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# *Desflurane Slightly Increases the Sweating Threshold but Produces Marked, Nonlinear Decreases in the Vasoconstriction and Shivering Thresholds*

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***Background:*** **Shivering is rare during general anesthesia. This observation suggests that anesthetics profoundly impair shivering. However, the effects of surgical doses of volatile anesthetics on control of shivering have yet to be evaluated. Furthermore, the effects of desflurane on sweating and thermoregulatory vasoconstriction remain unknown. Accordingly, the authors determined the concentration-dependent effects of desflurane on sweating, vasoconstriction, and shivering.**

***Methods:*** **Nine volunteers each were studied on three randomly ordered days: (1) control (no anesthesia); (2) a target end-tidal desflurane concentration of 0.5 minimum alveolar concentration (MAC; 3.5%); and (3) a target concentration of 0.8 MAC (5.6%). Each day, volunteers were warmed until sweating was induced and subsequently cooled until peripheral vasoconstriction and shivering was observed. Changes in skin temperature were arithmetically compensated using the established linear cutaneous contributions to control of each response. From the calculated thresholds (core temperatures triggering responses at a designated skin temperature of 34°C), the concentration-response relationship was determined.**

***Results:*** **Desflurane significantly and linearly increased the sweating threshold from 37.1 ± 0.3°C on the control day (mean ± SD), to 37.6 ± 0.4°C at 0.5 MAC, and to 38.1 ± 0.3°C at 0.8 MAC. Desflurane significantly, but nonlinearly, reduced the vasoconstriction and shivering thresholds. The sweating-to-vasoconstriction (interthreshold) range thus increased from 0.5 ± 0.3°C to 2.3 ± 0.7°C at 0.5 MAC and further to 4.6 ± 2.0°C at 0.8 MAC. The vasoconstriction-to-shivering range (difference between the respective thresholds) remained between 1.1 and 1.5°C on the three study days.**

***Conclusions:*** **The observed linear increase in the sweating threshold was similar in pattern and magnitude to that produced by most general anesthetics. The ≈3°C reduction in the vasoconstriction threshold by 0.8 MAC desflurane was similar to that observed previously during isoflurane and propofol anesthesia. However, the threshold was reduced less than expected at 0.5 MAC, suggesting that the dose-response relationship for vasoconstriction is nonlinear. Shivering was induced without difficulty in this study although the response is rare in surgical patients. It is likely that shivering during general anesthesia is rare because thermoregulatory vasoconstriction usually prevents body temperature from decreasing the required additional 1–1.5°C. (Key words: Anesthetics, volatile: desflurane. Thermoregulation: shivering; sweating; temperature; vasoconstriction.)**

PROPOFOL,[1] alfentanil,[2] and clonidine[3] all produce dose-dependent decreases in the vasoconstriction threshold (core temperature triggering vasoconstriction). Although these drugs produce different amounts of thermoregulatory inhibition, the vasoconstriction and shivering thresholds are comparably reduced in each case. That is, the vasoconstriction-to-shivering range (the difference between the response thresholds) remains essentially unchanged by drug administration. These data thus suggest that the major defenses against cold in humans, vasoconstriction and shivering, are similarly integrated by the central thermoregulatory control system.

In contrast to the thermoregulatory effects of propofol, alfentanil, and clonidine in humans,[1–3] low concentrations of isoflurane and sevoflurane essentially obliterate shivering in rabbits.[4] Furthermore, shivering

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is rarely observed in patients during general anesthesia, even though it is easy to induce intraoperative vasoconstriction.[5,6] Consistent with anesthetic-induced inhibition of shivering, postanesthetic shivering is rare—even in hypothermic subjects—until end-tidal isoflurane concentrations decrease to ≈0.25 minimum alveolar concentration (MAC).[7] These observations suggest that volatile anesthetics impair shivering, perhaps far out of proportion to their effects on vasoconstriction.

The effects of surgical doses of volatile anesthetics on shivering in humans, however, have yet to be determined. It thus remains unknown whether volatile anesthetics—like the intravenous drugs—comparably impair vasoconstriction and shivering, or if they inhibit shivering far more than vasoconstriction. Accordingly, we determined the relative effects of desflurane on vasoconstriction and shivering. Because the effects of desflurane on sweating are also unknown, we simultaneously determined the concentration-dependent effects of desflurane on sweating.

## Methods

With approval of the Committee on Human Research at the University of California, San Francisco, we studied nine male volunteers having these morphometric characteristics: age 29 ± 6 yr; height 172 ± 4 cm; and weight 71 ± 5 kg. None was obese, taking medication, or had a history of thyroid disease, dysautonomia, or Raynaud's syndrome.

Volunteers were each evaluated on 3 days: control (no anesthesia), a target end-tidal desflurane concentration of 0.5 MAC (3.5%), and a target end-tidal desflurane concentration of 0.8 MAC (5.6%). The treatment order was randomly assigned and at least 2 days were allowed between the desflurane days. All studies were conducted in the winter of 1995.

On each day, volunteers were warmed until sweating was observed and then gradually cooled until vasoconstriction and shivering occurred. Core-temperature response thresholds were then determined by arithmetically compensating for alterations in skin temperature using previously determined cutaneous contributions to thermoregulatory control.[1]

### *Treatment Protocol*

Studies started at approximately 9:30 AM and the volunteers fasted 8 h before arriving at the laboratory. They were minimally clothed and rested supine in a 22–23°C room during the protocol. Studies were scheduled so that thermoregulatory responses were triggered at similar times each day to minimize circadian fluctuations.

A catheter was inserted in a left forearm vein for fluid administration. Lactated Ringer's solution warmed to 37°C was initially infused at ≈100 ml/h. Throughout the protocol, arms were protected from active warming and cooling to avoid locally mediated vasomotion.[8] However, all other skin below the neck was similarly manipulated.

On appropriate days, anesthesia was induced without any premedication by infusion of propofol (≈5 mg/kg) and incremental concentrations of desflurane. A bolus injection of lactated Ringer's solution warmed to 37°C (≈10 ml/kg) was administered during induction of anesthesia; subsequently, warmed fluid was again administered at a rate of ≈100 ml/h. The volunteers breathed spontaneously *via* a face mask during most the study, but ventilation was assisted when necessary to maintain end-tidal $P_{CO_2}$ near 35 mmHg.

Skin and core temperatures were first increased gradually with a Bair Hugger forced-air warmer (Augustine Medical, Inc., Eden Prairie, MN) and circulating-water mattress (Cincinnati Sub-Zero, Cincinnati, OH) until significant sweating was achieved. Skin and core temperatures were then gradually decreased, using the circulating-water mattress and a prototype forced-air cooler (Augustine Medical, Inc.).[9] The study ended each day when shivering was detected.

Care was taken throughout the protocol to stimulate the volunteers minimally. Ambient lighting, for example, was dimmed and extraneous noise avoided. Temperature changes were restricted to ≤3°C/h because this rate is unlikely to trigger dynamic thermoregulatory responses,[10] and the transition from cutaneous warming to cooling was made gradually. And finally, the face mask was handled gently and movement of the volunteers was avoided during anesthetic administration.

### *Measurements*

Core temperature was recorded from tympanic membrane thermocomplex (donated by Mallinckrodt Anesthesiology Products, Inc., St. Louis, MO). Tympanic membrane temperature and distal esophageal temperatures correlate well under the circumstances of this study.[11] Mean skin surface temperature and cutaneous heat transfer were calculated from measurements at 15

area-weighted sites.[12,13] Temperatures were recorded at 5-min intervals from thermocouples connected to Iso-Thermex thermometers having an accuracy of 0.1°C (Columbus Instruments, Corp., Columbus, OH).

Sweating was continuously quantified on the left upper chest using a ventilated capsule.[14,15] A sustained sweating rate exceeding 40 $g \cdot m^{-2} \cdot h^{-1}$ was considered significant.[1] Absolute right middle fingertip blood flow was quantified using venous occlusion volume plethysmography at 5-min intervals.[16] A sustained decrease in fingertip blood flow to <0.25 ml/min identified significant vasoconstriction.

In previous similar studies, we used systemic oxygen consumption[1,2] or electromyographic activity[17] to quantify shivering. Because the Deltatrac metabolic monitor (SensorMedics Corp., Yorba Linda, CA) is not always reliable in patients ventilating spontaneously *via* a face mask, we chose electromyographic analysis in this study.

After mild skin abrasion and degreasing, silver/silver chloride monitoring electrodes were positioned to record the electrical activity of the right pectoralis and trapezius, and the quadriceps bilaterally. The active electrodes were positioned 4 cm apart and oriented in the direction of the muscle fibers.[7] After appropriate amplification (Model P511, Grass Instruments, Quincy, MA), the signals were recorded on a thermoelectric printer having a linear resolution to 1000 Hz (Dash-4, Astro-Med, Inc., West Warwick, RI). Onset of shivering was determined subsequently by an investigator blinded to treatment and core temperature: sustained, synchronous waxing and waning activity identified significant shivering.[18]

Heart rate and blood pressure were determined oscillometrically at 5-min intervals (Modulus CD, loaned by Ohmeda Inc., Salt Lake City, UT). End-tidal desflurane and $P_{CO_2}$ were measured using a Rascal anesthetic monitor (Ohmeda Inc., Salt Lake City, UT).

### *Data Analysis*

Hemodynamic responses, ambient temperature, and end-tidal desflurane 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.

The cutaneous contribution to sweating[19] and to vasoconstriction and shivering[20] is linear. We thus used measured skin and core temperatures in degrees centigrade at each threshold to estimate 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 $\beta$. $T_{Core(calculated)}$ 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.[1] We used a $\beta$ of 0.1 for sweating[19] and a $\beta$ of 0.2 for vasoconstriction and shivering.[20] The designated skin temperature was set at 34°C, a typical intraoperative value.

Response thresholds, the interthreshold range, and the vasoconstriction-to-shivering range were compared using repeated-measures analysis of variance and Dunnett's test for comparison to control. Linearity of the dose-response relationships for vasoconstriction and shivering were evaluated by comparing the threshold reduction per MAC fraction at 0.5 and 0.8 MAC using paired *t* tests. All results are presented as mean ± SD; $P < 0.05$ was considered statistically significant.

## Results

There were no clinically important differences in ambient temperature, relative humidity, heart rate, or end-tidal $P_{CO_2}$ on the three study days. Mean arterial blood pressure was reduced during desflurane administration, but the decrease was not clinically important (table 1). One volunteer did not show vasoconstriction or shivering during administration of 0.8 MAC desflurane, at minimum core and skin temperatures of 32.7 and 28.7°C, respectively. There were no complications associated with the study.

The interthreshold range was 0.5 ± 0.3°C on the control day, but increased to 2.3 ± 0.7°C with 0.5 MAC, and to 4.6 ± 2.0°C with 0.8 MAC. The vasoconstriction-to-shivering range on the control day was 1.0 ± 0.6°C and increased only slightly during desflurane administration to 1.2 ± 0.8°C with 0.5 MAC, and to 1.5 ± 1.1°C with 0.8 MAC (table 2, fig. 1).The sweating threshold increased linearly as desflurane concentration was augmented. However, 0.5 MAC desflurane pro-

**Table 1. Environmental and Anesthetic Data**

| | Control | 0.5 MAC | 0.8 MAC |
|---|---|---|---|
| End-tidal desfluane (%) | 0 | 3.7 ± 0.5* | 5.4 ± 0.28 |
| Ambient temperature (°C) | 22.0 ± 0.6 | 22.0 ± 0.6 | 22.6 ± 0.3 |
| Mean arterial blood pressure (mmHg) | 91 ± 7 | 82 ± 7* | 79 ± 6* |
| Heart rate (beat/min) | 62 ± 12 | 62 ± 6 | 63 ± 9 |
| End-tidal $P_{CO_2}$ | 36 ± 2 | 38 ± 4 | 39 ± 3 |

Values are mean ± SD.

* Statistically significant difference from control.

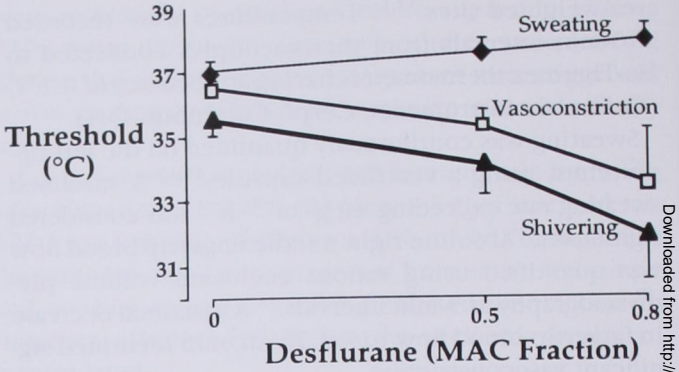


**Fig. 1. The sweating threshold increased linearly, but slightly, during desflurane anesthesia. Desflurane markedly, although nonlinearly, reduced the vasoconstriction threshold. Consequently, the interthreshold range (temperatures not triggering autonomic thermoregulatory defenses) increased enormously during desflurane administration. In contrast, the vasoconstriction-to-shivering range remained essentially unchanged. All thresholds differed significantly from control and from each other.**

duced significantly less relative inhibition of vasoconstriction than 0.8 MAC (2.5 ± 1.1 *vs.* 3.9 ± 2.2°C/MAC, respectively; $P = 0.01$). Desflurane similarly inhibited shivering significantly less at 0.5 than 0.8 MAC (2.8 ± 1.3 *vs.* 4.6 ± 1.3°C/MAC, respectively; $P = 0.01$). Eight of nine vasoconstriction and shivering residuals at 0.5 MAC exceeded zero. The cold-defense thresholds at 0.5 MAC were thus greater than predicted by linear regression, indicating that the concentration-dependence was nonlinear.

## Discussion

The sweating threshold was linearly increased during desflurane anesthesia. The magnitude of this increase, however, was small and similar to that observed previously during isoflurane[14] and propofol[1] administration. Available data thus suggest that general anesthetics usually produce a linear, but slight, increase in the sweating threshold.

Desflurane at 0.8 MAC reduced the vasoconstriction threshold 3.1 ± 1.8°C in volunteers. This inhibition is similar to that produced by a comparable potency of isoflurane in patients (3.9 *vs.* 3.7°C/MAC).[11] The concentration-response relationships are linear for sweating during desflurane and isoflurane[11] anesthesia, as they are for all three major thermoregulatory defenses during propofol anesthesia[1] and alfentanil sedation.[3] However, desflurane at 0.5 MAC produced relatively less inhibition of vasoconstriction than at 0.8 MAC (2.6 *vs.* 3.9°C/MAC), suggesting that the concentration-response relationship for vasoconstriction during desflurane anesthesia may be a nonlinear one. The concentration-dependence was comparably nonlinear for shivering, suggesting that both cold-responses are similarly controlled.

**Table 2. Mean Skin Temperatures, Core Temperatures, and Calculated Thresholds (at at Designated Mean Skin Temperature of 34°C)**

| | | Control | 0.5 MAC | 0.8 MAC |
|---|---|---|---|---|
| Sweating | Mean skin temperature (°C) | 36.3 ± 0.6 | 37.3 ± 0.4 | 37.7 ± 0.4 |
| | Core temperature (°C) | 36.8 ± 0.3 | 37.2 ± 0.3 | 37.7 ± 0.3 |
| | Threshold (°C) | 37.1 ± 0.3 | 37.6 ± 0.4 | 38.1 ± 0.3 |
| Vasoconstriction | Mean skin temperature (°C) | 33.3 ± 0.6 | 31.8 ± 0.7 | 29.3 ± 2.5 |
| | Core temperature (°C) | 36.7 ± 0.2 | 35.8 ± 0.4 | 34.6 ± 1.2 |
| | Threshold (°C) | 36.6 ± 0.2 | 35.3 ± 0.5 | 33.5 ± 1.7 |
| Shivering | Mean skin temperature (°C) | 30.0 ± 0.8 | 28.9 ± 1.4 | 26 ± 2 |
| | Core temperature (°C) | 36.5 ± 0.3 | 35.4 ± 0.7 | 33.9 ± 1.1 |
| | Threshold (°C) | 35.5 ± 0.5 | 34.1 ± 1.0 | 32.0 ± 1.4 |

Values are mean ± SD. All thresholds differed significantly from control and from each other.

The thermoregulatory (and other) effects of volatile anesthetics are more notable for their similarities than differences. Among the volatile anesthetics, the concentration-response relationship for vasoconstriction has been reported only for isoflurane.[11] Although the dose-dependence appeared linear in that investigation, this conclusion was based on an unanesthetized control group and a relatively small number of patients, all of whom were given more than 0.5 MAC. It thus remains possible that volatile anesthetics usually produce proportionally less inhibition of thermoregulatory vasoconstriction at low concentrations than at high ones. This conclusion, however, would mean that the dose-dependence of vasoconstriction and shivering during volatile anesthesia differs distinctly from the linear responses observed during propofol anesthesia[1] and alfentanil sedation.[2]

The relative ease with which shivering was induced in our volunteers contrasts with rare observations in anesthetized patients. Several factors probably combine to make shivering unusual in patients: (1) The core-temperature threshold was ≈32°C at an end-tidal desflurane concentration of 0.8 MAC—a temperature few surgical patients reach. The threshold would be further reduced at the greater concentrations usually used during surgery. (2) The shivering threshold on the control day was ≈1°C less than the vasoconstriction threshold, which is consistent with previous reports.[10] The vasoconstriction-to-shivering threshold remained 1–1.5°C during anesthesia. However, vasoconstriction usually minimizes further core hypothermia[21] by decreasing cutaneous heat loss[22] and constraining metabolic heat to the core thermal compartment.[23] It is thus unlikely that core temperature, in patients becoming sufficiently hypothermic to trigger protective thermoregulatory vasoconstriction, would decrease the additional 1–1.5°C required to initiate shivering.

The propofol concentration in plasma preventing movement in response to skin incision in 50% of patients ($CP_{50}$, MAC analog) is near 8 μg/ml.[24] A previous investigation indicates that 0.8 $CP_{50}$ of propofol (at a skin temperature of 34°C) reduces the vasoconstriction threshold to 32.7°C and the shivering threshold to 31.4°C.[1] These values are only slightly less than the thresholds observed during desflurane anesthesia, suggesting that surgical doses of both anesthetics produce comparable thermoregulatory inhibition. This result is consistent with our impression that the thermoregulatory effects of various general anesthetics are relatively similar.[25] Our conclusion, however, is somewhat confounded by the apparently nonlinear concentration-response relationship for desflurane. Because inhibition was less than expected at 0.5 MAC, propofol reduced the vasoconstriction and shivering thresholds considerably more than desflurane at the same anesthetic level.

In previous investigations of perianesthetic shivering, we used electromyographic analysis to evaluate tremor patterns.[7] Two tremor patterns were identified: (1) a common 4–8 cycle/min "waxing and waning" activity characteristic of normal shivering[18]; and (2) a 5–7-Hz "bursting" activity virtually identical to that produced by pathologic clonus.[7] Both patterns, however, were preceded by core hypothermia and peripheral vasoconstriction, and were thus thermoregulatory. Although a sustained increase in electromyographic activity defined significant shivering threshold in the current investigation, we made no effort to evaluate tremor patterns because each day's study ended soon after shivering was observed.

Our core temperature thresholds were derived by arithmetically compensating for changes in mean skin-surface temperature. Potential difficulties associated with this technique include the assumption that cutaneous contributions to thermoregulatory control remain constant during drug administration, and use of the same cutaneous contribution coefficients ($\beta$) in each volunteer—although the coefficient varies considerably among individuals.[20] There are currently no data evaluating the cutaneous contribution to thermoregulatory control during desflurane anesthesia. Furthermore, even the linearity of the core-to-skin contribution ratio has not been confirmed at skin temperatures from 26°C to 31°C (although the relationship was extremely linear at higher temperatures[20]). However, it is unlikely that such a fundamental factor as the skin-to-core ratio is substantially altered by anesthesia. We demonstrated previously that response thresholds during propofol administration were virtually identical when determined using the current model[1] and a previous one in which sentient skin temperature was kept constant.[26] To the extent that $\beta$ in individuals differ, calculated response thresholds in specific volunteers may be erroneous. Nonetheless, population averages—as reported here—will remain accurate.

Skin temperatures were changed at a rate of ≈3°C/h. We demonstrated previously that changes in core temperature up to 1.7°C/h do not trigger dynamic (*i.e.*, rate-activated) thermoregulatory responses.[10] However,

the rate at which skin temperature can be changed without triggering dynamic responses remains unknown. But given that core temperature contributes 5–10 times as much as skin temperature to thermoregulatory control,[10,19] it seems likely that the relatively slow rates of change used in this study produced steady-state rather than dynamic responses.

It is tempting to compare the thresholds reported here with those in another desflurane study in which mean skin temperature was kept constant.[27] However, results from these two investigations should *not* be compared directly because fingertip temperature was specifically protected from thermal manipulations in the current study, whereas it was maintained at an unusually high level in the other investigation. This difference is critical because high fingertip skin temperature markedly reduces the gain (incremental response intensity, once triggered) of arteriovenous shunt vasoconstriction.[27] Reduced gain artifactually decreases the vasoconstriction threshold, especially when intense vasoconstriction is considered significant, as it is in the current study.

We would have preferred to extend the range of tested desflurane concentrations. However, preliminary studies showed that nonparalyzed volunteers would not tolerate desflurane concentrations less than 0.5 MAC without excessive movement, which would prevent accurate finger flow measurements. These investigations similarly demonstrated that shivering could not be reliably induced at concentrations exceeding 0.8 MAC. (Even at 0.8 MAC, we failed to trigger vasoconstriction and shivering in one volunteer.) Consequently, we were restricted to a minimum desflurane concentration of 0.5 MAC and a maximum concentration of 0.8 MAC. Despite this narrow range, a nonlinearity in the dose-response relationship was readily apparent.

In summary, the observed linear and statistically significant, but slight, increase in the sweating threshold is similar to that produced by most general anesthetics. The $\approx 3^{\circ}C$ reduction in the vasoconstriction threshold by 0.8 MAC desflurane is similar to that observed previously during isoflurane and propofol anesthesia. However, the threshold was reduced less than expected at 0.5 MAC, suggesting that the dose-response relationships for vasoconstriction may be nonlinear. Shivering was induced without difficulty in this study, although the response is rare in surgical patients. It is likely that shivering during general anesthesia is rare because thermoregulatory vasoconstriction usually prevents body temperature from decreasing the required additional 1–1.5°C.

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