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Desflurane Reduces the Gain of Thermoregulatory Arteriovenous Shunt Vasoconstriction in Humans

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Background: **Thermoregulatory responses, such as arteriovenous shunt vasoconstriction, provide substantial protection against core hypothermia. A response can be characterized by its threshold (core temperature triggering response), gain (rate at which response intensity increases, once triggered), and maximum response intensity. Reduced gain decreases the efficacy of a thermoregulatory response at a given threshold because response intensity will increase more slowly than usual. The effects of general anesthesia on the gain of arteriovenous shunt vasoconstriction have not been reported. Accordingly, we tested the hypothesis that desflurane decreases the gain of centrally mediated vasoconstriction.**

Methods: **We studied seven healthy male volunteers. Each was studied twice: (1) desflurane (end-tidal concentration 0.4 minimum alveolar concentration); and (2) control (no anesthesia). Mean skin and fingertip temperatures were controlled at 35.5°C throughout the study. Core temperature was reduced at a rate of 1.5°C/h by central venous infusion of cold fluid. Fingertip arteriovenous shunt flow was measured using venous occlusion volume plethysmography at 1-min intervals. Flow was also evaluated using the perfusion index and laser Doppler flowmetry. Vasoconstriction thresholds were calculated as the core temperatures triggering fingertip flows of 1.0 ml/min (beginning of vasoconstriction) and 0.25 ml/min (intense vasoconstriction). The gain of vasoconstriction was considered to be the slope of the fingertip flow *versus* core temperature regression within the linear range from 1.0 ml/min to 0.15 ml/min. The minimum observed flow was considered maximum vasoconstriction intensity. Data are presented as means ± SD; $P < 0.01$ was considered statistically significant.**

Results: **The vasoconstriction threshold (when defined using a flow of 1.0 ml/min) was reduced from 36.8 ± 0.3°C to 35.6 ± 0.3°C by desflurane anesthesia ($P < 0.01$). Desflurane reduced the gain of vasoconstriction by a factor of three, from 2.4 to 0.8 $ml \cdot min^{-1} \cdot °C^{-1}$ ($P < 0.01$). Gains, as determined by the perfusion index and laser Doppler flowmetry, were likewise reduced ($P < 0.01$). The threshold on the control day was only 0.2 ± 0.1°C less when significant vasoconstriction was defined as a flow of 0.25 ml/min rather than 1.0 ml/min. Because gain was reduced, however, the threshold during desflurane administration was 0.8 ± 0.2°C less when significant vasoconstriction was defined by a flow of 0.25 ml/min. Minimum flows were comparable and near zero with and without anesthesia.**

Conclusions: **The threshold reduction (1.2°C/0.4 minimum alveolar concentration) was similar to that observed previously during isoflurane anesthesia. Similarly, it is established already that maximum vasoconstriction intensity is comparable with and without isoflurane anesthesia. However, the data also indicate that even relatively low desflurane concentrations markedly reduce the gain of vasoconstriction. It is likely that reduced gain (*i.e.*, slow onset of vasoconstriction) contributes to core hypothermia in some surgical patients. (Key words: Temperature: hypothermia. Thermoregulation: threshold; vasoconstriction.)**

THERMOREGULATORY responses can be characterized by their thresholds (core temperatures triggering responses), gains (rates at which response intensities increases, once triggered), and maximum response intensities.[1,2] The effects of general[3–5] and regional[6,7] anesthesia on response thresholds are reasonably well characterized. Similarly, the effects of age,[8,9] painful stimulation,[10,11] gender,[4,12,13] and vascular volume depletion[14] have been described.

Maximum response intensity of vasoconstriction[15] and sweating[4,16] appear reasonably well preserved dur-

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ing general anesthesia. Sweating gain is essentially normal during isoflurane[4] and enflurane[16] anesthesia, although shivering gain may be somewhat reduced during nitrous oxide administration.[17] The effects of general anesthesia on the gains of other thermoregulatory responses, however, have not been reported.

Insufficient gain will decrease the effectiveness of a thermoregulatory response, even at a given threshold, because response intensity will increase more slowly than usual. Reduced gain of thermoregulatory vasoconstriction would be clinically important because vasoconstriction is the primary intraoperative defense against core hypothermia.[18–20] Accordingly, we tested the hypothesis that desflurane decreases the gain of vasoconstriction.

Methods

With approval from the Committee on Human Research at the University of California, San Francisco and written informed consent, we studied seven male volunteers, each on two occasions. None was obese or taking medication, and none had a history of thyroid disease, dysautonomia, Raynaud's syndrome, or malignant hyperthermia. The volunteers' morphometric characteristics included: age 29 ± 6 yr, height 174 ± 2 cm, and weight 78 ± 12 kg.

Protocol

Studies started at approximately 9:30 AM and volunteers fasted during the 8 h preceding each study. Throughout the study, minimally clothed volunteers reclined on an operating room table set in chaise-lounge position.

The volunteers were each studied on two sequential days, once during 0.4 minimum alveolar concentration (MAC; 2.8%) desflurane anesthesia and once without anesthesia. On the first study day, an internal jugular catheter was inserted using echo sonography to locate the vessel and minimize risk of the procedure. Between study days, a small amount of heparin sodium was injected into the tubing, and the catheter was sealed.

On the desflurane day, general anesthesia was induced by administration of 200 mg propofol, 70% nitrous oxide, 0.1 mg/kg vecuronium, and incremental concentrations of desflurane to ≈10%. The volunteers' tracheas were then intubated and anesthesia was maintained with desflurane 0.4 MAC in air/oxygen. The patients' lungs were mechanically ventilated to maintain an end-tidal carbon dioxide partial pressure near 35 mmHg. Additional vecuronium was administered, as necessary, to maintain 1–2 mechanical twitches in response to supramaximal train-of-four stimulation of the ulnar nerve at the wrist. A catheter was inserted into the urinary bladder, and urine output was recorded at 30-min intervals.

Throughout the study period, mean skin and fingertip temperatures were controlled at 35.5°C by adjusting the temperature of circulating-water (Cincinnati Sub-Zero, Cincinnati, OH) and forced-air warmers (Augustine Medical, Inc., Eden Prairie, MN). After confirming that the volunteers' fingertips were vasodilated (see below), lactated Ringer's solution cooled to ≈3°C was infused *via* the central venous catheter at rates sufficient to decrease tympanic membrane temperature ≈1.5°C/h. Fluid was administered as long as fingertip blood flow continued to decrease; the study concluded when further reduction in core temperature no longer decreased finger flow. On the desflurane day only, 10 mg intravenous furosemide was administered when the infusion was started.

Measurements

Core temperature was recorded from the tympanic membrane using Mon-a-Therm thermocouples (donated by Mallinckrodt Anesthesiology Products, Inc., St. Louis, MO). Visual inspection with an otoscope confirmed that the ear canal was free of wax in each volunteer. The aural probe was then inserted by volunteers until they felt the thermocouple touch the tympanic membrane; appropriate placement was confirmed when volunteers easily detected gentle rubbing of the attached wire. The aural canal was occluded with cotton, the probe was securely taped in place, and a gauze bandage was positioned over the external ear. There is an excellent correlation between tympanic membrane and distal esophageal temperatures in the perianesthetic period.[3] Mean skin-surface temperature was determined from 15 area-weighted sites including the right fingertip.[15]

All temperatures were recorded using Mon-a-Therm thermocouples or probes incorporated into thermal flux transducers (Concept Engineering, Old Saybrook, CT), as described previously.[21] Temperatures were recorded from thermocouples connected to calibrated Iso-Thermex 16-channel electronic thermometers having an accuracy of 0.1°C and a precision of 0.01°C (Columbus Instruments International, Corp., Columbus, OH). Individual and mean-skin temperatures were

computed by a data acquisition system, displayed at 1-s intervals, and recorded at 1-min intervals.

Right index fingertip blood flow was quantified using volume plethysmography, as described previously.[22] Vascular tone also was evaluated on the right second finger using the perfusion index, which is derived from absorption of two infrared wave lengths.[23] Finally, fingertip flow was estimated using laser Doppler flowmetry with an integrating multi-probe (Periflux 3, Perimed Inc., Piscataway, NJ, wide-band setting) positioned on the fourth finger of the right hand.[24–26] Laser Doppler flowmetry evaluates both capillary and arteriovenous shunt flow, although the flowmeter we used is most sensitive to capillary flow.[27] All measures of flow were recorded at 1-min intervals.

Data Analysis

Fingertip flows vary constantly because sudomotor waves are superimposed on thermoregulatory shunt tone.[28,29] Additionally, there is some variability introduced by the measurement technique *per se*. Consequently, the raw finger flows from each study day were smoothed using a five-point moving average filter. Perfusion index and laser Doppler data were similarly smoothed.

Thresholds were defined by the core temperatures triggering: (1) a fingertip flow of $\approx$1 ml/min, which corresponds to a forearm minus fingertip skin-temperature gradient near 0°C (mild vasoconstriction); and (2) a fingertip flow of 0.25 ml/min, corresponding to a skin-temperature gradient near 4°C (intense vasoconstriction).[22]

The effect of core cooling on plethysmographic finger blood flow was determined as follows: (1) The core temperatures at flows of 1.0 ml/min on the control and desflurane days were designated thresholds in each subject. (2) Finger flows were then calculated relative to the individual threshold temperatures under each condition. Because flow measurements were taken at specific time intervals rather than fixed temperature intervals, available data from each volunteer within 0.1°C core temperature increments were averaged. Core temperature increments of 0.05°C were occasionally used for steep sections of the flow/temperature response curve. Subsequently, the population means were calculated from these individual averages. (3) Finally, the average flow values for the population were plotted relative to the mean thresholds with and without desflurane.

Inspection of preliminary volume plethysmographic data indicated that finger flows between $\approx$1.0 and 0.15 ml/min were roughly linear functions of core temperature both on the control day and during desflurane administration. Furthermore, these values define the clinically important range from mild to intense vasoconstriction. Gain of vasoconstriction on the control day was thus considered to be the slope of the population flow *versus* core temperature linear regression in the flow range of 1.0–0.15 ml/min. Gain during desflurane administration was calculated using the same temperature range. Gains of vasoconstriction, in terms of the perfusion index and laser Doppler flow, were considered to be the regression slopes over the same respective core temperature ranges.

Fingertip flow at the end of each study day—when further decrease in core temperature no longer reduced finger flow—identified the maximum vasoconstriction intensity. Thresholds and maximum vasoconstriction intensities with and without anesthesia were compared using two-tailed, paired *t* tests. Differences between the thresholds as defined by a finger flow of 1.0 ml/min and 0.25 ml/min were similarly compared using paired *t* tests. And finally, the gains of vasoconstriction with and without desflurane, were compared using *t* tests modified for use with regression slopes. Results are expressed as means ± standard deviations; differences were considered statistically significant when $P < 0.01$.

Results

Mean skin and fingertip temperatures were maintained nearly constant throughout the protocol (fig. 1). End-tidal desflurane concentrations averaged 2.8 ± 0.1% during the study. No volunteer experienced recall of events during administration of desflurane; there were no study-related complications.

Fluid was administered at rates of 35 ± 8 and 39 ± 8 ml/min during the control and desflurane trials, respectively (P = NS). However, more hypothermia was required during desflurane so total administered fluid differed significantly: 1.8 ± 1.2 *versus* 4.2 ± 1.5 l. Urine output was not recorded on the control day; however, urine output was 1.9 ± 0.8 l during desflurane administration.

Desflurane significantly reduced the gain of vasoconstriction as determined by volume plethysmography by a factor of three, from 2.4 to 0.8 $ml \cdot min^{-1} \cdot °C^{-1}$ ($P < 0.01$, fig. 2). Gains, as determined using the per-

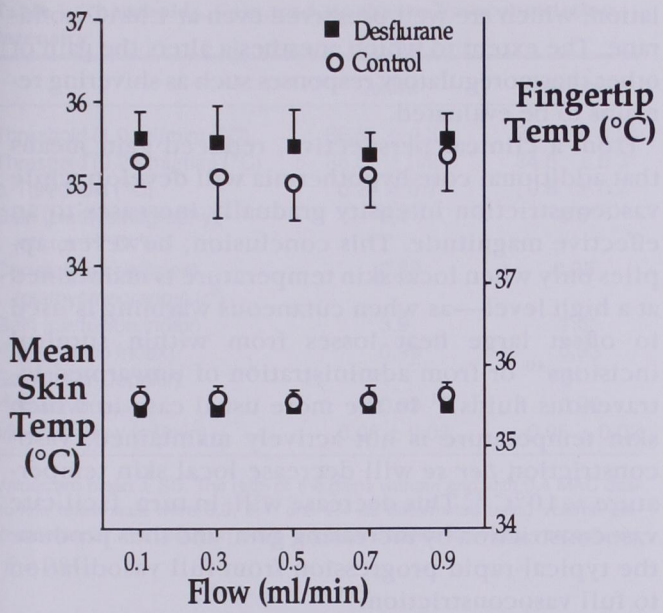

Fig. 1. Because both mean skin and fingertip temperatures influence thermoregulatory response thresholds and gain, both were kept nearly constant throughout the study. Temperatures are plotted against fingertip flow over the relevant range. Results are presented as means ± SD. The standard deviations for mean skin temperature during desflurane administration were less than the size of the markers. Finger temperatures were significantly greater during desflurane administration, but the difference is unlikely to be clinically important.

fusion index and laser Doppler flowmetry, were comparably reduced ($P < 0.01$, figs. 3 and 4).

The vasoconstriction threshold (when defined using a flow of 1.0 ml/min) was significantly reduced from 36.8 ± 0.3°C to 35.6 ± 0.3°C by desflurane anesthesia. The threshold on the control day was only 0.2 ± 0.1°C less when significant vasoconstriction was defined as a flow of 0.25 ml/min rather than 1.0 ml/min. Because gain was reduced, however, the threshold during desflurane administration was 0.8 ± 0.2°C less when significant vasoconstriction was defined as a flow of 0.25 ml/min rather than 1.0 ml/min. Minimum flows were near zero and comparable with and without anesthesia (table 1).

Discussion

Thermoregulatory vasoconstriction is the primary defense against intraoperative core hypothermia. (Shivering is rare during anesthesia and nonshivering thermogenesis is unimportant in anesthetized adults.[30]) Once triggered, vasoconstriction usually prevents further core hypothermia by decreasing cutaneous heat loss[15] and constraining metabolic heat to the core thermal compartment.[18] The clinical importance of this response is illustrated by exaggerated core hypothermia in patients given combined epidural/general anesthesia in whom sympathetic block prevents vasoconstriction in the legs.[19] Similarly, core cooling rates during induction of therapeutic hypothermia are reduced in vasoconstricted patients.[20]

Mean skin-surface temperature contributes ≈10–20% to central control of thermoregulatory defenses.[31,32] However, arteriovenous shunt[33,34] vasoconstriction is also mediated by local skin temperature. Local temperature dominates at low (*i.e.*, <20°C) and high (*i.e.*, >35°C) skin temperatures.[35–37] Although central control dominates at typical skin tempera-

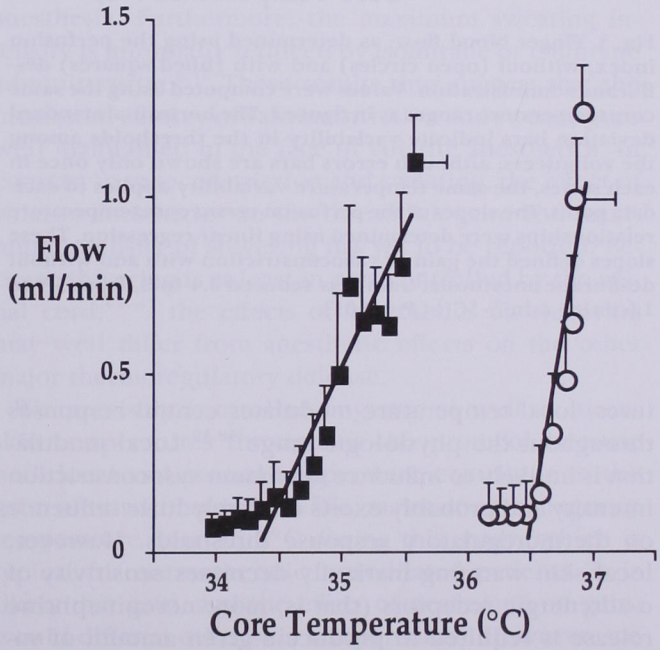

Fig. 2. Finger blood flow, as determined using volume plethysmography, without (open circles) and with (filled squares) desflurane administration. Values were computed relative to the thresholds (finger flow = 1.0 ml/min) in each subject. Flows of exactly 1.0 ml/min are not shown because flows in each person were averaged over 0.1 or 0.05°C increments; each data point thus includes both higher and lower flows. The horizontal standard deviation bars indicate variability in the thresholds among the volunteers; although errors bars are shown only at a flow near 1.0 ml/min, the same temperature variability applies to each data point. The slopes of the flow *versus* core temperature relationships (1.0 to ≈0.15 ml/min) were determined using linear regression. These slopes defined the gain of vasoconstriction with and without desflurane anesthesia. Gain was reduced by a factor of three, from 2.4 to 0.8 ml · min^{-1} · °C^{-1} ($P < 0.01$).

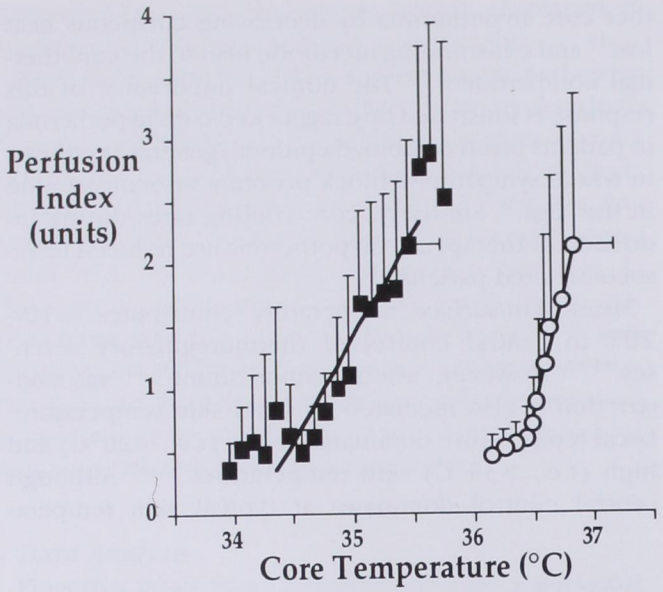

Fig. 3. Finger blood flow, as determined using the perfusion index, without (open circles) and with (filled squares) desflurane administration. Values were computed using the same core temperature ranges as in figure 2. The horizontal standard deviation bars indicate variability in the thresholds among the volunteers; although errors bars are shown only once in each series, the same temperature variability applies to each data point. The slopes of the perfusion *versus* core temperature relationships were determined using linear regression. These slopes defined the gain of vasoconstriction with and without desflurane anesthesia. Gain was reduced 2.4-fold, from 3.9 to 1.6 units · min^{-1} · °C^{-1} ($P < 0.01$).

tures, local temperature modulates central responses throughout the physiologic range.[38,39] Local modulation is unlikely to influence maximum vasoconstriction intensity and probably exerts relatively little influence on thermoregulatory response thresholds. However, local skin warming markedly decreases sensitivity of α-adrenergic receptors (that is, more norepinephrine release is required to produce a given amount of vasoconstriction).[38] The expected consequence of reduced receptor sensitivity is decreased gain.

Just 0.4 MAC desflurane reduced the gain of thermoregulatory vasoconstriction by a factor of 3. Reductions were similar when evaluated using laser Doppler flowmetry or the perfusion index. Vasoconstriction intensity, once triggered, thus increases gradually during desflurane administration. As a result, a larger than usual reduction in core temperature will be required to reach maximum vasoconstriction intensity. Reduced gain of vasoconstriction during desflurane anesthesia contrasts strikingly with the gain of sweating and active vasodilation, which are well preserved even at 1 MAC isoflurane. The extent to which anesthesia alters the gain of other thermoregulatory responses such as shivering remains to be evaluated.

From a clinical perspective, reduced gain means that additional core hypothermia will develop while vasoconstriction intensity gradually increases to an effective magnitude. This conclusion, however, applies only when local skin temperature is maintained at a high level—as when cutaneous warming is used to offset large heat losses from within surgical incisions[40] or from administration of unwarmed intravenous fluids.[41] In the more usual case in which skin temperature is not actively maintained, vasoconstriction *per se* will decrease local skin temperature ≈ 10°C.[15] This decrease will, in turn, facilitate vasoconstriction by increasing gain, and thus produce the typical rapid progression from full vasodilation to full vasoconstriction.[15]

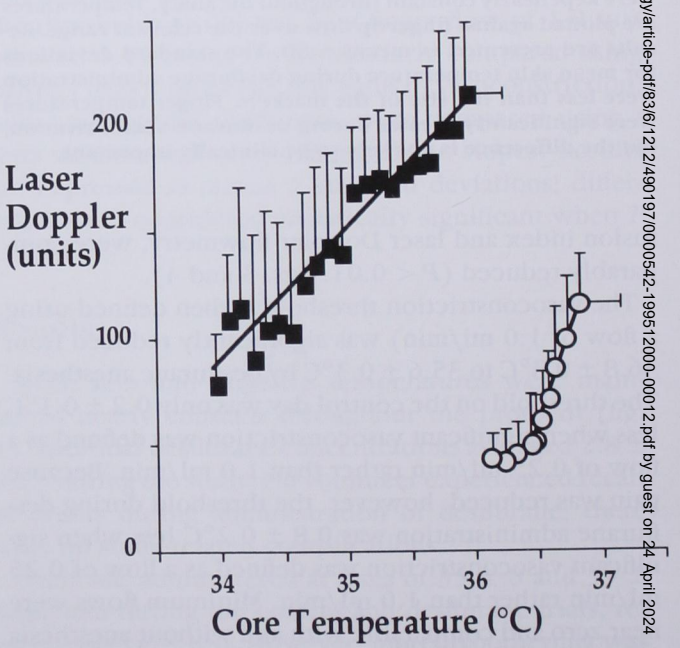

Fig. 4. Finger blood flow, as determined using laser Doppler flowmetry, without (open circles) and with (filled squares) desflurane administration. Values were computed using the same core temperature ranges as in figure 2. The horizontal standard deviation bars indicate variability in the thresholds among the volunteers; although errors bars are shown only once in each series, the same temperature variability applies to each data point. The slopes of the laser *versus* core temperature relationships were determined using linear regression. These slopes defined the gain of vasoconstriction with and without desflurane anesthesia. Gain was reduced 2.4-fold, from 171 to 73 units · min^{-1} · °C^{-1} ($P < 0.01$).

Table 1. Thresholds, Gain, and Maximum Vasoconstriction Intensity

	Control	Desflurane
Threshold (1.0 ml/min) (°C)	36.8 ± 0.3	35.6 ± 0.3*
Threshold (0.25 ml/min) (°C)	36.5 ± 0.2	34.6 ± 0.3*
Δ Threshold (°C)	0.2 ± 0.1	0.8 ± 0.2*
Gain (plethysmography) $ml \cdot min^{-1} °C^{-1}$	2.4	0.8*
Correlation coefficient (plethysmography) (r^2)	0.93	0.95
Gain (perfusion index)	3.9	1.6*
r^2 (perfusion index)	0.99	0.93
Gain (laser Doppler)	171	73*
r^2 (laser Doppler)	0.99	0.96
Minimum flow (ml/min)	0.05 ± 0.03	0.05 ± 0.02

Values are mean ± SD. The ratio of the gains without and with 0.4 MAC desflurane anesthesia were 3.0, 2.4, and 2.4 as determined using volume plethysmography, the perfusion index, and laser Doppler flowmetry, respectively.
* $P < 0.01$.

Thresholds are most formally identified by the core temperatures triggering initiation of thermoregulatory responses. To minimize potential bias, however, we have generally used objective endpoints. One endpoint we used for initiation of vasoconstriction is a forearm minus fingertip skin-temperature gradient of 0°C, which corresponds to a fingertip flow of ≈1 ml/min; conversely, an endpoint we have used for intense vasoconstriction is a skin-temperature gradient of 4°C, corresponding to a fingertip flow of ≈0.25 ml/min.[22]

When gain is high, it makes little difference which flow identifies "significant" vasoconstriction. For example, the difference between thresholds defined using 1.0 and 0.25 ml/min finger flow differed by only ≈0.2°C without anesthesia—a clinically unimportant distinction. As gain diminishes, however, the core temperature difference between the flows expands. Consistent with this theory, the threshold defined by a flow of 0.25 ml/min was ≈0.8°C less than when a flow of 1.0 ml/min was considered significant. A difference of this magnitude certainly could be important and might represent a systematic error in threshold studies. However, as specified earlier, this difference will only be apparent when extremity temperature is actively maintained to prevent the otherwise inevitable vasoconstriction-induced decrease in local skin temperature. Because we have always been careful to shield the extremities from active thermal manipulations during threshold studies, clinically important bias is unlikely to result from an anesthetic-induced reduction in gain.

All anesthetics evaluated so far reduce vasoconstriction thresholds.[25,42,43] And as expected, desflurane also decreased the vasoconstriction threshold. The threshold was reduced ≈1.2°C by 0.4 MAC desflurane, which is only slightly less than the reduction produced by isoflurane.[3] These data are consistent with our general impression that available volatile anesthetics produce roughly comparable thermoregulatory inhibition.[1] However, the vasoconstriction threshold—and probably other thermoregulatory thresholds as well—are altered by age,[8,9] hydration,[14] and painful stimulation.[10,11] Consequently, thresholds identified in the volunteers we studied should be extrapolated to patients with some caution.

Maximum vasoconstriction intensity (*i.e.*, minimum fingertip flow) was similar with and without desflurane. We previously reported comparable maximum vasoconstriction intensities with[15] and without[44] isoflurane anesthesia. Furthermore, the maximum sweating intensity is minimally reduced by isoflurane or enflurane administration.[4,16] These results thus suggest that the maximum efficacy of vasoconstriction and sweating are well maintained in the face of volatile anesthetics. In contrast to vasoconstriction and sweating, the effect of volatile anesthetics on the threshold, gain, and maximum intensity of shivering has yet to be reported. Because shivering is at least in part controlled by the spinal cord,[45–47] the effects of anesthetics on shivering may well differ from anesthetic effects on the other major thermoregulatory defense.

We precisely controlled fingertip as well as mean-skin temperatures throughout the protocol because both local and central temperature contribute to the gain of vasoconstriction. We maintained a fingertip temperature near 35.5°C during this study, which is typical for normothermic, vasodilated patients. It is likely that gain, and the effect of desflurane on gain, would differ at other skin temperatures. However, we were restricted to a relatively high skin temperature because in preliminary studies we found that lower mean skin temperatures did not reliably produce complete vasodilation on the control day.

Unavoidable consequences of maintaining high skin temperature include a reduction in the vasoconstriction threshold and a marked increase in the amount of fluid required to reduce core temperature. In preliminary studies we found it impossible to reach the vasoconstriction threshold and evaluate gain at higher desflurane concentrations (or higher skin temperatures) while reasonably restricting central venous fluid administra-

tion. As a result, we tested only a single, relatively low, alveolar partial pressure of desflurane. It is likely that gain is further reduced at greater anesthetic concentrations, but confirmation of this hypothesis will require a different study design.

Although administration rates were similar, more intravenous fluid was required during desflurane administration than on the control day. The effect of vascular volume expansion on the gain of thermoregulatory vasoconstriction remains unknown; to the extent that hyperhydration reduces gain, our results may overestimate desflurane-induced inhibition of vasoconstriction. However, urine output was copious on the desflurane day (nearly 2 l) because furosemide was administered. Consequently, it is likely that vascular volume expansion was comparable on the two treatment days.

Gain of thermoregulatory responses is defined by the rate at which response intensity increases, once triggered.[1] There is no physiologic requirement that gain for a particular response be a linear function of core temperature; nonetheless, response intensity *versus* core temperature plots for common thermoregulatory defenses often include relatively linear portions.[4,17,48] Such a linear portion was apparent for arteriovenous shunt vasoconstriction in the flow range between 1.0 and 0.15 ml/min.

Despite our efforts, fingertip temperature was generally 0.25–0.5°C higher during desflurane administration. However, it is unlikely that this small deviation explains the observed threefold reduction in gain. Although volume plethysmography is generally considered the "gold standard" for arteriovenous shunt flow, even this measure is subject to potential errors. Consequently, it is encouraging that gain, as evaluated using laser Doppler flowmetry and the perfusion index, was comparably reduced by desflurane administration. It is unlikely that these three different measures of flow all were incorrect.

In summary, desflurane reduced the vasoconstriction threshold $\approx$1.2°C. The centrally mediated gain of vasoconstriction, as determined by volume plethysmography, was reduced by a factor of three, from 2.4 to 0.8 $ml \cdot min^{-1} \cdot °C^{-1}$ ($P < 0.01$). Gains, as determined by the perfusion index and laser Doppler flowmetry, were likewise significantly reduced. Minimum flows were near zero and comparable with and without anesthesia. This threshold reduction was analogous to that observed previously during isoflurane anesthesia. Similarly, it is already established that maximum vasoconstriction intensity is comparable with and without isoflurane anesthesia. Our novel result is thus that even relatively low desflurane concentrations markedly reduce the gain of vasoconstriction. It is likely that reduced gain (*i.e.,* slow onset of vasoconstriction) contributes to core hypothermia in some surgical patients.

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