Propofol Linearly Reduces the Vasoconstriction and Shivering Thresholds

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Background: Skin temperature is best kept constant when determining response thresholds because both skin and core temperatures contribute to thermoregulatory control. In practice, however, it is difficult to evaluate both warm and cold thresholds while maintaining constant cutaneous temperature. A recent study shows that vasoconstriction and shivering thresholds are a linear function of skin and core temperatures, with skin contributing 20 ± 6% and 19 ± 8%, respectively. (Skin temperature has long been known to contribute ≈10% to the control of sweating.) Using these relations, we were able to experimentally manipulate both skin and core temperatures, subsequently compensate for the changes in skin temperature, and finally report the results in terms of calculated core-temperature thresholds at a single designated skin temperature.

Methods: Five volunteers were each studied on 4 days: (1) control; (2) a target blood propofol concentration of 2 μg/ml; (3) a target concentration of 4 μg/ml; and (4) a target concentration of 8 μg/ml. On each day, we increased skin and core temperatures sufficiently to provoke sweating. Skin and core temperatures were subsequently reduced to elicit peripheral vasoconstriction and shivering. We mathematically compensated for changes in skin temperature by using the established linear cutaneous contributions to the control of sweating (10%) and to vasoconstriction and shivering (20%). From these calculated core-temperature thresholds (at a designated skin temperature of 35.7°C), the propofol concentration–response curves for the sweating, vasoconstriction, and shivering thresholds were analyzed using linear regression. We validated this new method by comparing the concentration-dependent effects of propofol with those obtained previously with an established model.

Results: The concentration–response slopes for sweating and vasoconstriction were virtually identical to those reported previously. Propofol significantly decreased the core temperature triggering vasoconstriction (slope = −0.6 ± 0.1°C·μg·ml⁻¹, r² = 0.98 ± 0.02) and shivering (slope = −0.7 ± 0.1°C·μg·ml⁻¹, r² = 0.95 ± 0.05). In contrast, increasing the blood propofol concentration increased the sweating threshold only slightly (slope = 0.1 ± 0.1°C·μg·ml⁻¹, r² = 0.46 ± 0.39).

Conclusions: Advantages of this new model include its being nearly noninvasive and requiring relatively little core-temperature manipulation. Propofol only slightly alters the sweating threshold, but markedly reduces the vasoconstriction and shivering thresholds. Reductions in the shivering and vasoconstriction thresholds are similar; that is, the vasoconstriction-to-shivering range increases only slightly during anesthesia. (Key words: Anesthetics, intravenous; propofol. Temperature: regulation. Thermoregulation: shivering; sweating; vasoconstriction.)

BOTH skin and core temperatures contribute to thermoregulation. Consequentially, skin temperature is best kept constant when determining thermoregulatory response thresholds (which conventionally are expressed in terms of the triggering core-temperature). However, because the skin is the body’s major heat exchanger, it is difficult to evaluate both warm- and cold-response thresholds while maintaining constant cutaneous temperature.

Three models developed in recent years permit thresholds to be determined at constant sentient skin temperature. Although these techniques have proven useful, they have distinct limitations, including the need for epidural anesthesia, vigorous exercise, or insertion of a central venous cannula and administration of large fluid volumes. These limitations have re-
stricted general applicability, especially to drug testing. Consequently, we sought to develop a minimally invasive method of evaluating the thermoregulatory effects of sedative and anesthetic drugs.

The model we propose depends critically on an accompanying investigation in which we demonstrate that the thresholds for vasoconstriction and shivering are a linear function of skin and core temperatures and that skin temperature contributes 20 ± 6% and 19 ± 8% to vasoconstriction and shivering, respectively.9 That skin temperature contributes 10% to the control of sweating has long been established.1 This consistent and linear relation between skin and core temperature allows us to experimentally manipulate both skin and core temperature, subsequently compensate for the changes in skin temperature, and finally report our results in terms of calculated core-temperature thresholds at a single designated skin temperature.

We validated this new method by determining the concentration-dependent effects of propofol on thermoregulatory responses and then comparing these results with those obtained previously with one of the established models. Our previous investigation8 evaluated the effects of propofol only to a target blood concentration of 4 μg/ml; furthermore, only sweating and vasoconstriction thresholds were determined. We extended those results by administering propofol to a target concentration in blood of 8 μg/ml, which is the concentration in blood at which 50% of patients move in response to skin incision,10 and evaluating the shivering threshold. This is the first systematic investigation of shivering during anesthesia.

Materials and Methods

With approval from the Committee on Human Research at the University of California, San Francisco, we studied five healthy men. None had participated in our previous investigation of sweating and vasoconstriction thresholds during propofol sedation.8 None was obese, was taking medication, or had a history of thyroid disease, dysautonomia, Raynaud's syndrome, or malignant hyperthermia. The volunteers' weight was 175 ± 6 cm (mean ± SD), total body mass 78 ± 10 kg, and age 30 ± 7 yr. The lean body mass was 60 ± 5 kg, as calculated from height (centimeters) and total body mass (kilograms) by the formula: lean body mass = 1.1 × total body mass - 128 × (total body mass/height).2,11

Volunteers were studied on 4 randomly ordered days within a one-week period: (1) control (no propofol); (2) a target blood propofol concentration of 2 μg/ml; (3) a target blood propofol concentration of 4 μg/ml; and (4) a target blood propofol concentration of 8 μg/ml. On each day, we increased skin and core temperatures sufficiently to provoke sweating. Skin and core temperatures were subsequently reduced to elicit peripheral vasoconstriction and then shivering. To compare core-temperature thresholds, we mathematically compensated for changes in skin temperature using the established linear cutaneous contributions to the control of sweating1 and to vasoconstriction and shivering.9 Sentient skin temperature was 35.7 °C in our previous investigation of propofol8; consequently, we designated that value as our reference skin temperature.

Protocol

The volunteers fasted for 8 h before arriving at the laboratory. During the studies, they were minimally clothed and rested supine on a standard operating room table. Ambient temperature was maintained at 23.0 ± 0.6 °C.

An antecubital vein in the left arm was cannulated for fluid and drug administration. A vein on the opposite arm was cannulated for blood samples. Propofol was infused using a pump (9000, Ohmeda, Steeton, England) controlled by a computer programmed to target blood propofol concentrations of 2, 4, and 8 μg/ml. A plasma efflux model was chosen,12 using pharmacokinetic data derived from a previous study of propofol pharmacokinetics during hypothermia.13 Combined data for hypothermic and normothermic volunteers were used to program the pump.

Airway support and ventilatory assistance were applied as appropriate for the degree of sedation. No support was required at a target propofol concentration of 2 μg/ml; a laryngeal mask was frequently necessary when the target concentration was 4 μg/ml and always necessary at the highest propofol concentration. Ventilation was assisted when necessary to maintain normal end-tidal carbon dioxide tension because hypercapnia may influence thermoregulatory responses.14 Oxygen was administered as necessary to maintain the hemoglobin oxygen saturation >95%. When a laryngeal mask was used, respiratory gases were provided by an anesthesia machine (Modulus CD, Ohmeda, Madison, WI) that was modified to prevent rebreathing.

Fifteen minutes after the propofol infusion started, skin and core temperatures were gradually increased using a circulating-water mattress (Blanketrol II, Maxitherm mattress, Cincinnati Sub-Zero, Cincinnati, OH)
and a forced-air warmer (Bair Hugger, Augustine Medical, Eden Prairie, MN). The volunteers were wrapped in plastic to prevent evaporative heat loss during this period. Warming continued until significant sweating was documented.

We evaluated sweating first because all anesthetics so far tested decrease the vasoconstriction and shivering thresholds far more than they increase the sweating threshold. The studies would thus take far longer were the vasoconstriction and shivering thresholds determined first (because more total thermal manipulation would be required). Although this consistent order increased the chances of a time-dependent systematic error, it reduced volunteer risk and the potential for acute drug tolerance.

Skin and core temperatures were then gradually cooled using the circulating-water mattress and a prototype forced-air cooler (Augustine Medical). This device provides 1,000 l/min air at 14–15°C into a full-body disposable convective cover. The study ended each day when shivering was detected.

The heating and cooling devices were adjusted so that back and chest skin temperatures remained comparable. Skin and core temperatures were changed ≥2°C/h because we have previously shown that this rate does not trigger dynamic thermoregulatory responses. The arms were uncovered and protected from active warming and cooling to minimize locally mediated vasomotion. Warming and cooling was started at nearly the same time each day, to minimize circadian variations.

Measurements
Core temperature was recorded from the tympanic membrane using thermocouples (Mon-a-Therm, Mallinckrodt Anesthesiology Products, St. Louis, MO). Visual inspection with an otoscope confirmed that the ear canal was free of wax. 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 securely taped in place, and a gauze bandage positioned over the external ear. There is an excellent correlation between tympanic membrane and distal esophageal temperatures in the perianesthetic period. Mean skin-surface temperature was calculated from measurements at 15 area-weighted sites, as previously described. Temperatures were recorded from thermocouples connected to calibrated 16-channel electronic thermometers having an accuracy of 0.1°C and a precision of 0.01°C (Iso-Thermex, Columbus Instruments International, Columbus, OH).

Sweating was quantified on the left upper chest, just below the clavicle, using a ventilated capsule. As in a previous study, sustained sweating >40 g·m⁻²·h⁻¹ was considered significant. Absolute right middle fingertip blood flow was quantified using venous-occlusion volume plethysmography at 5-min intervals. A sustained decrease in fingertip blood flow to <0.25 ml/min identified significant vasoconstriction.

Shivering was evaluated using oxygen consumption, as measured by a metabolic monitor (DeltaTrac, SensorMedics, Yorba Linda, CA). The system was calibrated daily using a known mixture of gases and additionally calibrated numerous times by burning ethanol. Measurements were averaged over 1-min intervals and recorded every 5 min. The system was used in canopy mode on the control day and when the target propofol concentration was 2 μg/ml; it was switched into ventilator mode when a laryngeal mask was required at higher propofol concentrations. A sustained increase in oxygen consumption to 125% of baseline values identified significant shivering.

Peripheral venous blood was sampled for measurement of blood propofol concentration at 15-min intervals, starting shortly before thermoregulatory responses were expected and ending when each threshold was identified. Three-milliliter samples were stored in heparinized tubes at 4°C for as long as 10 weeks (blood propofol concentrations decrease by <0.2% per week at 4°C) and subsequently analyzed using a high-pressure liquid chromatography assay, modified from the method of Plummer. This assay is linear to at least 20 μg/ml and has a detection limit of 2 ng/ml and a coefficient of variation of ±1% at 2 μg/ml.

Heart rate was monitored continuously using three-lead electrocardiography. Oxyhemoglobin saturation was measured continuously by pulse oximetry, and blood pressure was measured oscillometrically at 5-min intervals at the left ankle with the anesthesia machine. End-tidal carbon dioxide concentrations were measured (Rascal monitor, Ohmeda, Salt Lake City, UT); gas sampled by this monitor was returned to the oxygen consumption monitor. Analog and serial thermoregulatory data were recorded at 5-min intervals by using a modification of a previously described data-acquisition system. Anesthetic data were recorded using Macintosh (Apple, Cupertino, CA)–based patient information management software (IdaCare, version
1.3, Premier Anesthesia Systems, Atlanta, GA). Both systems operated asynchronously on a Macintosh FX (Apple) computer.

Data Analysis
Ambient temperature and humidity, as well as mean arterial blood pressure and heart rate on each study day, were first averaged within each volunteer; the resulting values were then averaged among volunteers. Results for the 4 study days were compared by repeated-measures analysis of variance and Scheffé's F tests. Average skin temperatures, end-tidal carbon dioxide tensions, and blood propofol concentrations at the sweating, vasoconstriction, and shivering thresholds were similarly compared by repeated-measures analysis of variance and Scheffé's F tests.

Previous studies demonstrate that the cutaneous contribution to sweating and vasoconstriction and shivering is linear. We were thus able to use the measured skin and core temperatures in degrees Celsius at each threshold to calculate the core-temperature threshold that would have been observed had skin been at the designated temperature (T_core(calculated), eq A3 in appendix):

\[
T_{\text{core(calculated)}} = T_{\text{core}} + \left( \frac{\beta}{1 - \beta} \right) (T_{\text{skin}} - T_{\text{skin(designated)}})
\]

where \( \beta \) = the fractional contribution of mean skin temperature to the threshold; \( T_{\text{core}} \) = the measured core temperature; \( T_{\text{skin}} \) = actual skin temperature; and \( T_{\text{skin(designated)}} \) = designated skin temperature. On the basis of previous studies, we used a \( \beta \) of 0.1 for sweating and a \( \beta \) of 0.2 for vasoconstriction and shivering.

The designated skin temperature was set at 35.7°C because that was the sentient skin temperature in our previous evaluation of thermoregulation during propofol administration. From the calculated core-temperature thresholds on each of the 4 study days, propofol concentration–response curves for the sweating, vasoconstriction, and shivering thresholds were determined using linear regression. The average slopes and correlation coefficients for the five volunteers were then computed.

Because linear regression was used to determine individual concentration–response relations for each response, there was no requirement that drug blood concentrations be similar at different thresholds, nor similar among subjects. Thus, pharmacokinetic population variability (and the effects of core-temperature perturbations on drug disposition) did not introduce variability into the individual calculations of thermoregulatory concentration dependence.

The correlation coefficients for the concentration–response regressions indicated the extent to which the calculated core-temperature vasoconstriction and shivering thresholds were linear functions of propofol concentration. However, correlation coefficients tended to be poor when slopes are low. To further evaluate the extent to which responses and concentrations were linearly related, we thus calculated the residuals (difference between measured and predicted thresholds). The residuals for each response were then plotted against propofol concentrations. These values, in turn, were fit using a linear, least-squares regression. Nonlinearities in the concentration–response relations would be identified by an uneven distribution on these plots, or by significantly nonzero slopes.

In addition to the concentration–response regressions in each volunteer, a single regression for each response was determined from the combined data from all five volunteers. Variability in this population regression was expressed in terms of correlation coefficients and 95% confidence intervals. From these regressions, we also determined the sweating-to-vasoconstriction (interthreshold) range and the vasoconstriction-to-shivering range.

In our previous investigation of sweating and vasoconstriction thresholds during propofol anesthesia, we used epidural anesthesia to block thermal sensation from the lower body. Core temperature was then manipulated by heating and cooling the legs, while maintaining a constant upper-body skin temperature. To facilitate direct comparison between our current results and those we reported previously, we also calculated the slopes of the sweating and vasoconstriction responses, excluding the 8-µg/ml target concentration (so that the same propofol concentration range was considered in each case). For the purpose of this model-validation comparison, each set of data consisted of target blood propofol concentrations of 0, 2, and 4 µg/ml. Slopes of the concentration–response curves in the two studies were compared by using two-tailed, unpaired t tests. All results are presented as mean ± SD; \( P < 0.01 \) was considered statistically significant.

Results
Induction and maintenance of propofol anesthesia was smooth in all cases; no adverse effects were noted.
Volunteers typically were mildly sedated when the target concentration was 2 \( \mu g/ml \), deeply sedated when the target concentration was 4 \( \mu g/ml \), and fully anesthetized when the target concentration was 8 \( \mu g/ml \).

Ambient temperatures and relative humidity were comparable on each of the study days. Heart rates and end-tidal carbon dioxide tensions also were similar. Mean arterial pressure was significantly less when 8 \( \mu g/ml \) propofol was targeted than on the control day. By design, the blood propofol concentrations differed significantly on each of the treatment days (Table 1).

The propofol concentration was roughly half the target value of 8 \( \mu g/ml \) during shivering in the first volunteer because of an infusion protocol error.

The concentration–response slopes for vasoconstriction and shivering were nearly identical when all tested concentrations were used and when only target concentrations of 0, 2, and 4 \( \mu g/ml \) were included. Propofol at 2- and 4-\( \mu g/ml \) target blood concentration slightly decreased the sweating threshold whereas the threshold increased slightly when 8 \( \mu g/ml \) was targeted.

As a result, the concentration–response regression for sweating was \( r^2 = 0.98 \pm 0.02 \) and shivering (slope = \(-0.7 \pm 0.1 \text{C} \cdot \mu g^{-1} \cdot \text{ml}^{-1}; \ r^2 = 0.95 \pm 0.05 \)). The concentration–response relations for vasoconstriction and shivering were consistently linear, but the slopes varied among volunteers. In contrast, increasing blood propofol concentration increased the sweating threshold only slightly, and there was substantial variation among volunteers (slope = 0.1 ± 0.1 \text{C} \cdot \mu g^{-1} \cdot \text{ml}^{-1}; \ r^2 = 0.46 ± 0.39). The concentration-threshold slope for sweating differed only marginally from zero \( (P = 0.04) \) (Table 4 and fig. 1).

Analysis of residuals from the threshold versus blood propofol concentration regressions indicated that the vasoconstriction and shivering data were linear. Inspection of the sweating residuals suggested that responses were not entirely uniform over the tested concentration range: individual values tended to be less than those predicted by the regression at 2- and 4-\( \mu g/ml \) target concentrations, but tended to exceed predicted values when the target was 8 \( \mu g/ml \). As a result, the concentration–response slopes for sweating dif-

### Table 1. Environmental and Anesthetic Data

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>2 ( \mu g/ml )</th>
<th>4 ( \mu g/ml )</th>
<th>8 ( \mu g/ml )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambient temperature (°C)</td>
<td>22.5 ± 0.5</td>
<td>22.6 ± 0.5</td>
<td>23.2 ± 0.2</td>
<td>23.6 ± 0.4</td>
</tr>
<tr>
<td>Relative humidity (%)</td>
<td>39 ± 4</td>
<td>38 ± 1</td>
<td>35 ± 4</td>
<td>35 ± 3</td>
</tr>
<tr>
<td>Mean arterial blood pressure (mmHg)</td>
<td>97 ± 7</td>
<td>84 ± 3</td>
<td>86 ± 5</td>
<td>80 ± 9</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>63 ± 10</td>
<td>67 ± 4</td>
<td>71 ± 9</td>
<td>71 ± 9</td>
</tr>
<tr>
<td>End-tidal ( P_{CO_2} )</td>
<td>39 ± 1</td>
<td>40 ± 3</td>
<td>36 ± 2</td>
<td>35 ± 0</td>
</tr>
<tr>
<td>[Propofol] at sweating (( \mu g/ml ))</td>
<td>—</td>
<td>1.8 ± 0.3</td>
<td>3.9 ± 1.1</td>
<td>7.8 ± 0.5</td>
</tr>
<tr>
<td>[Propofol] at vasoconstriction (( \mu g/ml ))</td>
<td>—</td>
<td>1.6 ± 0.3</td>
<td>3.8 ± 0.8</td>
<td>6.5 ± 0.5</td>
</tr>
<tr>
<td>[Propofol] at shivering (( \mu g/ml ))</td>
<td>—</td>
<td>1.6 ± 0.2</td>
<td>3.6 ± 0.9</td>
<td>5.9 ± 1.0</td>
</tr>
</tbody>
</table>

On the control day, no propofol was given. 2-, 4-, and 8-\( \mu g/ml \) blood propofol concentrations were targeted on the other three days. Values are mean ± SD. *Blood pressure was significantly less on the 8-\( \mu g/ml \) day than on the control day \( (P < 0.01) \). By design the blood propofol concentrations differed significantly on each of the treatment days.

Anesthesiology, V 82, No 5, May 1995

### Table 2. Current and Previously Reported Sweating and Vasoconstriction Concentration–Response Slopes

<table>
<thead>
<tr>
<th></th>
<th>Current</th>
<th>Previous</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of volunteers</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Sweating (°C \cdot \mu g^{-1} \cdot \text{ml}^{-1})</td>
<td>-0.07 ± 0.15</td>
<td>-0.04 ± 0.09</td>
</tr>
<tr>
<td>Vasoconstriction (°C \cdot \mu g^{-1} \cdot \text{ml}^{-1})</td>
<td>-0.52 ± 0.19</td>
<td>-0.53 ± 0.34</td>
</tr>
</tbody>
</table>

Our current concentration–response slope for sweating and vasoconstriction was compared with those reported previously. To facilitate direct comparison with previous data, only concentrations up to a target blood propofol concentration of 4 \( \mu g/ml \) were included from the current study. See table 4 for complete results of the current study (including data when the target propofol concentration was 8 \( \mu g/ml \)). Values are mean ± SD. The results of the two studies were virtually identical and did not differ significantly (unpaired t tests).
Table 3. Mean Skin Temperatures, Core Temperatures, and Calculated Core Thresholds (with a Designated Skin Temperature of 35.7°C)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>2 µg/ml</th>
<th>4 µg/ml</th>
<th>8 µg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sweating</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean skin (°C)</td>
<td>36.5 ± 0.3</td>
<td>36.2 ± 0.5</td>
<td>36.8 ± 0.5</td>
<td>37.6 ± 0.4</td>
</tr>
<tr>
<td>Measured core (°C)</td>
<td>36.9 ± 0.3</td>
<td>36.7 ± 0.1</td>
<td>36.7 ± 0.6</td>
<td>37.4 ± 0.4</td>
</tr>
<tr>
<td>Calculated threshold (°C)</td>
<td>37.0 ± 0.3</td>
<td>36.8 ± 0.1</td>
<td>36.8 ± 0.6</td>
<td>37.6 ± 0.4</td>
</tr>
<tr>
<td><strong>Vasoconstriction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean skin (°C)</td>
<td>32.9 ± 0.9</td>
<td>33.0 ± 0.9</td>
<td>30.8 ± 1.2</td>
<td>28.4 ± 1.6</td>
</tr>
<tr>
<td>Measured core (°C)</td>
<td>37.1 ± 0.1</td>
<td>36.3 ± 0.4</td>
<td>35.6 ± 0.7</td>
<td>34.5 ± 0.8</td>
</tr>
<tr>
<td>Calculated threshold (°C)</td>
<td>36.4 ± 0.3</td>
<td>35.7 ± 0.6</td>
<td>34.4 ± 1.0</td>
<td>32.6 ± 1.1</td>
</tr>
<tr>
<td><strong>Shivering</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean skin (°C)</td>
<td>29.7 ± 1.1</td>
<td>28.1 ± 2.2</td>
<td>28.4 ± 1.6</td>
<td>26.2 ± 1.3</td>
</tr>
<tr>
<td>Measured core (°C)</td>
<td>37.1 ± 0.2</td>
<td>36.3 ± 0.3</td>
<td>35.4 ± 0.8</td>
<td>33.9 ± 0.8</td>
</tr>
<tr>
<td>Calculated threshold (°C)</td>
<td>35.6 ± 0.3</td>
<td>34.4 ± 0.6</td>
<td>33.6 ± 0.7</td>
<td>31.5 ± 0.7</td>
</tr>
</tbody>
</table>

Values are mean skin and core temperatures at sweating, vasoconstriction, and shivering, and the thresholds calculated from these values at each target propofol concentration. Values are mean ± SD.

...ferred slightly when only the 0–4 µg/ml target concentrations were included. Nonetheless, the residuals for sweating, vasoconstriction, and shivering all averaged 0.0, and the slopes of the residual regressions differed only slightly from zero (fig. 2).

Figure 3 shows the regressions for each threshold, calculated using the combined data from all volunteers. The interthreshold range (calculated from the combined regressions) was 0.2°C on the control day, but increased by 0.7 ± 0.1°C·µg⁻¹·ml⁻¹ during propofol administration. The vasoconstriction-to-shivering range on the control day was 1.0°C and increased only slightly during propofol administration.

Discussion

Both core and skin temperatures contribute to the control of thermoregulatory responses. Consequently, thresholds may be expressed in terms of mean body temperature, using an arithmetic combination of skin and core temperatures. (We distinguish here between average temperature of body tissues and control-weighted thermal input to central regulatory structures.) In theory, this single number is the easiest and most complete way to describe response thresholds at any combination of skin and core temperatures. Until recently, however, cutaneous contributions to vasoconstriction and shivering were unknown in humans (even the shapes of the core and skin contribution curves were unclear for cold responses). Furthermore, specific core and skin contributions may be situation-specific and likely depend on the rates at which temperatures change. As a result, it is conventional to express thermoregulatory response thresholds in terms of core temperature (at a specified skin temperature).

Because core-temperature thresholds depend on skin temperature, they can be directly compared only at constant skin temperature. It is usually difficult to determine these thresholds for a given thermoregulatory response (e.g., vasoconstriction) at different drug concentrations while maintaining constant skin temperature. But it is especially difficult to determine both cold- and warm-response thresholds at a single skin temperature. This requirement for constant skin temperature has proven sufficiently daunting that the thermoregulatory effects of few drugs are established in humans.

Three recently developed methods, however, allow the major thermoregulatory response thresholds to be determined at constant sentient skin temperature in steady-state conditions. Each has advantages, but none is easy to apply or generally useful for determining the thermoregulatory effects of sedative and anesthetic drugs. In the first model, developed by Mekjavic et al., skin temperature is kept constant by immersion in water at 25°C. The subjects then exercise vigorously to increase core temperature and subsequently cool passively. Although useful for evaluating the effects of low-dose nitrous oxide and other interventions, this model is of course unsuitable for evaluating general and regional anesthesia and might prove difficult for those...
PROPOFOL AND THERMOREGULATION

Table 4. Slopes and Correlation Coefficients ($r^2$) for Propofol–induced Inhibition of Sweating, Vasoconstriction, and Shivering

<table>
<thead>
<tr>
<th>Volunteer</th>
<th>Slope ($°C \cdot \mu g^{-1} \cdot ml^{-1}$)</th>
<th>$r^2$</th>
<th>Slope ($°C \cdot \mu g^{-1} \cdot ml^{-1}$)</th>
<th>$r^2$</th>
<th>Slope ($°C \cdot \mu g^{-1} \cdot ml^{-1}$)</th>
<th>$r^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.0</td>
<td>0.01</td>
<td>-0.5</td>
<td>0.95</td>
<td>-0.8</td>
<td>0.96</td>
</tr>
<tr>
<td>2</td>
<td>0.1</td>
<td>0.21</td>
<td>-0.8</td>
<td>0.99</td>
<td>-0.7</td>
<td>0.98</td>
</tr>
<tr>
<td>3</td>
<td>0.1</td>
<td>0.91</td>
<td>-0.5</td>
<td>0.98</td>
<td>-0.6</td>
<td>0.97</td>
</tr>
<tr>
<td>4</td>
<td>0.2</td>
<td>0.84</td>
<td>-0.4</td>
<td>0.97</td>
<td>-0.7</td>
<td>0.86</td>
</tr>
<tr>
<td>5</td>
<td>0.0</td>
<td>0.35</td>
<td>-0.7</td>
<td>0.98</td>
<td>-0.7</td>
<td>0.97</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0.1 ± 0.1</td>
<td>0.46 ± 0.39</td>
<td>-0.6 ± 0.1</td>
<td>0.98 ± 0.02</td>
<td>-0.7 ± 0.1</td>
<td>0.95 ± 0.05</td>
</tr>
</tbody>
</table>

Propofol significantly decreased the thresholds for vasoconstriction and shivering, but only slightly increased the sweating threshold. The slope of the sweating threshold differed only marginally from zero ($p = 0.04$). The vasoconstriction and shivering slopes differed significantly from zero, but not from each other. The low correlation coefficients for sweating result from the near-zero concentration–response slope. Variability in this response can be better estimated from the residual analysis presented in figure 2. Values are mean ± SD.

who are physically unfit or disabled. Furthermore, exercise *per se* decreases the sweating threshold, artificially reducing the sweating-to-shivering range.

The second model was initially described in 1990 and subsequently refined by Lopez et al. In that protocol, skin temperature is held constant while core temperature is reduced by central venous administration of cold intravenous fluid. This model has been used to determine the effects of thermoregulatory vasoconstriction on heat flux, the rate and gender-dependence of normal thermoregulatory responses, and the thermoregulatory effects of clonidine. It also can be applied in volunteers given volatile anesthetics. Potential difficulties with the technique include alteration of intravenous drug kinetics by rapid volume expansion and poor tolerance of fluid loading. Furthermore, central venous access is required and the extent of a core cooling is limited by the amount of fluid that can be safely administered.

The third model, developed by Leslie et al., was based on previous work by Lopez et al. and Ozaki et al. In that protocol, regional anesthesia is used to block thermal sensations from the lower body while upper-body skin temperature is kept constant. Thermal manipulations are then restricted to the insensate legs. An obvious difficulty with this protocol is the need for repeated and prolonged epidural anesthetics, with the attendant risks of nerve injury and drug toxicity. Furthermore, restricting warming and cooling to the legs results in slow core-temperature changes, even when the legs remain vasodilated. We found it easy to produce a complete sensory block, but in practice it proved difficult to maintain consistent lower body vasodilation. Leg dilation is required in this protocol if shivering thresholds are to be determined, because vasoconstriction otherwise isolates the core compartment from the legs, markedly reducing the rate at which core temperature can be manipulated. A final difficulty with this model is that epidural and spinal anesthesia themselves alter centrally mediated thermoregulatory responses. Practical difficulties with existing methods for evaluating thermoregulatory effects of drugs led us to seek an alternative. Our first step was to ascertain the fractional contribution of skin temperature to thermoregulatory control and to show that skin and core temperatures contributed linearly to thermoregulatory response thresholds. In brief, we determined the core-temperature thresholds for vasoconstriction and shivering, each at four different skin temperatures. These thresholds were plotted against skin temperature, and from the slopes of the resulting regression equations, we calculated the relative skin and core contributions to the control of each response. The relation between skin and core input was linear in each volunteer: skin temperature contributed $20 \pm 6\%$ to vasoconstriction and $19 \pm 8\%$ to shivering.

The cutaneous contributions to vasoconstriction and shivering were calculated at constant skin temperatures during isolated core cooling. However, no practical method exists to warm the core in isolation. Consequently, the cutaneous contribution to sweating usually has been determined by increasing skin temperature, which results in a passive increase in core temperature. Unpublished data.

Anesthesiology, V 82, No 5, May 1995

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key to our current model. Specifically, it allows us to experimentally manipulate both skin and core temperature, subsequently compensate for the changes in skin temperature, and finally report our results for warm- and cold-responsive in terms of calculated core-temperature thresholds at a single designated skin temperature. Because specific cutaneous contributions vary among individual persons (although remaining linear in each), the resulting concentration–response curves vary comparably among volunteers. However, the average effect of the test drug on the study population will be accurate. Comparison between the measured core temperatures and the calculated vasoconstriction and shivering thresholds emphasizes the importance

The independent contribution of skin temperature is then calculated using multiple regression. One difficulty with this approach is that rapid increases in skin temperature may trigger dynamic reductions in the sweating thresholds.\(^{25,31}\) Nonetheless, results from numerous studies are relatively consistent, concluding that the cutaneous contribution to sweating thresholds ranges from \(\approx 5\%^{10,41}\) to \(\approx 20\%^{42,45}\). The consensus, however, appears to be a cutaneous contribution to the control of sweating near 10\%,\(^1\) and we therefore used a \(\beta\) of 0.1 in our calculations. Fortunately, mean skin temperature exceeded our designated temperature by only 2\(^\circ\)C, even at the largest propofol dose. Consequently, even a relatively large error in our estimate of \(\beta\) would have little impact on the slope of the concentration–response slope for sweating.

A consistent and linear relation between skin and core temperature at the threshold for each response is the

\[\text{Sweating (\(^\circ\)C)}\]

\[\text{Constriction (\(^\circ\)C)}\]

\[\text{Shivering (\(^\circ\)C)}\]

\[\text{[Propofol] (\(\mu\)g/ml)}\]

Fig. 2. The residuals (difference between measured and predicted thresholds) for each thermoregulatory response were plotted against blood propofol concentration to confirm that the concentration-response relationships were linear. The slope of the residual regression for vasoconstriction was 0.000 (middle). The slope of the residual regression for shivering was -0.016 (bottom). Propofol at 2 and 4 \(\mu\)g/ml target blood concentration slightly decreased the sweating threshold, whereas the threshold increased slightly when 8 \(\mu\)g/ml was targeted. Nonetheless, the slope of the residual regression for sweating was -0.006 (top).

Anesthesiology, V 82, No 5, May 1995
PROPOFOL AND THERMOREGULATION

Fig. 3. Propofol increased the sweating threshold only slightly; thin upper regression with +95% confidence limits: threshold (°C) = -0.09[propofol(μg·ml⁻¹)] + 36.8, r² = 0.26. In contrast, propofol produced a linear decrease in the core temperature triggering vasoconstriction; middle regression with dashed lines showing +95% confidence limits: threshold (°C) = -0.06[propofol(μg·ml⁻¹)] + 36.5, r² = 0.84. Similarly, propofol linearly decreased the shivering threshold; thick lower regression with dashed lines showing -95% confidence limits: threshold (°C) = -0.65[propofol(μg·ml⁻¹)] + 35.6, r² = 0.89. These regression slopes differ from those reported in table 3 because they were calculated simultaneously from all results, rather than from individual volunteers.

A major advantage of our current approach is that it is essentially noninvasive (aside from administration of the test drug and sampling to measure blood concentrations). The thermoregulatory effects of most drugs can thus be evaluated by physicians and physiologists without anesthesia training. Furthermore, the method can be easily used to determine the thermoregulatory consequences of pregnancy, illness, and other conditions.

An additional and substantial advantage of this model is that only relatively small core-temperature deviations are required. As a result, larger drug doses (causing more thermoregulatory inhibition) can be tested. For example, the actual reduction in core temperature at the shivering threshold during administration of the highest target propofol concentration (8 μg/ml) was only ≈3°C. In contrast, with the model of Leslie et al., a core temperature of ≈31°C would have been required, and it would have been impossible to test this dose with either of the other two models.

Unlike the model of Leslie et al., in the current protocol the entire skin surface is available for warming, such that rapid core-temperature manipulations are possible. As a result, the study procedure is considerably easier and safer: (1) recovery is faster because total drug exposure is reduced; (2) reduced drug administration lessens the potential for acute tolerance (which may be especially problematic with opioids); and (3) the time elapsed between determination of warm- and cold-response thresholds is less, minimizing the effects of circadian variations.

The obvious major limitation of our current protocol is that it assumes constant and linear cutaneous contributions to thermoregulatory control during drug administration. Consistent with this assumption, the concentration-response slopes for sweating and vasoconstriction during propofol administration (0–4 μg/ml target concentrations) were virtually identical in our current study and in volunteers studied previously during epidural anesthesia. These data thus validate our new model and suggest that cutaneous thermoregulatory contributions remain linear and constant during propofol anesthesia. It is probable that the fractional contribution of skin and core temperatures is a relatively "primitive" thermoregulatory function that remains nearly constant in various circumstances.

This study extends our previous investigation by doubling the target blood propofol concentration to 8 μg/ml, which is the concentration of this drug in blood at which 50% of patients move in response to skin in-

Anesthesiology. V 82, No 5, May 1995
cision. In our previous investigation, propofol to a target concentration of 4 μg/ml had little influence on sweating. The sweating threshold, however, did increase slightly when the highest concentration was included in the analysis. This increase was less than that produced by one minimum alveolar concentration of isoflurane\textsuperscript{17} or enflurane.\textsuperscript{19} Propofol impaired vasoconstriction six times as much as sweating, compared with an approximately threefold difference for isoflurane.\textsuperscript{17,18}

This study further differs from our previous evaluation of thermoregulation during propofol administration\textsuperscript{8} because we also determined the shivering threshold. Of interest, shivering was impaired only slightly more than vasoconstriction (slopes $=-0.6 \pm 0.1$ and $-0.7 \pm 0.1 ^\circ \text{C} \cdot \mu \text{g}^{-1} \cdot \text{ml}^{-1}$, respectively), and we had no difficulty eliciting this response. No systematic evaluation of shivering during anesthesia has previously been published (although numerous studies evaluate postoperative shivering\textsuperscript{14,15}). However, shivering is rare in nonparalyzed patients given volatile anesthetics, even at core temperatures approaching 32° C. This anecdotal observation suggests that volatile anesthetics inhibit shivering more than propofol.

We restricted this study to men to validate our new method of testing thermoregulatory responses by comparing current results with those obtained previously using the epidural model.\textsuperscript{7} Because all the volunteers in that study were male, we similarly restricted our current investigation. (There are subtle differences in thermoregulatory responses in men and women\textsuperscript{10-12}; consequently, we often restrict studies to a single sex. However, the gender choice in specific studies is usually arbitrary and we often study women.\textsuperscript{19,47,47}) Similarly, we used a designated skin temperature of 35.7°C to match the sentient skin temperature in our previous evaluation of thermoregulation during propofol administration.\textsuperscript{8} All calculated thresholds would have been slightly greater had we used a more typical intraoperative skin temperature ($=34 ^\circ \text{C}$). However, slopes of the concentration–response curves would have been comparable.

In an accompanying study, we determined cutaneous contributions to vasoconstriction and shivering in near-steady-state conditions.\textsuperscript{9} In that study, temperatures were manipulated at $\pm 2 ^\circ \text{C}/h$ because we have previously shown that this rate does not trigger dynamic thermoregulatory responses (i.e., time-dependent rather than state-dependent).\textsuperscript{7} The rate at which skin and core temperatures were manipulated in our current study was similarly restricted. Because some skin surfaces contribute more to thermoregulatory control than others,\textsuperscript{16} we kept anterior and posterior skin temperatures comparable by independently adjusting the circulating-water and forced-air warmers. Finally, we made substantial efforts to minimize volunteer stress and discomfort (e.g., from suboptimal positioning or bladder distention). Without rigorous control of these and other factors (including circadian temperature variation), it is unlikely that responses would have been so consistent.

The mean interthreshold range in individual volunteers was $=0.6 ^\circ \text{C}$ (table 3), which considerably exceeds the $=0.2 ^\circ \text{C}$ we reported previously.\textsuperscript{8} In our previous investigation, we defined thresholds as the core temperature triggering the first detectable response. This definition conforms to the formal physiologic meaning of the term “threshold” and is appropriate for a specific study of interthreshold ranges. The current investigation differs in that our major question is the concentration-dependent effect of propofol on thermoregulatory responses. In this case, we chose rigorous definitions for thermoregulatory response thresholds. These strict criteria facilitate determination of threshold temperatures and minimize potential for bias. A disadvantage of strict criteria, however, is that body temperatures need to deviate further to trigger “significant” responses. Body temperature thus increased more before we considered sweating “significant,” and decreased more before we considered vasoconstriction “significant.” The result was a greater interthreshold range.

In summary, we present a new model for evaluating thermoregulatory effects in conditions such as drug administration, pregnancy, or illness. Specifically, we experimentally manipulated both skin and core temperatures and subsequently compensated for the changes in skin temperature using the relations between skin and core contributions to thermoregulatory control. We were able to report our results for warm and cold responses in terms of calculated core-temperature thresholds at a single designated skin temperature. Advantages of this model include its being nearly noninvasive and requiring relatively little core-temperature manipulation.

We validated this new technique by showing that propofol-induced inhibition of sweating and vasoconstriction, as determined by our new model, was virtually identical to that reported previously. However, the current study extends our previous investigation\textsuperscript{8}
by increasing the target blood propofol concentration to its concentration in blood at which 50% of patients move in response to skin incision. Furthermore, this is the first systematic investigation of shivering during anesthesia. Propofol, in concentrations to 8 μg/ml in blood, linearly reduced both the vasoconstriction and shivering thresholds by 0.6 ± 0.1 and 0.7 ± 0.1°C·μg·ml⁻¹·min⁻¹, respectively. The shivering threshold, however, increased only slightly. These data suggest that propofol inhibits sweating less than comparable doses of the volatile anesthetics, but impairs vasoconstriction more. Propofol reduced the shivering threshold only slightly more than the vasoconstriction threshold; that is, the vasoconstriction-to-shivering range increased only slightly during anesthesia.

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Anesthesiology. V 82. No 5. May 1995


Appendix:

Calculation of Core-temperature Thresholds

Previous studies demonstrate that the cutaneous contribution to sweating and to vasocostruction and shivering is linear. We therefore assumed a mean body temperature threshold for each response, having the form

\[ \text{thres}_{\text{swt}} = \beta T_{\text{skin}} + (1 - \beta) T_{\text{core}}. \tag{A1} \]

where \( \text{thres}_{\text{swt}} \) is the threshold for sweating, vasocostruction, or shivering in terms of mean body temperature (degrees Celsius); \( \beta \) is the fractional contribution of mean skin temperature to the threshold; and \( T_{\text{skin}} \) and \( T_{\text{core}} \) are the measured mean skin and core temperatures triggering each thermoregulatory response (degrees Celsius).

Because the \( \text{thres}_{\text{swt}} \) remains constant, the core-temperature threshold triggering one of the thermoregulatory responses \( T_{\text{core(calculated)}}</code>

\( T_{\text{core}} \) at a designated skin temperature \( \left( T_{\text{skin(designated)}} \right) \) (degrees Celsius) can be expressed by the equation

\[ \text{thres}_{\text{swt}} = \beta T_{\text{skin(designated)}} + (1 - \beta) T_{\text{core(calculated)}}. \tag{A2} \]

By subtracting equations A1 and A2 and rearranging the terms, we can then use \( T_{\text{skin}} \) and \( T_{\text{core}} \) at each threshold to calculate the core-temperature threshold that would have been observed had skin been at the designated temperature:

\[ T_{\text{core(calculated)}} = T_{\text{core}} + \frac{\beta}{1 - \beta} (T_{\text{skin}} - T_{\text{skin(designated)}}). \tag{A3} \]

Using this equation, the core-temperature thresholds for sweating, vasocostruction, and shivering can each be calculated for a single designated mean skin temperature, even when skin temperature was manipulated during the study.

On the basis of previous studies, we used a \( \beta \) of 0.1 for sweating and a \( \beta \) of 0.2 for vasocostruction and shivering. The skin-temperature correction factors, \( \beta/(1 - \beta), \) were thus 0.11 and 0.25, respectively.