Thermoregulatory responses to hyperthermia during isoflurane anesthesia in humans

DENNA E. WASHINGTON, DANIEL I. SESSLER, AZITA MOAYERI, BENJAMIN MERRIFIELD, JOSEPH McGUIRE, MARIE PRAGER, KUMAR BELANI, SHANNON HUDSON, AND MARC SCHROEDER

Department of Anesthesia, University of California, San Francisco 94143-0648; and Department of Anesthesiology, University of California, Los Angeles, California 90024; and Department of Anesthesiology, University of Minnesota, Minneapolis, Minnesota 55455

WASHINGTON, Denna E., Daniel I. Sessler, Azita Moayeri, Benjamin Merrifield, Joseph McGuire, Marie Prager, Kumar Belani, Shannon Hudson, and Marc Schroeder. Thermoregulatory responses to hyperthermia during isoflurane anesthesia in humans. J. Appl. Physiol. 74(1):82-87, 1993.—The authors tested the hypotheses that isoflurane anesthesia increases the threshold for sweating but minimally decreases the gain (sensitivity) or maximum intensity of this response and that thermoregulatory responses to hyperthermia are similar in anesthetized men and women. Sweating in response to core hyperthermia was studied in five men and five women during 0, 0.8, and 1.2% end-tidal isoflurane anesthesia. Thigh sweating was quantified by measuring gas flow, relative humidity, and temperature passing over a known surface area. The distal esophageal temperature triggering sweating was considered the sweating threshold, and gain was defined as the core temperature increment required to increase sweating rate from 25 to 75% of maximum observed intensity. The sweating threshold increased linearly with isoflurane concentration from 36.6 ± 0.1°C in the men and from 37.1 ± 0.3°C to 38.3 ± 0.2°C in the women. The thresholds were significantly higher in women than in men. Gain and maximum sweating intensities were similar at each anesthetic concentration and in men and women. These data indicate that isoflurane anesthesia significantly increases the threshold triggering thermoregulatory sweating but that gain and maximum sweating rate are relatively well preserved.

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 (1). General anesthesia decreases the threshold for thermoregulatory vasoconstriction from a normal temperature near 37°C to ~34.5°C (depending on the type of anesthetic and dose) (19, 23), but maximum vasoconstriction intensity remains well preserved (18). Thresholds for shivering (20) and nonshivering thermogenesis in infants (unpublished data) appear similarly reduced.

It is well established that intravenous anesthetics (e.g., pentobarbital sodium) increase the core temperature, triggering thermoregulatory sweating in animals (24). Furthermore, qualitative clinical observations suggest that the sweating threshold is increased by potent volatile anesthetics (16). However, the dose-dependent effects of modern volatile anesthetics on the thresholds, gains, and maximum intensities of sweating and active precapillary vasodilation remain unclear. Additionally, it is not known if thermoregulatory responses to heat stress are similar in anesthetized men and women.

We therefore tested the hypotheses that isoflurane anesthesia produces a dose-dependent increase in the threshold for sweating and active precapillary vasodilation but does not decrease gain or maximum intensity of these responses and that thermoregulatory responses to hyperthermia are similar in anesthetized men and women.

METHODS

With approval from our Committee on Human Research, we studied five male and five female volunteers. They had generally sedentary lifestyles and were not serious athletes. None was obese, taking medication other than oral contraceptives, or had a history of thyroid disease, dysautonomia, or Raynaud's syndrome. Women not using oral contraceptives were studied during the first 2 wk of their monthly cycles. Sweating and active vasodilation in response to induced hyperthermia were evaluated during hyperthermia alone (control) and during 0.8 and 1.2% (end-tidal concentrations) isoflurane anesthesia. Each anesthetic concentration was studied on a separate day, with treatment order randomly assigned.

Treatment protocol. Studies started at ~9:30 a.m., and volunteers fasted during the 8 h preceding each study. They were minimally clothed and reclined on their backs on a full-length circulating water blanket set at 42°C (Blanketrol II, Maxi-Therm blanket 276, Cincinnati Sub-Zero, Cincinnati, OH) that covered a standard operating room table. Ambient temperature was maintained near 22°C throughout all studies. The percentage of body fat in each volunteer was determined using infrared interactance (Futrex 1000, Futrex, Hagerstown, MD) (3).

Hyperthermia was induced without anesthesia on one study day. Anesthesia was induced on two other study days without any premedication by inhalation of isoflurane (3–4%), nitrous oxide (70%), and oxygen. Thiopental and opioids were not administered. Vecuronium (10 mg)
was administered intravenously to facilitate endotracheal intubation; muscle relaxation was subsequently maintained by an infusion of vecuronium (Program 2 syringe pump, Becton-Dickinson, Lincoln Park, NJ) adjusted to maintain zero to one twitch in response to supramaximal train-of-four electrical stimulation of the ulnar nerve at the wrist. Nitrous oxide was discontinued after induction, and the trachea of each patient was intubated. Mechanical ventilation was adjusted to maintain end-tidal PCO₂ near 35 Torr.

Anesthesia was maintained with isoflurane at an end-tidal concentration of 0.8 or 1.2% in oxygen (1.2% is a typical anesthetic dose). Steady-state end-tidal gas concentrations are in equilibrium with mixed-venous blood and correlate extremely well with brain partial pressures. Respiratory gas concentrations were quantified using the analog output of an end-tidal gas analyzer (Datex Medical Instrumentation, Tewksbury, MA).

Active warming on each study day was preceded by a 10-min control period during which baseline values were recorded. Volunteers were wrapped below the neck with thin plastic sheeting to prevent evaporation of sweat; two disposable covers were then placed over the chest and legs and connected to Bair Hugger forced-air warmers (model 200, Augustine Medical, Minneapolis, MN) (17). Volunteer’s arms were positioned at their sides and covered by plastic but not directly heated (to minimize locally mediated vasodilation). The forced-air warmer was set on “low” (~37°C) for 15 min, then increased to “medium” (~40°C) for an additional 15 min, and finally increased to “high” (~43°C) until esophageal temperature exceeded that producing maximal sweating by ~0.5°C. Warming was initiated slowly because the skin surface is far more sensitive to rapid than to slow thermal perturbations (8).

Lactated Ringer solution warmed to 40°C was infused into an antecubital vein on the right arm at a rate of 5 ml·kg⁻¹·h⁻¹ until sweating was clinically apparent; the infusion rate was then increased to 20 ml·kg⁻¹·h⁻¹ for the remainder of the study. These infusion rates were chosen to prevent dehydration during vigorous sweating.

Monitoring. Sweating on each thigh was quantified by passing 2.0 l/min of anhydrous oxygen across 6-cm-diameter circles of skin covered with air-tight, adhesive ostomy appliances (nos. 3706 and 3806, Hollister Products, Libertyville, IL). Cutaneous water loss (in g·m⁻²·h⁻¹) was calculated from the gas flow rate (model FMA-5000, Omega Engineering), temperature, and relative humidity (model HX93, Omega Engineering). Similar methods have been used by previous investigators (12). Oxygen flowing into the sweating sensor on the left thigh was at ambient temperature, and that sensor was exposed to the ambient environment during the study. The tubing supplying gas to the sensor on the right thigh and the sensor itself were covered by the forced air warming blanket.

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

Vasodilation in forearm capillaries was quantified using laser Doppler flowmetry (Periflux 3, Perimed, Piscataway, NJ) with the fiber-optic probe positioned on the radial side of the left midforearm (9, 19). Absolute left middle fingertip blood flow was quantified using venous-occlusion volume plethysmography at 5 min intervals (2).

Core temperature was measured in the distal fourth of the esophagus using disposable YSI series 700 thermistor probes (Mon-a-Therm, St. Louis, MO) connected to a thermometer (model 5831, Omega, Stamford, CT) with a precision of 0.01°C. Core temperatures just before the start of active warming (no isoflurane day) or induction of anesthesia (on the other 2 days) were considered control values. Tympanic membrane and skin surface temperatures were monitored using two-channel electronic thermometers (model 8700, Mallinckrodt, St. Louis, MO). The aural probe was inserted by the volunteers until they felt the thermocouple touch the tympanic membrane; we considered appropriate placement confirmed when the volunteers easily detected gentle rubbing of the attached wire. The probe was then securely taped in place, and the aural canal was occluded with cotton. As in our previous studies, area-weighted mean skin surface temperature was computed from measurements at 10 sites, using the following regional percentages: head, 6%; upper arms, 9%; forearms, 6%; hands, 4.5%; back, 19%; chest, 9.5%; abdomen, 9.5%; thigh, 19%; calves, 11.5%; and feet, 6% (5). The temperature of the gas within each sweating sensor and the adjacent skin surface temperature were also recorded.

Heart rate and oxyhemoglobin saturation were monitored continuously using three-lead electrocardiography and a pulse oximeter (N200, Nellcor, Hayward, CA). Blood pressure at the ankle was determined oscillometrically at 5-min intervals (Dinamap 1846 SX, Critikon, Tampa, FL). Analog data from the laser Doppler, thermometers, sweating sensors, respiratory gas monitor, and pulse oximeter were recorded at 2.5-min intervals, using a previously described data acquisition system (24). Each recorded value represented the mean of 64 determinations at 1 s intervals.

Data analysis. The maximum sweating rate in each study at each site was determined by inspection of the S-shaped sweating vs. esophageal temperature curve in each individual. The slope of the curve was determined by linear regression with the use of values from 25 to 75% of the maximum sweating rate. Gain is normally expressed as the slope of the sweating rate vs. core temperature curve. However, the observed change in esophageal temperature required to increase sweating from control to maximum values was small. To avoid dividing by numbers sometimes approaching zero and producing large (and nonparametric) values, we express gain as the temperature change required to produce a 25–75% maximum increase in sweating rate. Threshold temperatures were calculated from the intercept of the 25–75% regression line with background insensible water loss. The esophageal temperature triggering grade 2 sweating was considered the threshold for the forehead.

Variability in the laser Doppler values precluded a similar analysis of precapillary vasodilation. Instead, data...
TABLE 1. Morphometric and environmental data

<table>
<thead>
<tr>
<th>Age, yr</th>
<th>Wt, kg</th>
<th>Ht, cm</th>
<th>Fat, %</th>
<th>Tcore, °C</th>
<th>Hhum, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>29±6</td>
<td>75±4</td>
<td>175±5</td>
<td>22.4±1.3</td>
<td>38±5</td>
</tr>
<tr>
<td>Women</td>
<td>29±7</td>
<td>63±7*</td>
<td>166±3*</td>
<td>22.3±0.7</td>
<td>36±10</td>
</tr>
</tbody>
</table>

Values are means ± SD. Tcore, room temperature; Hhum, room humidity. * Significant difference between men and women.

RESULTS

The ages, weights, heights, percentage of body fat, prevailing room temperatures, and prevailing room humidities for the men and women are shown in Table 1. The women were significantly shorter, weighed less, and had a higher percentage of body fat; however, body habitus was nearly normal in all volunteers.

Measured end-tidal isoflurane concentrations, control core temperatures, and precapillary vasodilation thresholds are shown in Table 2. Core temperatures before active warming or induction of anesthesia were slightly but not significantly higher in women (~36.7 ± 0.2°C) than men (~36.5 ± 0.3°C).

Absolute finger blood flow did not increase significantly during the study. Precapillary vasodilation thresholds were significantly greater during anesthesia than during hyperthermia alone (although the increase in women was statistically significant only during 1.2% isoflurane). Although variability in the laser Doppler index precluded quantitative evaluation of vasodilation gain, it was high in all cases (e.g., ≥0.5°C required to increase response from 25 to 75% of maximum) and was apparently unaltered by isoflurane anesthesia.

TABLE 2. Isoflurane concentrations, control esophageal temperatures, and vasodilation thresholds

<table>
<thead>
<tr>
<th>% Isoflurane</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.0</td>
<td>0.81±0.01</td>
</tr>
<tr>
<td>Control esophageal temperature, °C</td>
<td>36.5±0.3</td>
<td>36.5±0.4</td>
</tr>
<tr>
<td>Vasodilation threshold, °C</td>
<td>37.0±0.2</td>
<td>38.0±0.4*</td>
</tr>
</tbody>
</table>

Values are means ± SD. * Significantly different from control (0% isoflurane) within each group. There were no statistically significant differences between men and women.
FIG. 1. Sweating rate from unwarmed site in single typical male volunteer shows threshold, thermosensitivity, and maximum intensity during hyperthermia alone (0%) and at 0.8 and 1.2% end-tidal isoflurane concentration. Thresholds were markedly increased by anesthesia; in contrast, gains and maximum sweating rates were relatively well preserved.

and did not increase significantly after sweating started (Fig. 3). Hemodynamic responses and the difference between esophageal and tympanic membrane temperatures were comparable in men and women.

**DISCUSSION**

Most operating rooms in developed countries are now air conditioned, and perioperative hypothermia is therefore the typically observed thermal disturbance. However, in tropical environments before air conditioning was used, anesthesia commonly caused hyperthermia (14). Although thresholds were not investigated [and many patients were given atropine, which prevents sweating (7)], sweating was reported in some hyperthermic patients. The purpose of the present study was to quantify hyperthermia-induced thermoregulatory sweating and active precapillary vasodilation during general anesthesia.

We chose to study isoflurane in part because it is currently the most commonly used anesthetic in the US. More importantly, we chose it because end-tidal gas monitoring of volatile anesthetics allows constant brain concentrations to be maintained for long periods of time. In contrast, determination of plasma concentrations of intravenous drugs requires laboratory analysis, and the results rarely are available until well after completion of the study. Because core temperature per se alters drug disposition and metabolism, it is especially difficult to maintain constant plasma concentrations while increasing core temperature (as required in this study). A limitation of previous studies of sweating during intravenous anesthesia is that plasma anesthetic concentrations were not measured (24).

We have previously demonstrated that various general anesthetics decrease the thermoregulatory threshold for vasoconstriction in response to core hypothermia (18, 19) and that the decrease produced by isoflurane anesthesia is dose dependent (23). Our current data indicate that isoflurane likewise produces a dose-dependent increase in the core temperature, triggering thermoregulatory sweating. Accordingly, the interthreshold range (i.e., core temperatures not triggering thermoregulatory responses) is increased approximately sevenfold by isoflurane anesthesia, from ~0.6 to ~4°C (11). Why isoflurane anesthesia should decrease thresholds for vasoconstriction ~3°C but increase the threshold for sweating and active precapillary vasodilation by only ~1°C remains unclear. However, an aggressive response to increasing core temperature is teleologically appropriate because hyperthermia is far more dangerous than comparable hypothermia.

Mean skin temperatures were significantly higher during isoflurane administration than without anesthesia. Previous studies suggest that skin temperature contributes ~10% of thermal input to the central thermoregulatory system (12). Consequently, it is likely that the esophageal temperatures triggering sweating during isoflurane administration would have been ~0.3°C higher had skin temperature been maintained near 35.5°C during all treatments.

The sweating thresholds in unanesthetized women were ~0.5°C higher than in men, and the thresholds remained higher at 0.8 and 1.2% isoflurane. The increase was only partially explained by differences in control

<table>
<thead>
<tr>
<th>TABLE 3. Mean and local skin temperatures, sensor gas temperatures, sweating threshold and gains, and maximum sweating rates</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>% Isoflurane</strong></td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td><strong>Mean skin temperature, °C</strong></td>
</tr>
<tr>
<td><strong>Skin near warmed sensor, °C</strong></td>
</tr>
<tr>
<td><strong>Skin near unwarmed sensor, °C</strong></td>
</tr>
<tr>
<td><strong>Gas in warmed sensor, °C</strong></td>
</tr>
<tr>
<td><strong>Gas in unwarmed sensor, °C</strong></td>
</tr>
<tr>
<td><strong>Threshold, °C</strong></td>
</tr>
<tr>
<td><strong>Gain, °C</strong></td>
</tr>
<tr>
<td><strong>Maximum, g - m⁻² - h⁻¹</strong></td>
</tr>
</tbody>
</table>

Values are means ± SD. Gain is normally expressed as slope of sweating rate vs. core temperature curve. However, observed change in esophageal temperature required to increase sweating from control to maximum values was small. To avoid dividing by numbers sometimes approaching 0 and producing large (and nonparametric) values, we express gain as temperature change required to produce a 25–75% of maximum increase in sweating rate. Sweating responses were virtually identical on the warmed thigh. * Significantly different from control (0% isoflurane) within each group. † Significantly different in men and women.
Threshold \( (^\circ C \) vs. Isoflurane (%) graph

- **Women**
- **Men**

**FIG. 2.** Thermoregulatory threshold for sweating (unwarmed thigh) increased linearly with increasing end-tidal isoflurane concentration. In men, regression equation was threshold \( (^\circ C \) = 36.6\(^\circ C \) + 1.3[isoflurane], \( r^2 = 0.94 \). In women, regression equation was threshold \( (^\circ C \) - 37.1\(^\circ C \) + 1.0[isoflurane], \( r^2 = 0.87 \).

Temperatures, which differed by only \(-0.2^\circ C\). These data are consistent with the observations of Havenith and Medendorp (6) that women sweat less than men (although they found that gender did not independently predict sweating once the subjects’ percentage body fat and surface-to-mass ratios were considered). Interestingly, the higher threshold in women was well preserved during anesthesia. These data suggest that isoflurane produced a consistent increase in the threshold in both men and women rather than an increase to a particular temperature.

Thresholds determined by qualitative observation of forehead moisture were similar to those obtained with quantitative sweating analysis. These data validate the method we used previously when reporting the sweating thresholds during routine surgery (16) and in patients undergoing cardiopulmonary bypass (21). Furthermore, similarity between the sweating thresholds obtained in this study (\(-38.2^\circ C\) during 1.2% isoflurane) and those reported previously (38.3 \pm 0.3^\circ C\) during 1.1 \pm 0.2% isoflurane) suggests that thresholds are similar in surgical patients and relatively unstimulated volunteers (16). The presence of similar sweating thresholds at the forehead and thigh is consistent with previous observations that sweating is triggered at similar core temperatures in different areas of the body (10).

Sweat production is largely neuronally mediated (by postganglionic cholinergic sympathetic nerves), but there also is a small degree of local control. Thus local sweating rates (at a given core and mean skin temperature) may be increased by local cutaneous warming (15). Although the air temperature in our warmed and unwarmed sensors differed by \(-6^\circ C\), skin temperatures differed much less (because evaporative heat loss kept the skin relatively cool) and did not produce significant differences in sweating rates. This observation is consistent with previous studies indicating that small differences in local temperature are of little consequence (15).

Physiological compensation for dehydration limits sweating and might have decreased our measured gains and maximum intensities (13). However, our volunteers presumably started each study day reasonably well hydrated, and intravenous fluid was administered at a rate far exceeding estimated cutaneous losses throughout each study. Thus it is unlikely that our data are confounded by inadequate fluid replacement.

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. Because end-tidal isoflurane concentrations were constant throughout each study, sweating appears to have been triggered by experimental hyperthermia.

Maximum sweating rates in our volunteers were similar to those reported previously (10, 12, 25), suggesting that our population was relatively representative of young healthy adults and our methods were free from serious systematic error. Maximum sweating intensities were relatively well preserved at each tested dose. Similarly, sweating gain at 0.8 and 1.2% isoflurane was comparable to control (unanesthetized) values. We have previously observed that maximum vasoconstriction intensities are similar in anesthetized patients (23) and unanesthetized volunteers (18). Moreover, the maximum intensity of nonshivering thermogenesis (in infants) appears well preserved (unpublished data). The preservation of gain and maximum response intensity for sweating during isoflurane anesthesia contrasts markedly with many other physiological responses such as the CO\(_2\) response curve, which is both “shifted to the right” and “flattened” during isoflurane anesthesia.

Sweating and vasoconstriction thresholds were similar in this study, as previously reported in unanesthetized humans (25). However, maximal cutaneous blood flow (as might be desired during microvascular surgery) may not occur until core temperature increases yet another degree Celsius. Previous studies indicate that hyperthermia increases entire forearm blood flow three- to fourfold (25). Because muscle flow increases little during heat stress (4), actual skin blood flow must increase far more than three- to fourfold.

**FIG. 3.** Difference between distal esophageal (esoph) and tympanic membrane (TM) temperatures. Average % difference was \(0.1-0.2^\circ C\) at 0% and did not increase significantly after sweating started. Temperature change of 0 identifies sweating threshold.
Variability in the minute-to-minute laser Doppler values precluded determination of active vasodilation gain and made detection of the vasodilation threshold difficult. This variability contrasts sharply with remarkably precise detection of the sweating threshold. The extent to which this variability results from the laser Doppler (22) or from inconsistent responses in our volunteers remains unclear.

In summary, the esophageal temperature sweating threshold increased linearly from 36.6 ± 0.1 to 38.1 ± 0.1°C in the men and from 37.1 ± 0.3 to 38.3 ± 0.2°C in the women. The thresholds at each isoflurane concentration were significantly higher during hyperthermia alone. Similarly, the thresholds were higher in women than men. Gain and maximum sweating intensities were similar at each anesthetic concentration and in men and women. These data indicate that isoflurane anesthesia significantly increases the esophageal temperature triggering thermoregulatory sweating but that the gain and maximum sweating rate are relatively well preserved.

We thank Mon-a-Therm for the donation of the thermometers and thermistors we used, Datex Medical Instrumentation for the loan of a Datex Capnomac, Becton-Dickinson for the loan of a Program 2 syringe pump, and Cincinnati Sub-Zero for the loan of a Blanketrol II. We also appreciate the donation of isoflurane anesthesia by Anaquest. This study was supported by National Institute of General Medical Sciences Grant R29-GM-39723.

These data were presented in part at the Annual Meeting of the American Society of Anesthesiologists, San Francisco, CA, in October 1991.

Received 13 December 1991; accepted in final form 16 July 1992.

REFERENCES


