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Isoflurane Produces Marked and Nonlinear Decreases in the Vasoconstriction and Shivering Thresholds

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Background: **Desflurane decreases the vasoconstriction and shivering thresholds disproportionately at high anesthetic concentrations. This result contrasts with the authors' previous report that isoflurane decreases the vasoconstriction threshold linearly. It is surprising that the basic shape of the concentration-response curve should differ with these two otherwise similar anesthetics. Therefore, the hypothesis that isoflurane produces a nonlinear reduction in the vasoconstriction threshold was tested. Because the effect of isoflurane on shivering remains unknown, the extent to which isoflurane reduces the shivering threshold also was determined.**

Methods: **Eight men volunteered to be studied on four randomly ordered days: (1) a target end-tidal isoflurane concentration of 0.55%, (2) a target concentration of 0.7%, (3) control (no anesthesia) and a target end-tidal concentration of 0.85%, and (4) a target end-tidal concentration of 1.0%. Volunteers were surface-cooled until peripheral vasoconstriction and shivering were observed. We arithmetically compensated for changes in skin temperature using the established linear cutaneous contributions to control for each response. From the calculated thresholds (core temperatures triggering responses at a designated skin temperature of 34°C), the concentration–response relation was determined.**

Results: **Isoflurane administration produced a dose-dependent reduction in the vasoconstriction and shivering thresholds, decreasing each ≈4.6°C at an end-tidal concentration of 1%. Residual analysis indicated that the vasoconstriction and shivering thresholds were decreased in a nonlinear fashion during isoflurane administration. The vasoconstriction-to-shivering range was 1.5 ± 0.8°C without isoflurane, and did not change significantly during isoflurane administration.**

Conclusions: **The vasoconstriction-to-shivering range remained unchanged by isoflurane administration. In this regard, the effects of isoflurane are similar to those of desflurane, propofol, and alfentanil. The current data differ from the authors' previous report, in that the dose-dependence for vasoconstriction was nonlinear, with isoflurane reducing the threshold disproportionately at higher anesthetic concentrations. Differing dose-dependence in the two studies may result either because the current study's volunteers were not exposed to surgical stimulation and were given less isoflurane, or because of design limitations in the previous protocol. (Key words: Anesthetics: volatile, isoflurane. Thermoregulation: shivering; temperature; vasoconstriction.)**

SEDATIVES and general anesthetics, with the exception of midazolam,[1] markedly impair thermoregulatory control. For example, the sweating threshold (triggering core temperature) is linearly increased by propofol,[2] alfentanil,[3] isoflurane,[4] and desflurane.[5] Reduction of the vasoconstriction and shivering thresholds also is a linear function of propofol[2] and alfentanil[3] concentrations. Desflurane, however, produces a nonlinear reduction in the major cold-response thresholds, reducing the vasoconstriction and shivering thresholds disproportionately at higher anesthetic concentrations.[5] This result contrasts with our previous report that isoflurane decreases the vasoconstriction threshold linearly.[6]

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Although it is not surprising that the magnitude of thermoregulatory inhibition should differ during desflurane and isoflurane administration, it is surprising that the basic shape of the concentration-response curve should differ with these two otherwise similar anesthetics. The desflurane data were accumulated using a carefully controlled, crossover design in volunteers.[5] In contrast, the isoflurane data were derived from an essentially uncontrolled clinical study.[6] We therefore tested the hypothesis that, contrary to our previous report, isoflurane produces a nonlinear reduction in the vasoconstriction threshold. Because the effect of isoflurane on shivering remains unknown, we took this opportunity to simultaneously determine the extent to which isoflurane reduces the shivering threshold.

Methods

With approval of the Committee on Human Research at the University of California, San Francisco, we studied eight male volunteers having the following morphometric characteristics: age 28 ± 5 yr; height 174 ± 7 cm; and weight 66 ± 8 kg. None was obese, was taking medication, or had a history of thyroid disease, dysautonomia, or Raynaud's syndrome.

Treatment Protocol

Volunteers were each evaluated on four days: (1) a target end-tidal isoflurane concentration of 0.55%, (2) a target concentration of 0.70%. (3) control (no anesthesia) and a target end-tidal concentration of 0.85%, and (4) a target end-tidal concentration of 1.00%. Thresholds were thus determined without anesthesia and at an isoflurane concentration of 0.85% on a single day. We were able to combine the two determinations and still retain good circadian control because vasoconstriction and shivering were easy to obtain without anesthesia. The treatment order was randomly assigned and at least two days were allowed between each study day. All studies were conducted in the spring of 1995.

Volunteers fasted 8 h before arriving at the laboratory, were minimally clothed, and rested supine in a 22–23°C room during the protocol. Studies were scheduled so that thermoregulatory responses in each volunteer were triggered at similar times to minimize circadian fluctuations. A catheter was inserted into a left forearm vein for fluid administration. Lactated Ringer's solution was initially infused at ≈100 ml/h. Throughout the protocol, arms were protected from active warming and cooling to avoid locally mediated vasomotion.[7] However, all other skin below the neck was similarly manipulated.

Anesthesia was induced without any premedication by infusion of propofol (≈2 mg/kg) and incremental concentrations of isoflurane. A bolus of lactated Ringer's solution (≈10 ml/kg) was administered during induction of anesthesia; subsequently, fluid was again administered at a rate of ≈100 ml/h. The volunteers breathed spontaneously, either *via* a face mask or laryngeal mask; however, ventilation was assisted when necessary to maintain end-tidal P_{CO_2} near 37 mmHg.

We took care throughout the protocol to minimally stimulate the volunteers. For example, ambient lighting was dimmed and extraneous noise was avoided. Skin temperature changes were restricted to ≤3°C/h because this rate is unlikely to trigger dynamic thermoregulatory responses.[8] And finally, we handled the face mask gently and avoided moving the volunteers during anesthetic administration.

Skin and core temperatures were gradually decreased, using a circulating-water mattress and forced-air cooler until significant vasoconstriction was achieved.[9] The thermoregulatory study ended each day when shivering was detected, but the volunteers subsequently participated in a brief study evaluating the effects of alfentanil administration on pupillary responses (unpublished data).

Measurements

Core temperature was recorded from the tympanic membrane (Mallinckrodt Anesthesiology Products, St. Louis, MO). Tympanic membrane temperature and distal esophageal temperatures correlate well under the circumstances of this study.[6] Mean skin-surface temperature and cutaneous heat transfer were calculated from measurements at 15 area-weighted sites.[10,11] Temperatures were recorded at 1-min intervals from thermocouples connected to Iso-Thermex thermometers having an accuracy of 0.1°C (Columbus Instruments, Columbus, OH).

Absolute right middle fingertip blood flow was quantified using venous occlusion volume plethysmography at 5-min intervals.[12] A sustained decrease in fingertip blood flow to <1.0 ml/min identified the beginning of vasoconstriction. Heart rate and blood pressure were determined oscillometrically at 5-min intervals (Modulus CD, Ohmeda, Salt Lake City, UT). End-tidal isoflurane and P_{CO_2} were measured using an Ohmeda Rascal monitor.

Table 1. Environmental and Anesthetic Data

	Target Isoflurane				
	0%	0.55%	0.70%	0.85%	1.0%
End-tidal isoflurane (%)	—	0.56 ± 0.01	0.72 ± 0.02	0.86 ± 0.02	1.02 ± 0.02
Ambient temperature (°C)	23.4 ± 0.5	23.1 ± 0.6	23.5 ± 0.8	23.3 ± 0.9	23.5 ± 0.7
Mean arterial blood pressure (mmHg)	89 ± 5	79 ± 6	76 ± 4	77 ± 5	75 ± 5
Heart rate (beats/min)	59 ± 6	61 ± 7	64 ± 8	58 ± 7	65 ± 12
End-tidal P_{CO_2} (mmHg)	—	37 ± 3	37 ± 3	37 ± 3	36 ± 1

All isoflurane concentrations and blood pressures differed significantly from the 0% target concentration. There were no other statistically significant differences. Results are presented as mean ± SD.

Electromyographic activity was used to quantify shivering. After mild skin abrasion and degreasing, silver/silver chloride monitoring electrodes were positioned to record the electrical activity of the right pectoralis and rectus abdominis, and the quadriceps bilaterally. The active electrodes were positioned 4 cm apart and oriented in the direction of the muscle fibers.[13] After appropriate amplification (Model P511, Grass Instruments, Quincy, MA), the signals were recorded on a thermoelectric printer having a linear resolution to 1,000 Hz (Dash-4, Astro-Med, West Warwick, RI). Onset of shivering was subsequently determined by an investigator blinded to treatment and core temperature: synchronous waxing-and-waning activity sustained for 5 min identified significant shivering.[14]

Data Analysis

Hemodynamic responses, ambient temperature, and end-tidal isoflurane and P_{CO_2} on each study day were first averaged within each volunteer, the resulting values were then averaged among volunteers. Results for each study day were compared using repeated-measures analysis of variance and Dunnett's tests for comparison to control (0% isoflurane).

The cutaneous contribution to vasoconstriction and shivering is linear.[15] We thus used measured skin and core temperatures in degrees centigrade at each threshold to calculate the core-temperature threshold that would have been observed had skin been maintained at a single designated temperature:

$$T_{core(calculated)} = T_{core} + \left(\frac{\beta}{1-\beta}\right)[T_{skin} - T_{skin(designated)}], \quad (1)$$

where the fractional contribution of mean skin temperature to the threshold was termed β. $T_{core(calculated)}$ thus equals the measured core temperature, T_{core}, plus a small correction factor consisting of $\beta/(1-\beta)$ multiplied by the difference between actual (T_{skin}) and designated [$T_{skin(designated)}$] skin temperatures. We have previously described the derivation, validation, and limitations of this equation.[2] We used a β of 0.2 for vasoconstriction and shivering.[15] The designated skin temperature was set at 34°C, a typical intraoperative value.

Response thresholds, the vasoconstriction-to-shivering range (difference between the vasoconstriction and shivering thresholds), hemodynamic, and respiratory data were compared using repeated-measures analysis of variance and Dunnett's test for comparison to control. First-order regression and residual analysis were used to evaluate linearity of the threshold dose-dependence. Results are presented as mean ± SD; $P < 0.05$ was considered statistically significant.

Results

There were no statistically significant or clinically important differences in ambient temperature, relative humidity, heart rate, or end-tidal P_{CO_2} on the five study days. Mean arterial blood pressure was reduced during isoflurane administration, but the decrease was not clinically important (table 1).

Isoflurane administration produced a dose-dependent reduction in the vasoconstriction and shivering thresholds, decreasing each ≈4.6°C at an end-tidal concentration of 1%. The vasoconstriction-to-shivering range was 1.5 ± 0.8°C without isoflurane, and did not change significantly during isoflurane administration (fig. 1 and table 2). Residual analysis indicated that the vasoconstriction and shivering thresholds decreased nonlinearly during isoflurane administration (fig. 2).

Table 2. Mean Skin Temperatures, Core Temperatures, Calculated Thresholds (at a Designated Mean Skin Temperature of 34°C), and the Vasoconstriction-to-Shivering Range

	Target Isoflurane Concentration				
	0%	0.55%	0.7%	0.85%	1.0%
Vasoconstriction					
Mean skin (°C)	35.3 ± 0.7	33.7 ± 0.6	32.9 ± 1	31.7 ± 1.1	29.5 ± 1.6
Core (°C)	37.0 ± 0.2	36.4 ± 0.2	35.9 ± 0.5	35.1 ± 0.7	33.6 ± 0.8
Threshold (°C)	37.3 ± 0.4	36.3 ± 0.3	35.7 ± 0.7	34.5 ± 0.9	32.5 ± 1.2
Shivering					
Mean skin (°C)	30.9 ± 1.4	31.2 ± 0.7	29.6 ± 1.5	28.8 ± 1.2	27.4 ± 1.5
Core (°C)	36.6 ± 0.5	36.0 ± 0.3	35.5 ± 0.8	34.6 ± 0.7	33.0 ± 0.8
Threshold (°C)	35.8 ± 0.8	35.3 ± 0.4	34.4 ± 1.0	33.3 ± 1.0	31.4 ± 1.0
Constriction-to-shivering (°C)	1.5 ± 0.8	1.0 ± 0.3	1.3 ± 0.5	1.2 ± 0.4	1.3 ± 0.7

All thresholds differed significantly from control and from each other. The vasoconstriction-to-shivering ranges did not differ significantly. Results are presented as mean ± SD.

Discussion

The normal vasoconstriction-to-shivering range (difference between the vasoconstriction and shivering thresholds) is ≈1°C.[8] Propofol,[2] desflurane,[5] alfentanil,[3] and clonidine[16] each reduce the vasoconstriction and shivering thresholds comparably. That is, the vasoconstriction-to-shivering range remains normal, although both thresholds are reduced by drug administration. Isoflurane, like the other sedatives and general anesthetics, reduced the vasoconstriction and shivering thresholds comparably. These data suggest that the major cold-defenses are similarly integrated and generally respond synchronously. The only apparent exception to this rule is meperidine, which reduces the shivering threshold twice as much as the vasoconstriction threshold.[17] This special antishivering activity of meperidine[18,19] may be mediated at the level of the spinal cord by the drug's κ-agonist activity.[20]

Isoflurane produced a nonlinear reduction in the vasoconstriction threshold, a result contrasting with with that of our previous report.[6] We must therefore ask why the results from these two investigations are divergent. The major reason appears to be that the methods in the two studies differed significantly in terms of thermoregulatory sophistication and control of potentially confounding factors.

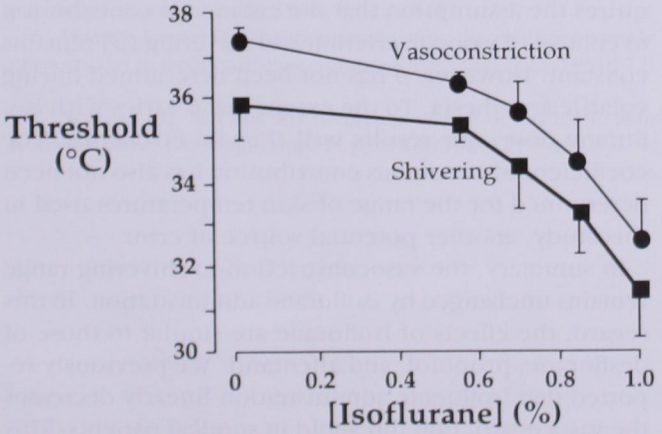

Fig. 1. Isoflurane produced a nonlinear reduction in the major cold-response thresholds, reducing the vasoconstriction and shivering thresholds disproportionately at higher anesthetic concentrations. Results are presented as means ± SD.

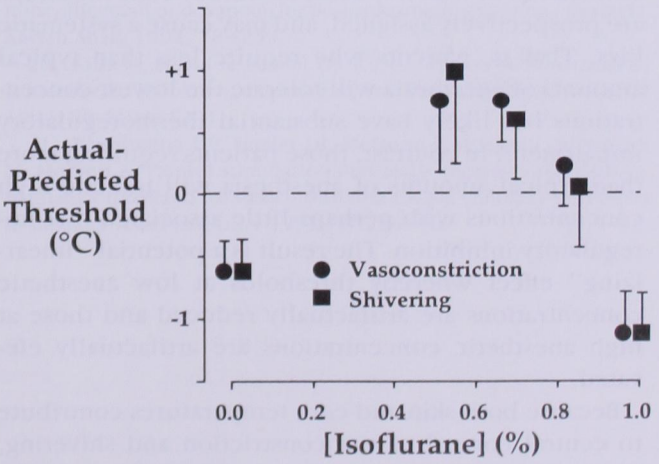

Fig. 2. The difference between actual thresholds and those predicted by individual linear regressions (residuals) are plotted against end-tidal isoflurane concentration. Error bars indicate 95% confidence intervals. That most of the confidence intervals do not cross the 0°C line indicates that dose-dependence of the thresholds is nonlinear.

An important difference between our current and previous evaluations of the vasoconstriction threshold during isoflurane anesthesia is that the original study was conducted in patients during surgery. Surgical stimulation almost inevitably confounds intraoperative studies. Painful stimulation during 0.8 minimum alveolar concentration enflurane anesthesia increases the vasoconstriction threshold,[21] although the dose-dependence of this effect has yet to be established. In addition, we have noticed that even mild stimulation, such as adjusting a face mask, can trigger vasoconstriction at very low anesthetic concentrations. Therefore, it seems likely that the confounding effect of painful stimulation is itself nonlinear. To the extent that this proves true, dose-response curves developed in volunteers should be extrapolated to surgical patients with caution.

An additional difference is that the current study evaluated relatively low isoflurane concentrations whereas most patients in our previous investigation were given higher concentrations. Isoflurane concentrations $\leq 1\%$ were used in the current protocol because it would have been difficult to determine the shivering thresholds at higher concentrations. A consequence of this design, however, is that the two studies evaluate somewhat different aspects of the dose-response curve.

Patients in our previous study[6] were randomly assigned to the highest or lowest isoflurane concentrations they could tolerate while maintaining adequate blood pressures. This scheme differs from a full randomization in which specific isoflurane concentrations are prospectively assigned, and may cause a systematic bias. That is, patients who require less than typical amounts of anesthesia will tolerate the lowest concentrations but likely have substantial thermoregulatory impairment. In contrast, those patients requiring more than typical amounts of anesthesia will tolerate high concentrations with perhaps little associated thermoregulatory inhibition. The result is a potential "linearizing" effect whereby thresholds at low anesthetic concentrations are artifactually reduced and those at high anesthetic concentrations are artifactually elevated.

Because both skin and core temperatures contribute to central control of vasoconstriction and shivering, thermoregulatory response thresholds would ideally be determined at a given mean skin temperature. At the time of our original study,[6] minimally invasive human methods for keeping sentient skin temperature constant while significantly varying core temperature did not exist. Consequently, we recorded mean skin temperature, but simply considered the vasoconstriction threshold to be the core temperature triggering vasoconstriction. Even now, no method has been developed that allows skin temperature to be maintained over a range of core temperatures sufficient to test isoflurane concentrations between 0 and 1%. However, the contribution of skin temperature to central control was recently shown to be $\approx 20\%$ in humans.[8] Using this value (and equation 1) allows us to compensate for changes in skin temperature and report thresholds at a constant skin temperature.

The thresholds we currently report were corrected for skin temperature using a designated value of 34°C. When we applied a similar compensation to our previous data, it had virtually no effect at low anesthetic concentrations because measured skin temperatures were near 34°C. However, calculated thresholds were ≈ 0.5°C less than observed core temperatures at the higher anesthetic concentrations because skin temperatures in these patients was 2–3°C less than 34°C. Failure to correct for the effects of skin temperature on thermoregulatory control thus produced a distinct linearizing bias: thresholds at low anesthetic concentrations were unchanged, but those at the highest concentrations were artifactually increased (compared with corrected values). These results emphasize the importance of controlling skin temperature during thermoregulatory protocols, or of compensating for experimentally induced changes when control is not possible.

Conversely, our method of calculating core temperature thresholds at designated skin temperature requires the assumption that the cutaneous contribution to control of vasoconstriction and shivering (β) remains constant. However, β has not been determined during volatile anesthesia. To the extent that β varies with isoflurane dose, our results will thus be erroneous. The coefficient of cutaneous contribution has also not been determined for the range of skin temperatures used in this study, another potential source of error.

In summary, the vasoconstriction-to-shivering range remains unchanged by isoflurane administration. In this regard, the effects of isoflurane are similar to those of desflurane, propofol, and alfentanil. We previously reported that isoflurane administration linearly decreases the vasoconstriction threshold in surgical patients. This study was only the third specifically quantifying thermoregulatory response thresholds during anesthesia, and showed that isoflurane—like halothane and nitrous

oxide/fentanyl—markedly reduces the core temperature triggering autonomic cold defenses. Our current data, however, indicate that the dose-dependence for vasoconstriction is nonlinear, with isoflurane reducing the threshold disproportionately at higher anesthetic concentrations. Differing dose-dependence in the two studies may result from nonlinear enhancement of thermoregulatory responses by surgical stimulation. However, differences more likely result from limitations of the previous study design, including a suboptimal randomization scheme and failure to correct for the effects of skin temperature on central thermoregulatory control.

Mallinckrodt Anesthesiology Products (St. Louis, MO) donated the thermocouples used in the study.

References

1. Kurz A, Sessler DI, Annadata R, Dechert M, Christensen R: Midazolam minimally impairs thermoregulatory control. Anesth Analg 1995; 81:393–8

2. Matsukawa T, Kurz A, Sessler DI, Bjorksten AR, Merrifield B, Cheng C: Propofol linearly reduces the vasoconstriction and shivering thresholds. ANESTHESIOLOGY 1995; 82:1169–80

3. Kurz A, Go JC, Sessler DI, Kaer K, Larson M, Bjorksten AR: Alfentanil slightly increases the sweating threshold and markedly reduces the vasoconstriction and shivering thresholds. ANESTHESIOLOGY 1995; 82:293–9

4. 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

5. Annadata RS, Sessler DI, Tayefeh F, Kurz A, Dechert M: Desflurane slightly increases the sweating threshold, but produces marked and non-linear decreases in the vasoconstriction and shivering thresholds. ANESTHESIOLOGY 1995; 83:1205–11

6. Støen R, Sessler DI: The thermoregulatory threshold is inversely proportional to isoflurane concentration. ANESTHESIOLOGY 1990; 72: 822–7

7. Wurster RD, McCook RD: Influence of rate of change in skin temperature on sweating. J Appl Physiol 1969; 27:237–40

8. Lopez M, Sessler DI, Walter K, Emerick T, Ozaki M: Rate and gender dependence of the sweating, vasoconstriction, and shivering thresholds in humans. ANESTHESIOLOGY 1994; 80:780–8

9. Kurz A, Sessler DI, Birnbauer F, Illievich U, Spiss C: Thermoregulatory vasoconstriction impairs active core cooling. ANESTHESIOLOGY 1995; 82:870–6

10. Sessler DI, McGuire J, Moayeri A, Hynson J: Isoflurane-induced vasodilation minimally increases cutaneous heat loss. ANESTHESIOLOGY 1991; 74:226–32

11. Matsukawa T, Sessler DI, Sessler AM, Schroeder M, Ozaki M, Kurz A, Cheng C: Heat flow and distribution during induction of general anesthesia. ANESTHESIOLOGY 1995; 82:662–73

12. Rubinstein EH, Sessler DI: Skin-surface temperature gradients correlate with fingertip blood flow in humans. ANESTHESIOLOGY 1990; 73:541–5

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

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

15. 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 thresholds in humans. ANESTHESIOLOGY 1995; 82:1160–8

16. Delaunay L, Bonnet F, Liu N, Beydon L, Catoire P, Sessler DI: Clonidine comparably decreases the thermoregulatory thresholds for vasoconstriction and shivering in humans. ANESTHESIOLOGY 1993; 79: 470–4

17. Kurz A, Sessler DI, Annadata R, Larson M, Bjorksten A, Dechert M, Christensen R: Meperidine slightly increases the sweating threshold, but markedly decreases the vasoconstriction and shivering thresholds (abstract). ANESTHESIOLOGY 1995; 83:A169

18. Guffin A, Girard D, Kaplan JA: Shivering following cardiac surgery: Hemodynamic changes and reversal. J Cardiothorac Vasc Anesth 1987; 1:24–8

19. Lyons B, Carroll M, McDonald N: A randomized trial of pethidine, alfentanil or doxapram for post-anaesthetic shivering (abstract). Anesth Analg 1994; 78:S259

20. Kurz M, Belani K, Sessler DI, Kurz A, Larson M, Blanchard D, Schroeder M: Naloxone, meperidine, and shivering. ANESTHESIOLOGY 1993; 79:1193–1201

21. Washington DE, Sessler DI, McGuire J, Hynson J, Schroeder M, Moayeri A: Painful stimulation minimally increases the thermoregulatory threshold for vasoconstriction during enflurane anesthesia in humans. ANESTHESIOLOGY 1992; 77:286–90