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# *Physiologic Responses to Hyperthermia during Epidural Anesthesia and Combined Epidural/Enflurane Anesthesia in Women*

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***Background:*** **During combined epidural/isoflurane anesthesia, the core temperature triggering finger-tip vasoconstriction is ≈1° C less than that triggering redilation. This hysteresis suggests that thermoregulatory responses are not dependent entirely on current thermal status (state-dependence), but may be influenced also by the system's recent thermal history (direction-dependence). Once triggered, the gain and maximum response intensity of many thermoregulatory responses is nearly normal during isoflurane anesthesia. However, it remains unknown whether preserved gain and maximum response intensities are a characteristic paradigm describing thermoregulatory responses to general anesthetics. Also unknown is whether the sweating and pre-capillary vasodilation thresholds are comparably impaired by different volatile anesthetics. Accordingly, the authors tested the hypotheses that, during one minimum alveolar concentration of enflurane anesthesia: (1) there is a direction-dependent hysteresis for sweating; (2) the sweating and active vasodilation thresholds increase ≈1.2° C, as they do during one minimum alveolar concentration of isoflurane; and (3) the gain and maximum intensity of sweating are well preserved.**

***Methods:*** **Six female volunteers each were studied on 2 days, once during epidural anesthesia alone and once with combined enflurane (1.7%)/epidural anesthesia. On each study day, core hyperthermia was induced by cutaneous warming restricted to the legs. Warming continued until chest sweating reached maximal values; the volunteers then were cooled gradually until sweating stopped. The core temperature at which the sweating rate departed from baseline values was considered the activation threshold. Gain was expressed as the slope of the sweating rate *versus* core temperature curve within the range 25–75% of the maximum sweating rate. Hysteresis was evaluated by subtracting the tympanic membrane temperature at which the sweating rate suddenly increased during warming (approximately 25% above baseline values) from that at which sweating precipitously decreased during cooling (approximately 75% of maximum values).**

***Results:*** **The sweating threshold was 1.4 ± 0.7° C higher during combined enflurane/epidural anesthesia than during epidural anesthesia alone. Maximum intensity was ≈700 $g \cdot m^{-2} \cdot h^{-1}$, and the gain ≈1,300 $g \cdot m^{-2} \cdot h^{-1} \cdot {}^{\circ} C^{-1}$ during each treatment. No hysteresis was detected on either study day.**

***Conclusions:*** **One minimum alveolar concentration of enflurane increased the sweating threshold only slightly more than previously reported for isoflurane. As in previous studies of sweating and vasoconstriction during isoflurane anesthesia, gain and maximum response intensity were well preserved during enflurane anesthesia. An increase in the interthreshold range (temperatures not triggering thermoregulatory responses), with little change in gain and maximum response intensities, appears to be the typical effect of volatile anesthetics. Sweating during enflurane anesthesia appears to be state-dependent and little influenced by the direction of core temperature perturbations. (Key words: Anesthetics, volatile: enflurane. Hyperthermia. Temperature, regulation: setpoint; sweating; threshold; vasodilation. Temperature, measurement: esophagus; skin; tympanic membrane. Thermoregulation.)**

THERMOREGULATORY responses can be described in terms of their thresholds (core temperature triggering response), gains (slope of the response intensity *vs.* core temperature curve), and maximum intensities. These responses generally are considered state-dependent. That is, efferent responses usually can be predicted from instantaneous afferent input without regard to the system's recent history.[2,3] This concept of state-dependence includes a well established rate-dependence; rapid skin temperature changes, for example, contribute far more to thermoregulatory control than do slow changes of comparable magnitude.[4]

Linear models incorporating both static temperatures and rates of change fail to uniformly predict human thermoregulatory responses to sudden environmental changes.[5] Even more complicated models sometimes predict responses differing substantially from experimental data.[6] Wyss *et al.* proposed that better predic-

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tion might require thermoregulatory models incorporating the system's "recent history," perhaps including the effects of time or the direction of core temperature change.[5] Consistent with this possibility, we have observed that arteriovenous shunt redilation does not necessarily occur at the same core temperature as that triggering vasoconstriction in anesthetized patients.[7]

The direction-dependence of thermoregulatory responses to isolated core temperature changes has not been evaluated extensively because it has proved difficult to manipulate core temperature while maintaining skin temperature constant. Core temperature, however, can be altered independently of sentient skin when regional anesthesia is used to block thermal input from the lower body. Because the legs are insensate, this protocol provides a test of thermoregulatory responses to core temperature perturbations. Using this model, we recently demonstrated that redilation during combined epidural/isoflurane anesthesia occurs at a core temperature $\approx 1°$ C greater than that triggering vasoconstriction.[7]

While the etiology of this hysteresis remains unclear, it suggests that thermoregulatory responses are not dependent entirely on current thermal status (state-dependence), but also may be influenced by the system's recent thermal history (direction-dependence). To determine whether direction dependence is a characteristic of thermoregulatory responses during general anesthesia, we asked whether sweating demonstrates a similar hysteresis.

General anesthesia decreases the threshold for responses to cold[8–12] but increases those for warmth,[13,14] thereby substantially augmenting the interthreshold range (core temperatures not triggering autonomic thermoregulatory responses). Once triggered, however, the gain and maximum intensity of vasoconstriction,[15] nonshivering thermogenesis (unpublished data), and sweating during isoflurane anesthesia[14] are nearly normal. These data suggest that altered thresholds with well preserved gains and maximum intensities might be a general paradigm describing the thermoregulatory effects of general anesthetics.[16]

It remains unknown whether gains and maximum response intensities are comparable with other anesthetics. Also unknown is whether the sweating and precapillary vasodilation thresholds are comparably impaired by different volatile anesthetics. Because we previously evaluated the threshold, gain, and maximum intensity of sweating during isoflurane anesthesia, we chose this time to administer enflurane. Accordingly, we tested the hypotheses that, during one minimum alveolar concentration (MAC) enflurane anesthesia: (1) there is a direction-dependent hysteresis for sweating; (2) the sweating and active vasodilation thresholds increase $\approx 1.2°$ C, as they do during 1 MAC isoflurane; and (3) the gain and maximum intensity of sweating are well preserved.

## Methods

With approval from the Committee on Human Research at the University of California, San Francisco, we studied six female volunteers having the following morphometric characteristics: age 30 ± 8 yr, height 167 ± 8 cm, and weight 65 ± 13 kg. Their percentage of body fat was 26 ± 6, as determined using infrared interactance (Futrex 1000, Futrex, Hagerstown, MD).[17]

These volunteers were not conditioned athletes, but two exercised daily. None was obese or taking medication other than hormonal contraceptives or had a history of thyroid disease, dysautonomia, or Raynaud's syndrome. Women not using hormonal contraceptives were studied during the first 10 days of their monthly cycles.

Volunteers were studied on 2 separate days, randomly assigned. Sweating and active vasodilation in response to induced hyperthermia were evaluated on 1 study day during epidural anesthesia alone, and on the other with combined enflurane (1.7% end-tidal concentration) and epidural anesthesia. We restricted the study to female volunteers because sweating thresholds are 0.3–0.5° C greater in women than men.[14]

### *Treatment Protocol*

Studies started at approximately 8:30 AM and volunteers fasted during the 8 preceding h. All volunteers were minimally clothed and reclined on their backs on a standard operating room table, with legs placed on a circulating water blanket set at 42° C (Blanketrol II, Maxi-Therm blanket #276, Cincinnati Sub-Zero, Cincinnati, OH). Ambient temperature was maintained at 22.5 ± 0.9° C throughout the studies.

Cutaneous evaporative heat loss was prevented by wrapping the volunteers with thin plastic sheeting below the neck and placing a plastic shower cap over the head. To minimize anesthetic-induced redistribution hypothermia,[18,19] a forced-air warming cover (Model 300, Augustine Medical, Eden Prairie, MN) was positioned over the legs and up to the T12 dermatome. The cover was connected to a Bair Hugger® forced-air warmer (Model 200, Augustine Medical) set on me-

dium (≈40° C) while study monitors were being attached.[20] The arms and chest were covered with plastic sheeting and cotton blankets but were not actively warmed.

An epidural catheter was inserted *via* the L3–L4 interspace using standard technique and injected with a test dose (3 ml) of 1.5% 2-chloroprocaine (Abbott Laboratories, North Chicago, IL) with epinephrine 1:100,000. A 17-ml bolus of 1.5% 2-chloroprocaine without epinephrine was administered slowly 5 min later, and the catheter subsequently infused with the same solution at 12–15 ml/h to maintain anesthesia for the duration of the study.

Combined enflurane/epidural anesthesia was induced (on the appropriate study day), without premedication, by inhalation of enflurane 3–4% in 70% $N_2O$ and oxygen. Thiopental and opioids were not administered. Vecuronium bromide (0.1 mg/kg) was administered intravenously to facilitate tracheal intubation and subsequently infused at a rate sufficient to maintain 0–1 twitches in response to train-of-four stimulation of the ulnar nerve at the wrist. Nitrous oxide was discontinued after induction, and the trachea of each volunteer was intubated. Mechanical ventilation was adjusted to maintain end-tidal $P_{CO_2}$ near 35 mmHg. Airway humidification was provided by placing a Pall Biomedical Products (Glen Cove, NY) heat-and-moisture exchanging filter between the Y-piece of the circle system and the endotracheal tube.

Anesthesia was maintained with enflurane at an end-tidal concentration of 1.7% in oxygen, using a Modulus® CD integrated anesthesia system (Ohmeda, Madison, WI). Respiratory gas concentrations were quantified using a calibrated end-tidal gas analyzer (Datex Medical Instrumentation, Tewksbury, MA). After induction of enflurane anesthesia, a bladder catheter was inserted to prevent bladder distention and to monitor hydration.

Core hyperthermia was induced by increasing the setting on the Bair Hugger® forced-air warmer to high (≈43° C) while maintaining the temperature of the circulating water blanket at 42° C. Active lower body warming continued until tympanic membrane temperature was 0.5° C greater than the temperature causing maximal upper body sweating or until tympanic membrane temperature exceeded 41° C. Volunteers subsequently were cooled slowly by turning off the Bair Hugger®, then removing the disposable cover from the legs, decreasing the circulating water temperature to 35° C, and removing the plastic sheeting from the legs. Cooling was continued until sweating rate and capillary flow returned to baseline values or until 8 h of enflurane anesthesia elapsed.

To avoid the potential effects of dehydration on sweating, we infused lactated Ringer's solution warmed to 40° C into an antecubital vein on the right arm at a rate of 5 $ml \cdot kg^{-1} \cdot h^{-1}$ until sweating started. The infusion rate was then increased to 15–20 $ml \cdot kg^{-1} \cdot h^{-1}$ for the remainder of the study to prevent dehydration during vigorous sweating.

*Measurements*

We considered lack of cutaneous cold sensation in response to an alcohol-soaked gauze pad to indicate sensory nerve blockade. The dermatomal block level produced by epidural anesthesia was evaluated at 30-min intervals during epidural anesthesia alone and before induction of and after emergence from enflurane anesthesia. Sympathetic nerve blockade was confirmed by absence of sweating on the legs.

To document adequate hydration, we recorded urinary output and specific gravity at 1-h intervals *via* bladder catheterization during combined epidural/enflurane anesthesia.

Core temperature was measured at the left tympanic membrane using Mallinckrodt® thermocouples. The aural probe was inserted by volunteers until they felt the thermocouple touch the tympanic membrane; appropriate placement was confirmed when volunteers easily detected a gentle rubbing of the attached wire. The probe was securely taped in place and the aural canal occluded with cotton. Tympanic membrane temperatures correlate well with distal esophageal temperatures during induced hyperthermia.[14] On combined enflurane/epidural anesthesia study days, distal esophageal temperatures also were recorded.

Area-weighted, mean upper skin-surface temperature was computed from measurements at seven sites by assigning the following regional percentages to each area: head 11%, upper arms 17%, forearms 11%, hands 5%, fingers 4%, back 34%, and chest 18%.[21] Core and skin-surface temperatures were recorded from thermocouples connected to two Iso-Thermex® 16-channel electronic thermometers having an accuracy of 0.1° C and a precision of 0.01° C (Columbus Instruments International, Columbus, OH). Accuracy of these thermometers was confirmed by comparison to a mercury-in-glass reference thermometer.

Sweating on the chest was quantified by passing 2.0 L/min of anhydrous oxygen across a 6-cm-diameter cir-

cle of skin covered with an air-tight adhesive ostomy appliance (stock #3706 and #3806, Hollister®, Libertyville, IL). Cutaneous water loss ($g \cdot m^{-2} \cdot h^{-1}$) was calculated from the gas flow rate (Model FMA-5000, Omega Engineering), gas temperature, and relative humidity (Model HX93, Omega Engineering). Similar methods have been used by previous investigators.[22] Oxygen flowing into the sweating sensor was at ambient temperature, and the sensor was exposed to the ambient environment during the study.

At 5-min intervals, forehead sweating was qualitatively evaluated: a sweating grade of 0 was assigned when the skin appeared dry, a grade of 1 when some moisture was detected, and a grade of 2 when distinct beads of sweat were visible. The forehead was swabbed dry using a gauze pad immediately after each evaluation.

Forearm capillary flow was evaluated using laser Doppler flowmetry (Periflux 3, Perimed, Piscataway, NJ) with the fiberoptic probe positioned on the radial side of the right mid-forearm.

Anesthetic data were obtained from the Capnomac® and Modulus® CD system, including end-tidal carbon dioxide, end-tidal enflurane concentration, oscillometric blood pressure, and $Sp_{O_2}$. These data were recorded at 20-s intervals using IdaCare™ version 1.3 (Hermes Systems s.a., Angleur, Belgium), a Macintosh®-based (Apple computer, Cupertino, CA) patient information management software. Thermoregulatory data (*e.g.*, temperatures, sweat rate, humidity) were recorded at 1–5-min intervals using a modification of a previously described data-acquisition system.[23] The two systems operated asynchronously on a Macintosh FX computer.

*Data Analysis*

The sweating and forearm pre-capillary flow values at initiation of active warming were considered baseline values. Inspection of the sweating *versus* tympanic membrane temperature loop revealed that the increasing and decreasing segments both were S-shaped. Within the range of values between 25% and 75% of the maximum, sweating rate typically increased or decreased rapidly, with little additional change in core temperature.

The core temperature at which the sweating rate departed from baseline values was considered the sweating activation threshold, and the temperature at which it returned to baseline the termination threshold. The maximum sweating rate was determined by inspection of the sweating *versus* tympanic temperature loop in each individual. Gain was expressed as the slope of the sweating rate *versus* core temperature curve within the range 25–75% of the maximum sweating rate. Similarly, during cooling, the slope within the range 75–25% of the maximum sweating rate was considered the abatement rate.

The term hysteresis refers to the difference between the core temperature triggering sweating and that arresting sweating. To evaluate hysteresis, we subtracted the tympanic temperature at which the sweating rate suddenly increased during warming (approximately 25% above baseline values) from that at which sweating precipitously decreased during cooling (approximately 75% of maximum values). A positive hysteresis thus indicates that sweating began to decrease at a lower temperature than that triggering the initial rapid increase.

As in previous studies,[13] the tympanic membrane temperature triggering grade 2 forehead sweating was considered the activation threshold for this site; the temperature at which sweating returned to grade 0 identified the termination threshold for the forehead.

The core temperature at which the laser Doppler perfusion index departed from baseline values was considered the activation threshold for pre-capillary vasodilation. Variability in the laser Doppler values precluded quantitative evaluation of vasodilation gain. Because Doppler values are only an index, maximum values were reported as a percentage of initial values.

Hyperthermia-induced changes in the sweating activation thresholds, maximum intensities, termination thresholds, and hysteresis with and without enflurane anesthesia were compared using paired $t$ tests. Gain and abatement rates on the 2 study days were compared using Mann-Whitney U tests. All values are expressed as mean ± SD; differences were considered significant when $P < 0.01$.

## Results

There were no statistically significant differences in ambient temperature, ambient humidity, or baseline core temperatures on the 2 treatment days. Urinary output was copious and specific gravity low during combined enflurane/epidural anesthesia, indicating that adequate hydration was maintained during sweating. Epidural anesthesia produced loss of cutaneous cold sensation in the legs, ranging from T9 to T11. The absence of sweating on the volunteers' legs further in-

dicated complete sympathetic blockade.[24] Upper body skin temperature (at the sweating threshold) was ≈1.3° C higher during combined enflurane/epidural anesthesia than during epidural anesthesia alone, reflecting the higher core temperature required to trigger sweating during general anesthesia (table 1).

There were no clinically important or statistically significant changes in mean blood pressure in any volunteer when the sweating threshold was reached; in contrast, heart rate increased ≈20 beats/min. The entire warming and cooling protocol required ≈5 h without enflurane, and ≈7 h during general anesthesia.

End-tidal enflurane concentration averaged 1.70 ± 0.02% and rarely deviated more than 0.03% from our target of 1.70%. Core temperature typically increased and decreased at ≈0.7° C/h. Table 2 lists the activation thresholds, gains, maximum intensities, abatement rates, termination thresholds, and hysteresis for sweating during epidural anesthesia alone and combined enflurane/epidural anesthesia. As expected, the two volunteers who exercised daily had substantially greater maximum sweat rates: 977 and 1,085 $g \cdot m^{-2} \cdot h^{-1}$ *versus* 520 ± 130 $g \cdot m^{-2} \cdot h^{-1}$ in the remaining four volunteers.

The sweating threshold was 1.4 ± 0.7° C greater during combined enflurane/epidural anesthesia than during epidural anesthesia alone. Maximum intensities were slightly lower when enflurane was administered ($P = 0.02$), but the difference was not clinically important. Gains were similar with and without enflurane anesthesia and similar to the abatement rate during epidural anesthesia alone. The abatement rate was substantially lower during combined epidural/enflurane anesthesia than during epidural anesthesia alone, but the decrease was not quite statistically significant ($P = 0.03$). Large standard deviations for the sweating gain and abatement rate reflect the nonparametric values obtained by dividing sweating rates by small temperature changes.

**Table 1. Ambient Temperature and Humidity, Urine Output, Epidural Block Level, and Upper Body Skin Temperature**

| | Epidural Alone | Epidural/ Enflurane |
|---|---|---|
| Ambient temperature (° C) | 22.1 ± 0.9 | 23.0 ± 0.9 |
| Ambient humidity (%) | 42.9 ± 0.9 | 42.1 ± 0.9 |
| Urine volume (ml/h) | — | 280 ± 40 |
| Urine specific gravity | — | 1.004 ± 0.003 |
| Loss of cold sensation | T10 | T10 |
| Upper body skin temperature (° C) | 37.3 ± 0.5 | 38.6 ± 0.7* |
| Baseline temperature (° C) | 37.0 ± 0.3 | 36.9 ± 0.7 |

* Upper body skin temperature (at the sweating threshold) was ~1.3° C higher during combined enflurane/epidural anesthesia than during epidural anesthesia alone. Urine volume and specific gravity were not recorded during epidural anesthesia alone.

**Table 2. Sweating Data**

| | Epidural Alone | Epidural/ Enflurane |
|---|---|---|
| Activation threshold (° C) | 37.4 ± 0.5 | 38.8 ± 0.4* |
| Gain ($g \cdot m^{-2} \cdot h^{-1} \cdot ° C^{-1}$) | 1200 ± 590 | 1440 ± 950 |
| Maximum ($g \cdot m^{-2} \cdot h^{-1}$) | 750 ± 300 | 630 ± 270 |
| Abatement rate ($g \cdot m^{-2} \cdot h^{-1} \cdot g\ C^{-1}$) | −1650 ± 1340 | −490 ± 260 |
| Termination threshold (° C) | 37.1 ± 0.2 | 38.3 ± 0.5* |
| Hysteresis (° C) | 0.1 ± 0.2 | −0.3 ± 0.4 |
| Forehead activation (° C) | 37.7 ± 0.3 | 39.1 ± 0.4* |
| Forehead termination (° C) | 37.5 ± 0.6 | 38.8 ± 0.9 |

* Significantly different from those recorded during epidural anesthesia alone. The abatement rate was substantially lower during combined enflurane/epidural anesthesia than during epidural anesthesia alone, but the decrease was not statistically significant ($P = 0.03$).

The termination thresholds were ≈0.4° C less than the activation thresholds, differences that were not statistically significant. No hysteresis was detected on either study day (fig. 1). The qualitative forehead sweating activation threshold was slightly higher than the quantitative sweating threshold on each study day. This mainly was due to two volunteers who reported that they rarely sweat on the forehead, even during vigorous exercise (table 2).

Forearm capillary flow, measured by laser Doppler, increased consistently during hyperthermia. The activation threshold for pre-capillary vasodilation was slightly higher than the sweating threshold when the volunteers were given epidural anesthesia only; however, during combined enflurane/epidural anesthesia, vasodilation started at a lower temperature than sweating. As a result, the capillary perfusion thresholds did not differ significantly during the two treatments. Hyperthermia increased forearm capillary perfusion approximately threefold during each treatment (table 3). In several cases, capillary flow remained elevated at the end of each study because core temperatures had not yet returned to baseline (*i.e.*, our limit of 8 h of anesthesia elapsed before cooling was complete). We were unable to determine vasodilation gain reliably because of minute-to-minute alterations in the laser Doppler index and variability in the volunteer's responses.

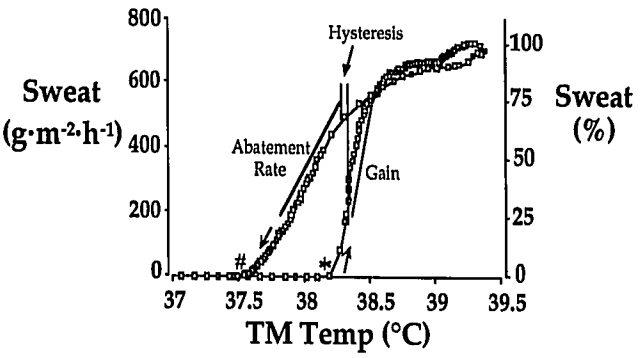


**Fig. 1. The sweating rate plotted *versus* core temperature in a typical volunteer given combined epidural/enflurane anesthesia. Each point represents the average value during a 5-min acquisition epoch. Absolute sweating rate is shown on the left axis; the right axis shows percentage of the maximum sweating rate. The tympanic membrane (TM) temperature at which the sweating rate departed from baseline values was considered the sweating activation threshold (*), and the temperature at which it returned to baseline defined the termination threshold (#). Gain was expressed as the slope of the sweating rate *versus* core temperature curve within the range 25–75% of the maximum sweating rate. Similarly, during cooling, the slope within the range 75–25% of the maximum sweating rate was considered the abatement rate. These slopes are indicated by slanting lines. Vertical lines indicate the core temperature at which sweating rate increased to 25% of its ultimate maximum value; during cooling, the core temperature at which sweating decreased to 75% of maximum is similarly shown. The hysteresis is the difference between these two values, in this cases ≈0.1° C.**

## Discussion

We previously demonstrated that 1 MAC isoflurane anesthesia increases the sweating threshold 1.2° C in women.[14] One minimum alveolar concentration of enflurane similarly increased the sweating threshold 1.4 ± 0.7° C. The slightly greater effect of enflurane may reflect variability in the data or a real difference between the two anesthetics. But even were their thermoregulatory effects identical, a greater increase would be expected with our current protocol because cutaneous warm input was blocked by epidural anesthesia. The present volunteers, therefore, would tolerate a higher core temperature than actively warmed volunteers with intact cutaneous sensation.

Enflurane anesthesia (0.75 MAC) reduces the threshold for vasoconstriction ≈2° C to 35.1 ± 0.6° C.[11] However, 1 MAC enflurane increased the threshold for sweating only by ≈1.4° C. Isoflurane also impairs the vasoconstriction threshold[10] far more than the sweating threshold.[14] Why volatile anesthetics should impair responses to cold more than those to warmth remains unclear. However, an aggressive response to increasing core temperature is teleologically appropriate because hyperthermia is far more dangerous than comparable hypothermia. The net effect remains a large increase in the interthreshold range (core temperatures *not* triggering thermoregulatory responses), from <0.6° C to ≈4° C.[25]

Once triggered, the sweating rate increased rapidly from control to nearly maximal values during epidural anesthesia alone; gain was equally high during combined enflurane/epidural anesthesia. Such high gain contributes to the normally precise control of core temperature and is typical for sweating[3] and other thermoregulatory responses.[23,26]

Higher sweating rates in individuals who exercise regularly are a well known thermoregulatory adaptation.[27] In part, because of the exaggerated sweating in the two volunteers who exercised daily, average sweating rate in our current study was considerably higher than that we reported previously.[14] But more importantly, we previously measured sweating from the thigh. Since sweating is an active process requiring intact sympathetic nerves,[24,28] we could not use the thigh in a protocol requiring epidural anesthesia. In our current volunteers, we measured sweating on the chest, a site producing more sweat than the legs.[14,27] Our average maximum sweating values were similar to those others have recorded from the chest.[27]

Maximum sweating values were slightly less during combined enflurane/epidural anesthesia than during epidural anesthesia alone. Similarly, we previously reported that isoflurane anesthesia slightly decreased the maximum sweating rate.[14] In neither study were the decreases clinically important. We previously observed that maximum vasoconstriction intensities are similar in anesthetized patients[10] and unanesthetized volunteers.[23] Moreover, the maximum intensity of nonshivering thermogenesis in anesthetized infants appears normal (unpublished data). Well preserved gain and maximum response intensity for sweating during anes-

**Table 3. Vasodilation Data**

| | Epidural Alone | Epidural/ Enflurane |
|---|---|---|
| Laser threshold (° C) | 37.6 ± 0.4 | 38.3 ± 0.6 |
| Maximum (% of baseline) | 340 ± 130 | 320 ± 150 |

The activation thresholds for precapillary vasodilation, as detected by laser Doppler flowmetry, did not differ significantly on the 2 study days. Hyperthermia increased forearm capillary perfusion approximately threefold during each treatment.

thesia contrasts markedly with many other physiologic responses such as the $CO_2$-response curve, which is both shifted to the right and "flattened." A substantially increased interthreshold range with relatively well preserved gain and maximum response intensity thus may be the characteristic thermoregulatory response to volatile anesthetics.[16]

We define hysteresis by the core temperatures initiating a sudden increase and decrease in the sweating rate. During epidural anesthesia alone, the core temperature at which the sweating rate suddenly increased during induction of hyperthermia was similar to that at which the sweating rate suddenly decreased during cooling. Thus, we were unable to detect a direction-dependent hysteresis for sweating during epidural anesthesia alone, which is consistent with previous observations.[29]

We also were unable to detect a hysteresis for sweating during combined enflurane/epidural anesthesia; likewise, the activation and termination thresholds were comparable. Because the abatement rate was lower than the gain during combined epidural/enflurane anesthesia, the sweating curves did not quite overlap during warming and cooling. Nonetheless, the sweating curve during cooling was shifted only a few tenths of a degree (C) from that during warming. Lack of direction-dependence for sweating contrasts with our previous demonstration of a significant hysteresis for vasoconstriction under similar circumstances.[7] These data suggest that direction-dependence is not characteristic of thermoregulatory responses during general anesthesia.

During our studies of both isoflurane[7] and enflurane anesthesia, the regulatory system was shielded from active cutaneous warming and cooling by epidural blockade; however, vasoconstriction and sweating were, perforce, measured from sensate skin. Both responses are mediated primarily by central thermoregulatory control.[26,30] Both also are influenced by local skin temperature.[3,22,31] Arteriovenous shunt vasoconstriction decreases finger blood flow >10-fold,[32] thereby decreasing fingertip temperature $\approx$10° C.[12] Local cutaneous hypothermia is not thought to alter arteriovenous shunt flow significantly[33]; nonetheless, decreased finger temperature may have prolonged shunt constriction even when the centrally mediated drive to conserve heat dissipated. In contrast, temperature of skin near the sweating monitor changed little during the course of the current study, minimizing impact of local control.

Two components contribute to thermoregulatory vasodilation. The first results from release of tonic precapillary tone and is under considerable local control.[5] In contrast, active vasodilation in response to hyperthermia is a neurogenic process observed only in humans (even baboons do not demonstrate this response to heat).[28] The exact mechanism of active vasodilation remains unclear[34] but apparently involves release of a yet to be identified transmitter from sweat glands.[28] Active vasodilation typically occurs at core temperatures well above those causing maximal sweating.

Warming in our protocol was continued only to slightly higher temperatures than required for maximal sweating because otherwise we would not have had sufficient time to complete the required gradual cooling. Since higher core temperatures are required to initiate active vasodilation than sweating, it is not surprising that capillary flow increased only threefold. Although similar increases have been observed in previous sweating studies,[27] much larger increases (*e.g.*, 15–20-fold) have been reported by others.[35] Presumably, we would have observed more vasodilation had we continued warming further past the point of maximum sweating.

Sweating was quantified only on the chest. Since the threshold and maximum intensity of sweating differs by body region,[24] our results cannot be extrapolated directly to other skin surfaces. However, the increase in the sweating threshold produced by enflurane anesthesia likely would be comparable in other locations. This conclusion is supported by similar thresholds on the chest and forehead. Similarly, comparable gain and maximum sweating intensity during epidural anesthesia with and without enflurane presumably are not restricted to the chest. We deliberately kept the rates of core warming and cooling low to prevent exaggerated responses to rapid thermal perturbations.[22] Our results likely would differ had we altered core temperature more rapidly.

Not all sweating is thermoregulatory: sweating and tearing are well known indicators of anesthetic levels insufficient to prevent autonomic responses to surgical pain. However, our volunteers were not undergoing surgery, and sweating was never observed near control temperatures. Since end-tidal enflurane concentrations were constant throughout each study, sweating appears to have been triggered by experimental hyperthermia.

Water loss from vigorous sweating easily exceeds 1 L/h.[36] Sufficient sweating thus can produce dehydration, which limits further sweating, apparently *via* a

direct osmotic effect on hypothalamic neurons.[37] We limited the effects of dehydration by aggressively hydrating our volunteers once sweating started. Our efforts apparently were successful because urinary output was copious, and the specific gravity low during combined enflurane/epidural anesthesia days. Although the urinary output and specific gravity was not measured when the volunteers were given epidural anesthesia only, sweating rates were comparable, and the same amount of intravenous fluid was administered. It thus is unlikely that dehydration altered sweating gain or maximum intensity in our volunteers.

We tested only a single dose of enflurane and therefore cannot state with assurance how other doses might influence sweating or vasodilation. However, impairment of vasoconstriction, sweating, and vasodilation all are linear functions of isoflurane dose.[14] It thus seems probable that enflurane also impairs thermoregulation as a linear function of dose.

Epidural anesthesia blocked direct perception of active leg warming and cooling. However, upper body skin temperature was not exactly constant during the study: it increased parallel with core temperature and was thus $\approx 1.3°$ C higher at the sweating threshold during combined epidural/enflurane anesthesia than during epidural anesthesia alone. It is unlikely that this relatively small increase substantially altered the observed responses.

In summary, no direction-dependent hysteresis for sweating was detected during epidural anesthesia alone or during combined epidural/enflurane anesthesia. One minimum alveolar concentration of enflurane increased the sweating threshold only slightly more than was reported previously for isoflurane. As in previous studies of sweating and vasoconstriction during isoflurane anesthesia, gain and maximum response intensity were well preserved during enflurane anesthesia. An increase in the interthreshold range (temperatures not triggering thermoregulatory responses), with little change in gain and maximum response intensities, appears to be the typical effect of volatile anesthetics.

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