Relative Contribution of Skin and Core Temperatures to Vasoconstriction and Shivering Thresholds during Isoflurane Anesthesia

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Background: Thermoregulatory control is based on both skin and core temperatures. Skin temperature contributes ~20% to control of vasoconstriction and shivering in unanesthetized humans. However, this value has been used to arithmetically compensate for the cutaneous contribution to thermoregulatory control during anesthesia—although there was little basis for assuming that the relation was unchanged by anesthesia. It even remains unknown whether the relation between skin and core temperatures remains linear during anesthesia. We therefore tested the hypothesis that mean skin temperature contributes ~20% to control of vasoconstriction and shivering, and that the contribution is linear during general anesthesia.

Methods: Eight healthy male volunteers each participated on 3 separate days. On each day, they were anesthetized with 0.6 minimum alveolar concentrations of isoflurane. They then were assigned in random order to a mean skin temperature of 29, 31.5, or 34°C. Their cores were subsequently cooled by central-venous administration of fluid at ~3°C until vasoconstriction and shivering were detected. The relation between skin and core temperatures at the threshold for each response in each volunteer was determined by linear regression. The proportionality constant was then determined from the slope of this regression. These values were compared with those reported previously in similar but unanesthetized subjects.

Results: There was a linear relation between mean skin and core temperatures at the vasoconstriction and shivering thresholds in each volunteer: $r^2 = 0.98 \pm 0.02$ for vasoconstriction, and $0.96 \pm 0.04$ for shivering. The cutaneous contribution to thermoregulatory control, however, differed among the volunteers and was not necessarily the same for vasoconstriction and shivering in individual subjects. Overall, skin temperature contributed $21 \pm 8\%$ to vasoconstriction, and $18 \pm 10\%$ to shivering. These values did not differ significantly from those identified previously in unanesthetized volunteers: $20 \pm 6\%$ and $19 \pm 8\%$, respectively.

Conclusions: The results in anesthetized volunteers were virtually identical to those reported previously in unanesthetized subjects. In both cases, the cutaneous contribution to control of vasoconstriction and shivering was linear and near 20%. These data indicate that a proportionality constant of ~20% can be used to compensate for experimentally induced skin-temperature manipulations in anesthetized as well as unanesthetized subjects. (Key words: Temperature; thermoregulation.)

HUMAN core temperature is highly regulated because even small deviations from the target temperature range provoke effective thermoregulatory defenses.¹ The core temperatures (at a given skin temperature) triggering thermoregulatory defenses identify the thresholds for each response.² The problem, however, is that both core

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and skin temperatures contribute to thermoregulatory control mechanisms.\textsuperscript{3–6} This makes experimental determination of core-temperature thresholds challenging because it is difficult to independently manipulate core and skin temperatures in humans.

Three models have been developed that permit accurate determination of core-temperature response thresholds in humans. The first involves exercise-induced hyperthermia followed by gradual core cooling while skin temperature is kept constant by water immersion.\textsuperscript{7} The difficulty here is that exercise \textit{per se} significantly increases the sweating threshold.\textsuperscript{8,9} The second model produces isolated core cooling by central-venous administration of ice-cold fluid.\textsuperscript{10} The obvious limitation of this technique is that the degree of core cooling is restricted by the amount of fluid that can be given safely. The third model restricts thermal manipulation to the legs in subjects in whom lower-body thermal sensation is prevented by neuraxial anesthesia.\textsuperscript{11} The major limitations of this method are the requirement for neuraxial anesthesia and the fact that both epidural\textsuperscript{12} and spinal\textsuperscript{13} anesthesia themselves alter thermoregulatory response thresholds.

All of these models remain useful, but their limitations preclude general application. This led to development of a fourth model in which both skin and core temperatures are manipulated, with subsequent arithmetic compensation for the contribution of skin temperature.\textsuperscript{14} This model is noninvasive and can be used over a wide range of skin and core temperatures—as is often necessary for testing drugs that markedly impair thermoregulatory defenses. However, it depends critically on knowing the contribution of mean skin temperature to central control of thermoregulatory responses, as expressed by the equation:

\[
\text{Threshold}_{\text{MBT}} = \beta T_{\text{skin}} + (1 - \beta)T_{\text{core}},
\]

where \(T_{\text{MBT}}\) is the sweating or vasodilation threshold in terms of mean body temperature, \(T_{\text{skin}}\) is mean skin temperature, and \(T_{\text{core}}\) is core temperature, all in degrees Celsius. The proportionality constant, \(\beta\), indicates the cutaneous contribution to the threshold.

The contribution of mean skin temperature to the thresholds for sweating is approximately 10%,\textsuperscript{4} whereas Cheng \textit{et al.}\textsuperscript{15} showed that skin contributes \(\sim 20\%\) to control of vasoconstriction and shivering in unanesthetized humans. The difficulty, however, is that arithmetic compensation for the cutaneous contribution to thermoregulatory control has also been used extensively during anesthesia,\textsuperscript{14,16,17} although there was no specific support for the assumption that the proportionality constant remained unchanged. It even remains unknown whether the relation between skin and core temperatures is linear during anesthesia. We therefore tested the hypothesis that the mean skin temperature contributes \(\sim 20\%\) to control of vasoconstriction and shivering in anesthetized men, and that the contribution is linear.

**Methods**

With approval from the Committee on Human Research at the University of California, San Francisco, and informed consent, we studied eight healthy male volunteers, each on 3 separate days. None was obese, was taking medication, or had a history of thyroid disease, dysautonomia, or Raynaud's syndrome. The volunteers' demographic and morphometric characteristics included (mean \(\pm\) SD): age 29 \(\pm\) 4 yr, height 177 \(\pm\) 9 cm, weight 79 \(\pm\) 10 kg, and body fat 24 \(\pm\) 5% as determined using infrared interactance (Futrex 1000, Futrex, Hagerstown, MD).\textsuperscript{18}

To avoid circadian fluctuations, studies were scheduled at the same time each day. The volunteers fasted for 8 h before each study day and rested supine on a standard operating room table. During the studies, they were minimally clothed and ambient temperature was maintained near 22°C.

**Protocol**

On each study day, a catheter was inserted in a left forearm vein. Anesthesia was induced with intravenous propofol (\(\sim 5\) mg/kg). Volunteers were paralyzed with 0.25 mg/kg mivacurium, and the trachea intubated with a tube coated with lidocaine jelly. At hourly intervals, a few milliliters of 4% topical lidocaine were injected just above the endotracheal tube cuff \textit{via} a pediatric feeding tube.

A 16-g catheter was then inserted into the superior vena cava \textit{via} the right jugular vein. Anesthesia was maintained with isoflurane at an end-tidal concentration of 0.6 minimum alveolar concentration (MAC) in 30% oxygen. Twenty minutes after induction of anesthesia, complete recovery from mivacurium paralysis was documented with supermaximal train-of-four stimulation of the ulnar nerve at the wrist. Subsequently, the volunteers breathed spontaneously; however, ventilation was assisted when necessary to maintain end-tidal pressure of carbon dioxide (\(\text{P}_{\text{ETCO}}\)) near 40 mmHg. A Foley catheter was inserted to prevent bladder distention.
Mean skin temperature on each study day was maintained at a randomly assigned target temperature of 34, 31.5, or 29°C. The designated skin temperature was maintained by a circulating-water mattress (Blanketrol II, Maxi-Therm blanket, Cincinnati Sub-Zero, Cincinnati, OH) and forced-air cover (Bair Hugger or Polar Air, Augustine Medical, Eden Prairie, MN). The devices were adjusted to keep both anterior and posterior and upper-and lower-body temperatures near the target values. The arms were shielded from active warming and cooling to avoid locally mediated vasomotion.

After the designated skin temperature had been reached, the volunteers were cooled by central-venous infusion of lactated Ringer’s solution at -3°C, as previously described. The solution was cooled by passing it through an aluminum cardiopulmonary bypass heat exchanger immersed in an ice-and-water slurry. The infusion rate was initially 10 ml/min, and it was adjusted at 1-min intervals to maintain a core cooling rate near 1.5°C/h. The maximum infusion rate was 120 ml/min. We have previously demonstrated that a cooling rate of 1.5°C/h does not trigger dynamic thermoregulatory responses. On study days in which the total infused volume exceeded 60 ml/kg, a single 10-mg intravenous bolus of furosemide was given.

On each study day, we continued core cooling through vasoconstriction until the shivering threshold was identified. Therefore, both the vasoconstriction and shivering thresholds were determined at three different skin temperatures in each volunteer. Anesthesia was then discontinued, and the bladder and intravenous catheters were removed.

Measurements
Core temperature was recorded from the tympanic membrane using Mon-a-Therm thermocouples (Mallinckrodt Anesthesiology Products, St. Louis, MO). The aural probes were 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 aural canal was occluded with cotton, the probe securely taped in place, and a gauze bandage positioned over the external ear. Mean skin-surface temperature was calculated from measurements at 15 area-weighted sites. Temperatures were recorded at 1-min intervals from thermocouples connected to a calibrated Iso-Thermex thermometer having an accuracy of 0.1°C and a precision of 0.01°C (Columbus Instruments, Columbus, OH).

Absolute right middle fingertip blood flow was quantified using venous-occlusion volume plethysmography at 5-min intervals. Oxygen consumption was evaluated by indirect calorimetry (Deltatrac, SensorMedics, Yorba Linda, CA). The metabolic monitor was set to the spontaneous mode. The system was calibrated daily using a known mixture of gases. Measurements were averaged over 1-min intervals.

Heart rate and oxyhemoglobin saturation were measured continuously using pulse oximetry, and blood pressure was determined oscillometrically at 5-min intervals at the left ankle. PetCO₂ was measured from the intratracheal tube during anesthesia. Each study day ended after shivering was detected.

Data Analysis
As in previous studies, significant vasoconstrictor threshold was defined by a decrease in fingertip blood flow to <0.25 ml/min. This flow corresponds to intense vasoconstriction (a forearm-minus-fingertip, skin-temperature gradient near 4°C). As in previous studies, a sustained increase in oxygen consumption of at least 30% identified shivering.

Core temperature thresholds from each volunteer were plotted against mean skin temperature at the times of vasoconstriction and shivering, and a least-squares linear regression was fit to the values to obtain the relation:

\[ T_{\text{core}} = ST_{\text{skin}} + K \]  

(2)

where \( S \) is the slope of the regression equation and \( K \) is the intercept.

The slope of these individual regression equations thus indicated the extent to which skin warming increased thermoregulatory tolerance for core hypothermia (i.e., how much skin warming was required to produce a given reduction in the vasoconstriction and shivering thresholds). To determine the fractional contribution of skin temperature to thermoregulatory control of vasoconstriction and shivering (\( \beta \)), we rearranged equation 1:

\[ T_{\text{core}} = \left( -\frac{\beta}{1-\beta} \right) T_{\text{skin}} + \frac{\text{Threshold}_{\text{shtr}}}{1-\beta}. \]  

(3)

Combining equations 2 and 3 gives

\[ S = -\frac{\beta}{1-\beta}. \]  

and consequently that...


Table 1. Ambient Temperature, Anesthetic Management, and Core Cooling Rates on the Three Study Days

<table>
<thead>
<tr>
<th></th>
<th>Target Skin Temperature (°C)</th>
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<tbody>
<tr>
<td></td>
<td>34</td>
</tr>
<tr>
<td>Mean skin temperature (°C)</td>
<td>Vasoconstriction</td>
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<td></td>
<td>Shivering</td>
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<td>Ambient temperature (°C)</td>
<td>Vasoconstriction</td>
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<td></td>
<td>Shivering</td>
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<tr>
<td>End-tidal P&lt;sub&gt;CO2&lt;/sub&gt; (mmHg)</td>
<td>Vasoconstriction</td>
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<td></td>
<td>Shivering</td>
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<tr>
<td>End-tidal [isoflurane] (%)</td>
<td>Vasoconstriction</td>
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<tr>
<td></td>
<td>Shivering</td>
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<tr>
<td>Core cooling rate (°C/h)</td>
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</table>

The first line of each row represents data obtained at the vasoconstriction threshold whereas the second line shows the results at the shivering threshold. Per protocol, mean skin temperatures differed significantly among the study days. Ambient temperature, end-tidal P<sub>CO2</sub>, and end-tidal isoflurane concentration did not differ between the vasoconstriction and shivering thresholds. The core cooling rates did not differ significantly on the three study days. Data are mean ± SD.

\[
\beta = \frac{S}{S - 1} \quad (5)
\]

where \(\beta\) is the proportionality constant.\(^{15}\)

The correlation coefficients for the skin versus core regressions indicated the extent to which the vasoconstriction and shivering thresholds were linear functions of skin and core temperatures. The cutaneous contributions to vasoconstriction and shivering (\(\beta\)) during isoflurane anesthesia were compared with values obtained previously in unanesthetized male volunteers with two-tailed unpaired \(t\) tests.\(^{15}\)

Core cooling rates were calculated by linear regression, using temperatures obtained between the vasoconstriction and shivering thresholds. Ambient temperature, P<sub>ETCO2</sub>, heart rate, and mean arterial pressure were recorded at each threshold. Results on each study day were compared using analysis of variance and Scheffe’s F tests. Results are expressed as means ± SDs; differences were considered significant when \(P < 0.05\).

**Results**

There were no complications associated with the study, and none of the volunteers developed pulmonary edema. Two volunteers began to experience vasoconstriction at mean skin temperatures of 29.8°C and at 29.7°C, just before the lowest target skin temperature was reached. Cooling at the highest skin temperature (34°C) required the largest amount of fluid administration: 6.5 ± 1.8 L. The volunteers required 1.5 ± 0.6 L of lactated Ringer’s solution on the 31.5°C day, and only 0.6 ± 0.2 L when mean skin temperature was maintained at 29°C.

Per protocol, mean skin temperatures differed significantly among the study days. Core cooling rates were similar on the three study days. Ambient temperatures, P<sub>ETCO2</sub>, and end-tidal isoflurane concentrations were similar at each threshold and on each study day (table 1). There was no significant difference in heart rate or mean arterial blood pressure among the days.

There was a linear relation between mean skin and core temperatures at the vasoconstriction and shivering thresholds in each volunteer: \(r^2 = 0.98 ± 0.02\) for vasoconstriction, and \(0.96 ± 0.04\) for shivering. The cutaneous contribution to thermoregulatory control, however, differed among the volunteers (fig. 1). Overall, skin temperature contributed 21 ± 8% to vasoconstriction, and 18 ± 10% to shivering (table 2). The cutaneous contributions to vasoconstriction and shivering did not differ significantly from those identified previously in similar, but unanesthetized, male volunteers: 20 ± 6% and 19 ± 8%, respectively.

There was no correlation between the cutaneous contributions to vasoconstriction and shivering in individual men (\(r^2 = 0.15\)). One volunteer, for example, had a 15% cutaneous contribution to vasoconstriction but only a 2% contribution to shivering. Data from another volunteer yielded only 8% skin contribution to vasoconstriction, 21% for shivering. The mean difference between skin contribution to thermoregulatory control of vasoconstriction and of shivering was 3 ± 13% (fig. 2).

**Discussion**

Our data indicate that the cutaneous contribution to thermoregulatory control is linear during isoflurane anesthesia, with the regression correlation coefficients...
being 0.98 ± 0.02 for vasoconstriction and 0.96 ± 0.04 for shivering. In this regard, our results resemble those of a previous study of our laboratory conducted by Cheng et al.,15 who also observed a highly linear relationship.

The cutaneous contribution to the control of vasoconstriction varied among the volunteers, with the range spanning 8–34%. The cutaneous contribution to shivering differed even more among the volunteers. Furthermore, there was no correlation between the cutaneous contributions to vasoconstriction and shivering within each volunteer. These data indicate that the proportionality constants for vasoconstriction and shivering vary greatly, even within the same individual. In this regard also, our results are similar to those reported by Cheng et al.,15 in which comparable intra- and interindividual variability was observed. These results suggest that thermal afferent signals may be integrated independently in regard to control of vasoconstriction and shivering. Independent integration modes would be consistent with the impression of some investigators that the spinal cord contributes more to control of shivering than to other thermoregulatory responses.25,26

The average cutaneous contribution to control of vasoconstriction was 21 ± 8%, which is virtually identical to the 20 ± 6% observed in unanesthetized men.15 Skin temperature contributed 18 ± 10% to the

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**Fig. 1.** Individual mean skin and core temperatures at the vasoconstriction (squares) and shivering (circles) thresholds in the eight volunteers. There was a linear relation between mean skin and core temperatures at the vasoconstriction and shivering thresholds in each volunteer (lines): $r^2 = 0.98 \pm 0.02$ for vasoconstriction and $0.96 \pm 0.04$ for shivering. Overall, skin temperature contributed $21 \pm 8\%$ to vasoconstriction and $18 \pm 10\%$ to shivering.
control body temperature at a slightly higher temperature than men, even during the follicular phase of the menstrual cycle. Core temperatures are an additional 0.3–0.7°C greater during the remaining portions of the cycle. However, we have previously demonstrated that the relationship between skin and core temperature is linear in unanesthetized female volunteers and that the cutaneous contribution to control of vasoconstriction and shivering is near 20%. Thus, it seems likely that the shape and nature of this relationship would be similar in anesthetized women.

Preliminary studies indicated that our intubated volunteers would not tolerate isoflurane concentrations less than 0.6 MAC. Furthermore, this MAC fraction approaches the threshold for memory. We also found that higher anesthetic concentrations could not be used because they decreased the shivering threshold to the point at which it could not be reached with a safe fluid volume if mean skin temperature was kept at 34°C. Consequently, 0.6 MAC was the only anesthetic dose we tested. It thus remains possible that the cutaneous contribution to vasoconstriction and shivering differs at other concentrations, although it seems unlikely that such a fundamental thermoregulatory process is highly dose-dependent. More importantly, isoflurane was the only anesthetic tested; the cutaneous contribution to thermoregulatory control may differ with opioids, sedatives, or other anesthetics.

A limitation of our study is that large volumes of fluid were burned.
were required on the study day with a 34°C target skin temperature. Dehydration significantly increases the sweating threshold; similarly, excessive hydration may reduce it. However, the sweating threshold was not determined in this study. Although dehydration synergistically augments vasoconstriction, excessive vascular volume does not influence the threshold or gain of vasoconstriction. It is also unlikely that vascular volume has any effect on shivering. Only a small amount of fluid was required on the study days thus suggests that the relatively large fluid volume given on 1 day did not significantly alter the response thresholds.

In summary, there was a highly linear relation between mean skin and core temperatures at the vasocn- striction and shivering thresholds in each volunteer: $R^2 = 0.98 \pm 0.02$ for vasoconstriction and $0.96 \pm 0.04$ for shivering. There was substantial variability in the cutaneous contribution to control of vasoconstriction and shivering, both among and between volunteers. Skin temperature contributed 21 ± 8% to control of vasoconstriction and 18 ± 10% to shivering in our volunteers. These average contributions are virtually identical to those reported previously in unanesthetized volunteers. A proportionality constant of $\approx 20\%$ can thus be used to compensate for experimentally induced skin-temperature manipulations in anesthetized as well as unanesthetized subjects.

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