system was used in canopy mode on the control day and in respirator mode on the isoflurane anesthesia day. Both methods provide measurements with an absolute accuracy of 5–10%.[9-11] Changes in volatile anesthetic concentrations can produce small measurement artifacts,[12] but steady-state levels have little influence. Measurements were averaged over 1-min intervals and recorded every minute. Shivering activity of the right pectoralis and quadriceps was also evaluated electromyographically, as previously described.[8]

Data Analysis

A sustained increase in oxygen consumption identified the shivering threshold. The maximum intensity of shivering was identified by an oxygen consumption that failed to increase further despite continued reduction in core temperature. The gain of shivering was determined as the slope of oxygen consumption *versus* core

Table 1. Environmental, Hemodynamic, Respiratory, and Thermoregulatory Data

	Control	Isoflurane
Ambient temperature (°C)	21.2 ± 0.9	21.6 ± 0.9
Relative humidity (%)	40 ± 9	40 ± 5
Mean arterial blood pressure (mmHg)	94 ± 10	73 ± 6*
Heart rate (beats/min)	64 ± 11	73 ± 18
End-tidal P_{CO_2} (mmHg)	40 ± 4	43 ± 2*
Fluid volume (L)	2.0 ± 0.7	4.1 ± 1.2*
Mean skin temperature (°C)	31.1 ± 0.2	31.0 ± 0.1
Preinduction oxygen consumption (ml/min)	226 ± 40	241 ± 42
Shivering threshold (°C)	36.4 ± 0.3	34.2 ± 0.8*
Gain of shivering ($ml \cdot min^{-1} \cdot °C^{-1}$)	−684 ± 266	−1483 ± 752*
Gain of shivering (intensity/°C)	−1.6 ± 1.4	−8.4 ± 9.7*
Shivering maximum intensity (ml/min)	706 ± 144	489 ± 80*

Data are mean ± SDs. Initial oxygen consumption is before induction of anesthesia on the isoflurane day.

* Statistically significant difference from control.

temperature regression during its initial ascent toward the maximum observed value. The gain of shivering was also determined by the slope of the integrated electromyographic intensity *versus* core temperature regression, using root-mean square values of 1-min electromyographic acquisition intervals. In both cases, the data series were smoothed using 5-min running-average filters. The shivering threshold, gains, and maximum intensity were later determined by an investigator blinded to treatment and core temperature.

Hemodynamic responses, ambient temperature, relative humidity, and end-tidal carbon dioxide pressure on each study day were first averaged within each volunteer, and data obtained between the onset of shivering and the maximum intensity were included. The resulting values were averaged among volunteers. Results on the two study days were compared using two-tailed, paired *t* tests. The gains of shivering as determined by oxygen consumption and electromyography were non-parametrically distributed and thus compared using the Wilcoxon test.

As in previous investigations,[3] we used a modification of the electromyographic analysis technique developed by Stiles.[13] Fast Fourier transform analysis of the electromyographic signals was preceded by a four-step amplitude demodulation[13,14] consisting of (1) digital full-wave rectification, (2) second-order Butterworth lowpass filtering to 32 Hz, (3) 10-fold decimation in time, and (4)

zero-padding to increase the number of points in the data set to a power of two. Amplitude demodulation of the electromyogram produces patterns well correlated with limb acceleration.[14]

To determine the intensity of each frequency in the 5 – 14 Hz band, we computed the power spectrum, using a resolution of 0.05 Hz. These frequencies include broad-spectrum shivering (tonic) activity, usually peaking between 8 – 12 Hz,[13] and the regular 5 – 7 Hz bursting clonic tremor sometimes observed after isoflurane anesthesia.[3,15] The percentage of signal power within the clonic 5 – 7 Hz range was determined on the control day and during isoflurane anesthesia. All data between the onset of shivering and the maximum shivering intensity were included in this analysis. The clonic percentage on the two study days were compared using two-tailed, paired *t* tests. All results are presented as means ± SDs; probability values <0.05 were considered significant.

Results

Mean skin temperatures were kept nearly constant throughout the protocol. End-tidal isoflurane concentrations averaged 0.71 ± 0.01% during the study. Ambient temperature, relative humidity, heart rate, and mean skin temperature were comparable on each study day.
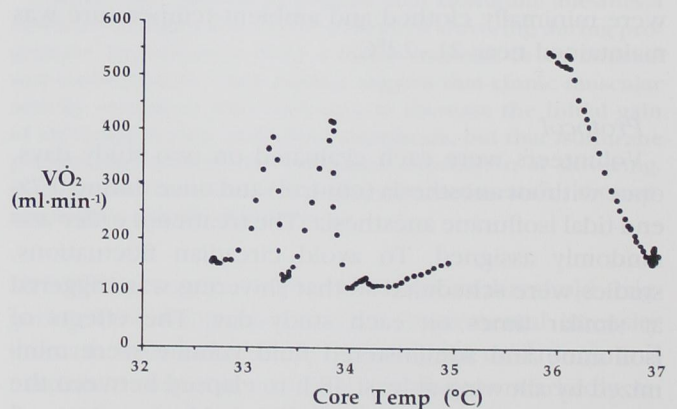

Fig. 1. Representative oxygen consumption data from the ninth volunteer. Isoflurane decreased the shivering threshold and the maximum intensity of shivering but increased the gain of shivering. Shivering during isoflurane (*at left*) had a characteristic saw-tooth pattern in which bouts of intense shivering were interrupted by quiescent periods. In contrast, shivering on control days (*at right*) increased nearly linearly from baseline values until maximum intensity was reached and subsequently remained nearly constant during further core cooling. In both cases, the data series were smoothed using a 5-min running-average filter.
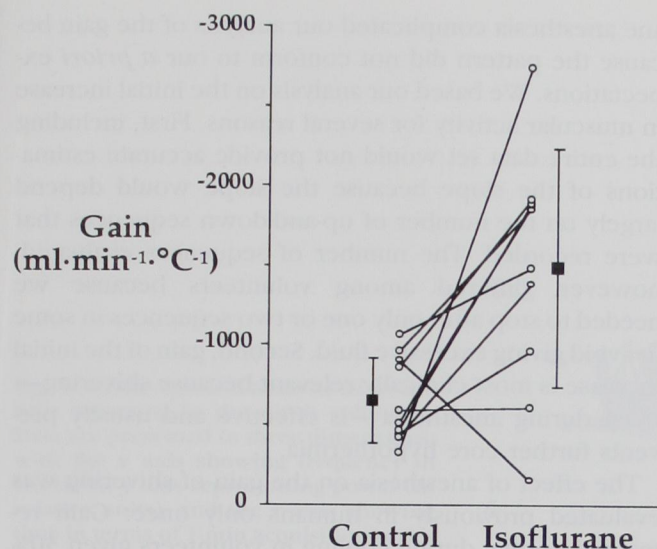
Fig. 2. Individual gains of shivering (*open circles*), as determined by the slope of oxygen consumption *versus* core temperature regressions, on the control and isoflurane study days. Means are shown as filled squares, along with the associated standard deviations. The gain of shivering, as determined by oxygen consumption, increased significantly during isoflurane anesthesia.

Mean arterial blood pressure was significantly lower during isoflurane than on the control day. End-tidal carbon dioxide pressure was slightly but significantly higher during isoflurane than on the control day. Significantly more lactated Ringer's solution was required when isoflurane was administered than on the control day. Initial (preinduction) oxygen consumption was comparable in the two studies. Oxygen consumption decreased 28%, from 241 ± 42 to 173 ± 30 ml/min after induction of anesthesia ($P < 0.001$; table 1).

Isoflurane significantly decreased the shivering threshold, from 36.4 ± 0.3 to $34.2 \pm 0.8°C$. Oxygen consumption and electromyographic activity on the control day increased nearly linearly from baseline values until maximum intensity was reached and subsequently remained nearly constant during further core cooling. In contrast, shivering during isoflurane administration was characterized by bursts of intense shivering that nearly linearly increased oxygen consumption and electromyographic activity from baseline to maximum values with only small further reductions in core temperature. With additional cooling, however, shivering intensity then diminished, often back to baseline values, before again rapidly increasing to maximum levels. The result was thus an overall saw-toothed pattern that differed markedly from that observed on the control day and in previous investigations (fig. 1).

The saw-toothed shivering pattern during isoflurane administration was an unexpected finding. Consequently, about one half of the studies were stopped after maximum shivering intensity was observed but before the saw-tooth pattern was demonstrated. Two peaks were evident in three patients, whereas three and four peaks were evident in two others. This pattern was equally apparent on the oxygen consumption and electromyographic records. Among the volunteers demonstrating multiple peaks, the maximum intensity for each was similar. The average temperature difference between the peaks was $0.4 \pm 0.3°C$ as determined by oxygen consumption and $0.4 \pm 0.2°C$ as determined from the electromyographic record.

Because shivering intensity during isoflurane administration increased from baseline to maximum values with only slight additional core cooling, the gain as determined by oxygen consumption was significantly higher than on the control day: -1483 ± 752 *versus* -684 ± 266 ml $\cdot$ min $\cdot^{-1}°C^{-1}$ (fig. 2). The gain of shivering, as assessed electromyograpically, was also significantly higher on the isoflurane day (fig. 3). In contrast, the maximum intensity of shivering was significantly lower
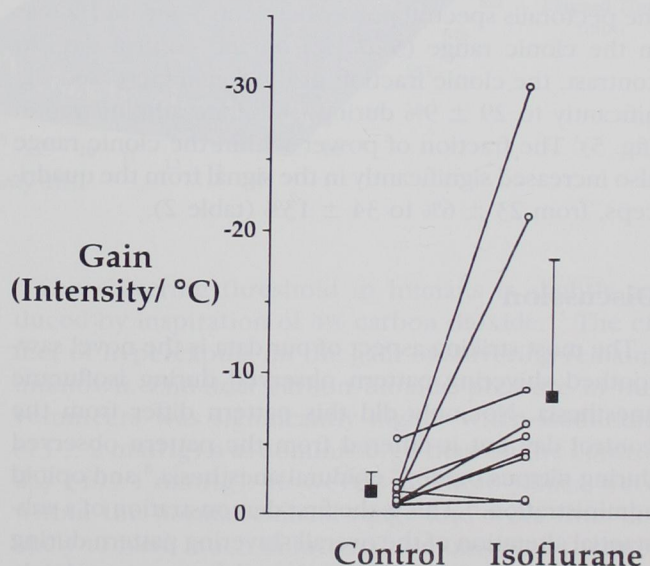

Fig. 3. Individual gains of shivering (*open circles*), as determined by the slope of electromyographic intensity *versus* core temperature regressions, on the control and isoflurane study days. Means are shown as filled squares, along with the associated standard deviations. The gain of shivering, as determined electromyographically, increased significantly during isoflurane anesthesia.
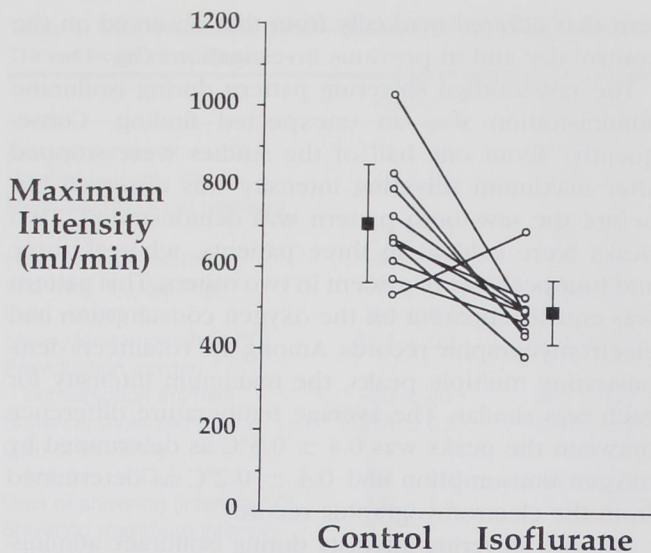
Fig. 4. Maximum shivering intensity (*open circles*), as determined by oxygen consumption, on the control and isoflurane study days. Means are shown as filled squares, along with the associated standard deviations. The maximum intensity of shivering decreased significantly during isoflurane anesthesia.

during isoflurane administration compared with the control day: 489 ± 80 *versus* 706 ± 144 ml/min (fig. 4).

Electromyographic analysis indicated that $20 \pm 6\%$ of the pectoralis spectral power between 5 and 14 Hz was in the clonic range (5–7 Hz) on the control day. In contrast, the clonic fraction of the signal increased significantly to $29 \pm 9\%$ during isoflurane administration (fig. 5). The fraction of power within the clonic range also increased significantly in the signal from the quadriceps, from $23 \pm 6\%$ to $34 \pm 13\%$ (table 2).

Discussion

The most striking aspect of our data is the novel saw-toothed shivering pattern observed during isoflurane anesthesia. Not only did this pattern differ from the control day but it differed from the pattern observed during nitrous oxide,[16] epidural anesthesia,[8] and opioid administration.[17] This is the first demonstration of a substantial alteration of the overall shivering pattern during progressive core hypothermia, and it was completely unexpected. Whether this saw-tooth pattern is a macroscopic manifestation of the 5–7 Hz clonic tremor observed previously during isoflurane anesthesia[3] or an entirely new phenomenon remains unclear.

The novel shivering pattern observed during isoflur-

ane anesthesia complicated our analysis of the gain because the pattern did not conform to our *a priori* expectations. We based our analysis on the initial increase in muscular activity for several reasons. First, including the entire data set would not provide accurate estimations of the slope because the slope would depend largely on the number of up-and-down sequences that were recorded. The number of sequences evaluated, however, differed among volunteers because we needed to stop after only one or two sequences in some to avoid giving excessive fluid. Second, gain of the initial increase is most clinically relevant because shivering—even during anesthesia—is effective and usually prevents further core hypothermia.

The effect of anesthesia on the gain of shivering was evaluated previously in humans only once: Gain remained normal during cooling in volunteers given 30% nitrous oxide and was slightly reduced during rewarming.[16] Isoflurane, however, differs from nitrous oxide in facilitating a 5–7 Hz clonic tremor.[3] This clonic muscular activity differs from normal tonic shivering, which usually has demodulated frequencies peaking between 8–12 Hz[13] and a slow 4–8 cycle/min "waxing-and-waning" pattern.[18] As might be expected from previous observations,[3] electromyographic power in frequencies associated with clonus increased when the volunteers were given isoflurane. This anesthetic-induced clonic activity appears to be thermoregulatory but is nonetheless presumably superimposed on normal cold-induced shivering. Consistent with this theory, isoflurane anesthesia significantly increased the gain of shivering, at least as determined by the initial increase in muscular activity.

Ultimate intensity of thermoregulatory defenses is thought to reflect maximum activity of peripheral effectors. To the extent that this theory is accurate, drug-induced modulations of central threshold and gain may not alter maximum intensity. The maximum intensity of sweating, for example, remains normal during isoflurane anesthesia, although the sweating threshold is elevated.[19] The maximum intensity of vasoconstriction is similarly preserved during volatile anesthesia,[20] although the threshold[2] and gain[7] are reduced. In distinct contrast to the effects of isoflurane on the maximum intensity of sweating and vasoconstriction, isoflurane reduced maximum shivering intensity ≈30%. It seems likely that reduced maximum shivering intensity resulted from a peripheral inhibition of skeletal muscular activity rather than impaired central control. Consistent with this supposition, volatile anesthetics de-

Fig. 5. Power spectral analysis of pectoralis shivering in the ninth volunteer. Data are presented in three dimensions, with the *x* axis showing frequency in Hertz, the *y* axis representing power (in relative units), and the *z* axis showing time in terms of 1-min acquisition series (S1, S2, and so on). The fraction of power between 5 and 14 Hz that was in the 5–7 Hz clonic range was 25% on the control day (*A*) and 48% during isoflurane (*B*). This is not a typical example but was chosen to illustrate the saw-tooth response and the shift to clonic frequencies during isoflurane administration.
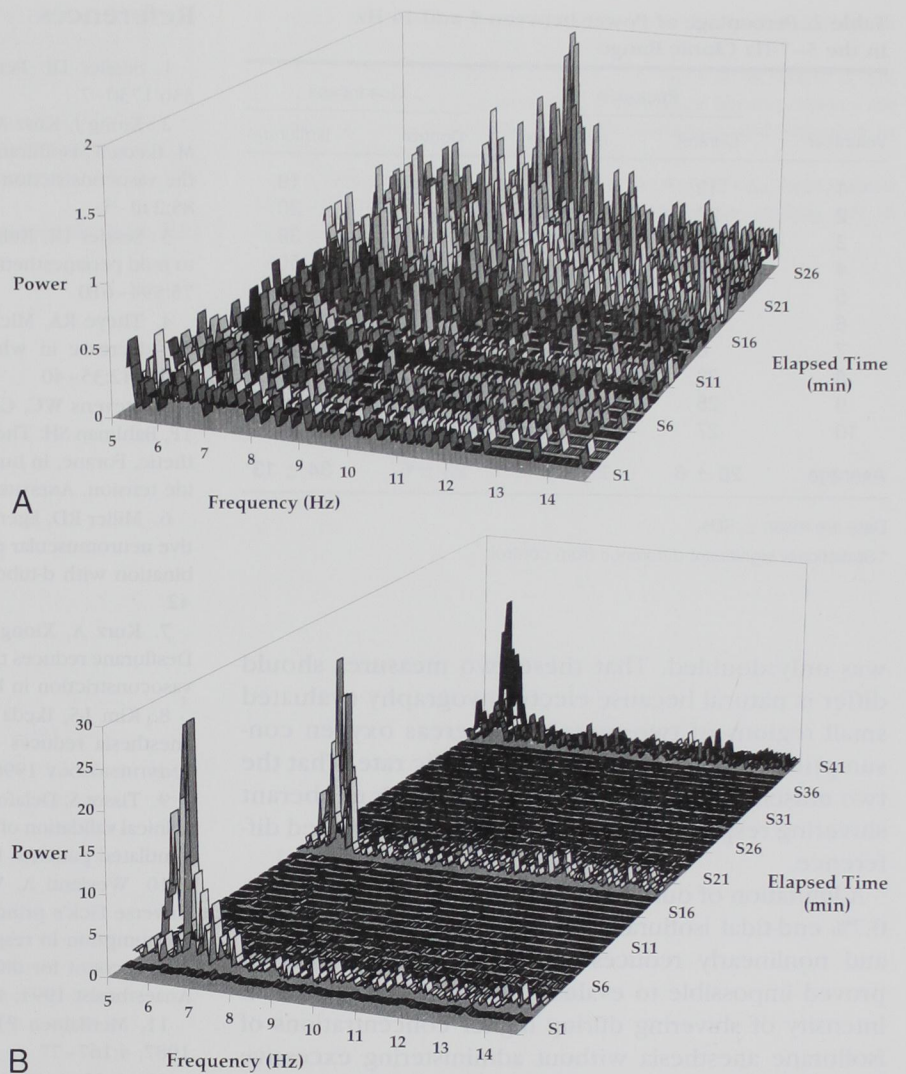
crease systemic oxygen consumption,[4,5] a reduction that is largely restricted to nonsplancnic tissues.[21] Volatile anesthetics also inhibit skeletal muscle strength *in vitro*.[6]

The observed shivering threshold was 34.2°C in volunteers given 0.7% isoflurane. After adjustment for differences in mean skin temperature,[22] this value was ≈1°C lower than observed previously.[2] A lower threshold may, in part, be explained by differing models: central *versus* cutaneous cooling. However, the dose–response curve for thermoregulatory inhibition by isoflurane is remarkably steep in this concentration range. Consequently, the entire discrepancy could be explained by the end-tidal isoflurane concentration differing only 0.1% in the two studies.

The shivering threshold in humans is slightly reduced by inspiration of 4% carbon dioxide.[23] The effect of hypercapnia on the gain of shivering remains unknown. End-tidal carbon dioxide pressure in our volunteers was significantly higher when isoflurane (43 ± 2 mmHg) was administered than on the control day (40±4 mmHg). However, all these values were within the normal clinical range and were thus unlikely to have much influenced the observed thermoregulatory responses.

The gain of shivering, as determined by oxygen consumption and electromyographic activity, was significantly increased by isoflurane. However, electromyographic gain was increased by a factor of five, whereas gain determined by oxygen consumption

Table 2. Percentage of Power between 5 and 14 Hz in the 5–7-Hz Clonic Range

	Pectoralis		Quadriceps	
Volunteer	Control	Isoflurane	Control	Isoflurane
1	19	20	31	19
2	22	22	28	30
3	26	20	22	39
4	14	28	22	50
5	20	27	30	34
6	19	29	13	11
7	8	29	14	37
8	22	41	22	32
9	25	48	23	56
10	27	26	23	35
Average	20 ± 6	29 ± 9*	23 ± 6	34 ± 13*

Data are mean ± SDs.

* Statistically significant difference from control.

was only doubled. That these two measures should differ is natural because electromyography evaluated small regions of two muscles, whereas oxygen consumption estimated systemic metabolic rate. That the two muscles were chosen because of their exuberant shivering response only compounds the observed difference.

A limitation of our protocol is that we examined only 0.7% end-tidal isoflurane. Because isoflurane markedly and nonlinearly reduces the shivering threshold,[2] it proved impossible to evaluate the gain and maximum intensity of shivering during higher concentrations of isoflurane anesthesia without administering excessive amounts of fluid or inducing unacceptable hypothermia. Conversely, the volunteers failed to tolerate endotracheal intubation at lower concentrations of isoflurane anesthesia. Tracheal intubation was necessary, because it proved impossible to maintain an adequate mask seal to accurately record oxygen consumption during intense shivering.

In conclusion, isoflurane decreased the shivering threshold and the maximum intensity of shivering but increased the initial gain of shivering. Shivering during isoflurane anesthesia was associated with a significant increase in electromyographic power in frequencies associated with clonus. These results suggest that clonic activity combines with shivering to increase the gain of shivering, whereas isoflurane peripherally inhibits maximum expression of this thermoregulatory defense.

References

1. Sessler DI: Perioperative hypothermia. N Engl J Med 1997; 336:1730–7

2. Xiong J, Kurz A, Sessler DI, Plattner O, Christensen R, Dechert M, Ikeda T: Isoflurane produces marked and non-linear decreases in the vasoconstriction and shivering thresholds. ANESTHESIOLOGY 1996; 85:240–5

3. Sessler DI, Rubinstein EH, Moayeri A: Physiological responses to mild perianesthetic hypothermia in humans. ANESTHESIOLOGY 1991; 75:594–610

4. Theye RA, Michenfelder JD: Individual organ contributions to the decrease in whole-body VO_2 with isoflurane. ANESTHESIOLOGY 1975; 42:35–40

5. Stevens WC, Cromwell TH, Halsey MJ, Eger EI II, Shakespeare TF, Bahlman SH: The cardiovascular effects of a new inhalation anesthetic, Forane, in human volunteers at constant arterial carbon dioxide tension. ANESTHESIOLOGY 1971; 35:8–16

6. Miller RD, Eger EI, Way WL, Stevens WC, Dolan WM: Comparative neuromuscular effects of forane and halothane alone and in combination with d-tubocurarine in man. ANESTHESIOLOGY 1971; 35:38–42

7. Kurz A, Xiong J, Sessler DI, Dechert M, Noyes K, Belani K: Desflurane reduces the gain of thermoregulatory arterio-venous shunt vasoconstriction in humans. ANESTHESIOLOGY 1995; 83:1212–9

8. Kim J-S, Ikeda T, Sessler DI, Turakhia M, Jeffrey R: Epidural anesthesia reduces the gain and maximum intensity of shivering. ANESTHESIOLOGY 1998; 88:851–7

9. Tissot S, Delafosse B, Bertrand O, Bouffard Y, Viale JP, Annat G: Clinical validation of the Deltatrac monitoring system in mechanically ventilated patients. Intensive Care Med 1995; 21:149–53

10. Weyland A, Weyland W, Sydow M, Weyland C, Kettler D: [Inverse Fick's principle in comparison to measurements of oxygen consumption in respiratory gases. Does intrapulmonary oxygen uptake account for differences shown by different system methods?]. Anaesthesist 1994; 43:658–66

11. Merilainen PT: Metabolic monitor. Int J Clin Monit Comput 1987; 4:167–77

12. Aukburg SJ, Geer RT, Wollman H, Neufeld GR: Errors in measurement of oxygen uptake due to anesthetic gases. ANESTHESIOLOGY 1985; 62:54–9

13. Stiles RN: Reciprocal innervation: Phase analysis of demodulated EMGs from antagonistic muscles. J Appl Physiol 1973; 34:294–8

14. Fox JR, Randall JE: Relationship between forearm tremor and the biceps electromyogram. J Appl Physiol 1970; 29:103–8

15. Rosenberg H, Clofine R, Bialik O: Neurologic changes during awakening from anesthesia. ANESTHESIOLOGY 1981; 54:125–30

16. Passias TC, Mekjavic IB, Eiken O: The effect of 30% nitrous oxide on thermoregulatory responses in humans during hypothermia. ANESTHESIOLOGY 1992; 76:550–9

17. Ikeda T, Sessler DI, Tayefeh F, Negishi C, Turakhia M, Marder D, Bjorksten AR, Larson MD: Meperidine and alftentanil do not reduce the gain or maximum intensity of shivering. ANESTHESIOLOGY 1998; 88:858–65

18. Israel DJ, Pozos RS: Synchronized slow-amplitude modulations in the electromyograms of shivering muscles. J Appl Physiol 1989; 66:2358–63

19. Washington D, Sessler DI, Moayeri A, Merrifield B, Prager M, McGuire J, Belani K, Hudson S, Schroeder M: Thermoregulatory responses to hyperthermia during isoflurane anesthesia in humans. J Appl Physiol 1993; 74:82-7

20. Sessler DI, Hynson J, McGuire J, Moayeri A, Heier T: Thermoregulatory vasoconstriction during isoflurane anesthesia minimally decreases heat loss. ANESTHESIOLOGY 1992; 76: 670-5

21. Sellden E, Branstrom R, Brundin T: Augmented thermic effect of amino acids under general anaesthesia occurs predominantly in extra-splanchnic tissues. Clin Sci 1996; 91:431-9

22. Cheng C, Matsukawa T, Sessler DI, Kurz A, Merrifield B, Lin H, Olofsson P: Increasing mean skin temperature linearly reduces the core-temperature thresholds for vasoconstriction and shivering in humans. ANESTHESIOLOGY 1995; 82:1160-8

23. Johnston CE, Elias DA, Ready AE, Giesbrecht GG: Hypercapnia lowers the shivering threshold and increases core cooling rate in humans. Aviat Space Environ Med 1996; 67:438-44