The Thermoregulatory Threshold in Infants and Children Anesthetized with Isoflurane and Caudal Bupivacaine

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Hypothermia in anesthetized adults provokes centrally mediated, peripheral thermoregulatory vasoconstriction at threshold temperatures ≈2.5°C below normal. The weight dependence of thermoregulatory vasoconstriction was evaluated in 33 unpremedicated pediatric patients receiving isoflurane/oxygen anesthesia (end-tidal concentrations ≈0.9%) and caudal anesthesia with bupivacaine. The patients were prospectively assigned to four weight groups (5–10 kg, 10–20 kg, 20–50 kg, and 30–50 kg). Central temperature was measured at the tympanic membrane, and average skin surface temperature was determined from four cutaneous sites: mean body temperature was calculated from central and average skin temperatures. Finger blood flow was determined using laser Doppler flowmetry and forearm–fingertip skin temperature gradients. Significant peripheral vasoconstriction was prospectively defined as a laser Doppler flow index 50% of the value recorded 10 min after induction of anesthesia. Thermoregulatory thresholds were defined as the tympanic membrane or mean body temperatures at which significant vasoconstriction occurred. Vasoconstriction occurred in 32 of the patients at temperatures ranging from 34.4 to 35.5°C. Central and mean body threshold temperatures did not differ among the groups, and were similar to those observed previously in adults. There was a good correlation between laser Doppler flowmetry and forearm–fingertip skin temperature gradients in individual patients. (Key words: Anesthesia, local; bupivacaine. Anesthesiology, volatile: isoflurane. Anesthetic techniques: caudal. Brain: hypothalamic. Hypothermia. Measurement technique, blood flow: laser Doppler. Temperature, measurement: skin; tympanic membrane. Thermoregulation: threshold, setpoint.)

Central hypothermia produces thermoregulatory vasoconstriction in adults anesthetized with halothane,¹ N₂O/fentanyl,² and isoflurane,³ but the response thresholds are approximately 2.5°C less than those in unanesthetized volunteers. We also know that hypothermia causes thermoregulatory vasoconstriction in unanesthetized infants and children⁴ but not the extent to which general anesthesia inhibits thermoregulation in these patients. Accordingly, we investigated whether the thermoregulatory threshold for vasoconstriction is weight dependent in infants and children anesthetized with isoflurane.

Human regulatory responses to thermal perturbations are determined by both central and skin surface temperatures.⁵ The total thermal input to hypothalamic regulatory centers can be approximated by mean body temperature, a calculated parameter incorporating the estimated importance of input from various tissues.⁶,⁷ To evaluate the effect of cutaneous input on thermoregulatory responses of anesthetized infants and children, we calculated the threshold for peripheral vasoconstriction using both central and mean body temperatures. We identify these parameters, respectively, as the central threshold and the mean body threshold.

We previously demonstrated in adults that skin-surface temperature gradients (forearm–fingertip) correlate with perfusion determined using the laser Doppler index.² We now correlate these two measures of perfusion in children and infants to assess the value of skin surface temperature gradients in measuring peripheral blood flow.

Methods

With approval from the Ethical Committee of the Hospital for Sick Children, we studied 33 ASA physical status 1 or 2 pediatric patients after obtaining written, informed consent from their parents. None was obese, taking medication, or had a history of thyroid disease, dystautonomia, Raynaud’s syndrome, malignant hyperthermia, or recent fever. All patients weighted between 5 and 50 kg and were scheduled to undergo elective abdominal surgery lasting 3–4 h. We studied consecutive qualifying patients who were prospectively assigned to four weight groups: 5–10 kg, 10–20 kg, 20–30 kg, and 30–50 kg. No preanesthetic medication was given.

Anesthesia was induced with isoflurane and 70% N₂O in oxygen, and the trachea of each patient was intubated following administration of 0.1 mg/kg vecuronium. Patients’ lungs were mechanically ventilated, with respiratory rate and tidal volume (≈12 ml/kg) adjusted as needed to maintain an end-tidal P₉₅O₂ near 35 mmHg. Bupivacaine (1.0–1.25 ml/kg of 0.125%) was injected into the epidural space via a caudal approach immediately following induction of endotracheal anesthesia.

Intraoperatively, muscle relaxation was maintained with intravenous (iv) administration of 0.05 mg/kg vecuronium as needed to maintain a one or two twitch mechanical response to stimulation of the ulnar nerve by a
peripheral nerve stimulator. Caudal analgesia was supplemented with isoflurane in 50% oxygen delivered via a circle system; end-tidal isoflurane concentrations were maintained near 0.9%. No barbiturates or opioids were given during surgery.

End-tidal gases were sampled from a piece of polyethylene tubing inserted through the endotracheal tube to a position estimated to be 2 cm above the carina.\textsuperscript{8} End-tidal isoflurane concentrations were quantified using a Capnomac\textsuperscript{®} (Datex Medical Instrumentation, Inc., Tewksbury, MA) end-tidal gas analyzer.

The operating room was maintained at a normal temperature (21 ± 0.6°C) for all patients to provide similar cutaneous input to the thermoregulatory system. Intravenous fluids (10–15 ml·kg\textsuperscript{-1}·h\textsuperscript{-1}) were not warmed and were administered in similar weight-adjusted quantities in each group. Respiratory gases were not humidified, and warming blankets were not used.

Temperatures were monitored using disposable thermocouples and Model 6500 digital thermometers (Mon-a-Therm,\textsuperscript{9} Inc., St. Louis, MO), which require no user calibration and have a precision of 0.1°C when used with the Mon-a-Therm\textsuperscript{®} thermometers. Skin surface temperatures were monitored using disposable, 1-cm diameter, self-sticking thermocouples, and central temperatures were monitored using a flexible, cotton-covered thermocouple placed in contact with the tympanic membrane. Average skin surface temperatures were calculated using a standard formula: \(0.5(t_{\text{chest}} + t_{\text{upper arm}}) + 0.2(t_{\text{high}} + t_{\text{tail}})\). Mean body temperature was estimated using the following formula: \(0.66(t_{\text{central}}) + 0.34(t_{\text{skin}})\).\textsuperscript{6}

Peripheral vasoconstriction was evaluated using a Periflux\textsuperscript{®} S (Perimed, Piscataway, NJ) laser Doppler monitor and skin surface temperature gradients.\textsuperscript{10} The laser Doppler monitor provides a perfusion index based on the number and velocity of red blood cells in the outer 1 mm of skin. Perfusion determined using this technique correlates well with \(^{133}\text{Xenon washout}\)\textsuperscript{11} and dynamic capilloscopy.\textsuperscript{12} We positioned the fiberoptic laser probe perpendicular to the skin opposite the nail bed on the second finger. The monitored arm did not have an iv catheter or blood pressure cuff, and all thermocouple sites were fully exposed to room air.

Skin temperature gradients are calculated by subtracting fingertip surface temperature from forearm surface temperature.\textsuperscript{2,10,13} The forearm thermocouple was placed on the radial side of the arm, midway between the wrist and the elbow; the fingertip probe was positioned on the tip of the index finger (opposite the nail bed) adjacent to the finger used for laser Doppler flow determinations.

We previously demonstrated in adults that significant vasoconstriction (a skin temperature gradient ≥4°C) corresponded to a 30% decrease in the laser Doppler perfusion index.\textsuperscript{8} Because skin temperature gradients have not been validated in children and infants, we used the laser Doppler perfusion index (which is relatively independent of patient size) as the primary measure of flow in these patients. Accordingly, we prospectively defined the thermoregulatory thresholds as the tympanic membrane temperature (central threshold) and mean body temperature (mean body threshold) at which the laser Doppler perfusion index first decreased to 50% of the value recorded 10 min after induction of anesthesia.

Skin surface and tympanic temperatures, laser Doppler perfusion index, and end-tidal isoflurane concentration were recorded every 10 min from induction until closure of the surgical incision. After closure of the surgical wound, intraoperative and postoperative management were determined by the attending anesthesiologist. Continuous variables were analyzed using one-way or repeated-measures analysis of variance as appropriate. Correlation between the laser Doppler perfusion index and skin temperature gradients and between tympanic and average skin surface temperatures were analyzed using least-squares regression analysis. All values are expressed as the mean ± SD. Differences were considered significant when \(P < 0.05\).

### Results

Patients' weight, age, gender, central and mean body thresholds, time of vasoconstriction, and end-tidal isoflurane concentration at the time of vasoconstriction appear in table 1. The four groups differed significantly only in weight and age.

Thirty-two of our 33 patients developed significant peripheral vasoconstriction at tympanic (central threshold) temperatures between 34.4 and 55.3°C (fig. 1). The central thermoregulatory threshold did not differ among the weight groups, except for a trend toward higher threshold temperatures in smaller patients (\(P = 0.065\)). The one patient (14 kg) in whom vasoconstriction did not occur had a minimum tympanic temperature of 34.5°C during an operation lasting 200 min.

Mean body temperatures at the time of vasoconstriction (mean body threshold) ranged from 33.2–34.5°C. Skin surface temperatures rarely changed more than 1°C throughout the study. Because of technical difficulties, we were unable to measure average skin surface temperature in two patients who vasoconstricted. There were no significant differences in central or mean body threshold temperatures among the study groups (fig. 2).

The correlation between the laser Doppler perfusion index and skin temperature gradients in individual patients was good (\(r = 0.92 ± 0.09\)). The strength of this correlation did not differ by group. When all 657 observations in the 33 patients were analyzed together, the correlation remained good: gradient = 0.96 (laser) + 0.12
The tympanic temperature and mean body thermoregulatory thresholds are indicated in the columns marked TM (°C) and MBT (°C), respectively. End-tidal isoflurane concentrations are not age-corrected. Values are expressed as means ± standard deviations. There were no statistically significant differences between the groups in gender, threshold temperature, time of vasoconstriction, or end-tidal isoflurane concentration.

\( r = 0.84 \). A 50% decrement in the laser Doppler index corresponded to a skin temperature gradient of \( \approx 5^\circ \) C, which is similar to the \( 4^\circ \) C previously observed in adult patients. When the threshold temperatures in each weight group were calculated using a skin temperature gradient of \( 4^\circ \) C, the results were virtually identical to those calculated using a 50% decrease in the laser Doppler index.

Intraoperative blood pressures were controlled by fluid administration; vasoconstrictor medications were never administered. No blood transfusions were required during surgery, and no patient became hypotensive or hypertensive at the time of thermoregulatory vasoconstriction. Although recovery duration and other outcome parameters were not formally evaluated, no adverse consequences of mild perianesthetic hypothermia were identified in these patients.

**Discussion**

Vasoconstriction and nonshivering heat production are the only thermoregulatory defenses against hypothermia available to anesthetized, paralyzed patients. General anesthesia decreases the central temperature threshold triggering peripheral thermoregulatory vasoconstriction by \( \approx 2.5^\circ \) C in adults. Our results indicate that inhibition of thermoregulatory vasoconstriction is similar in anesthetized infants and children, and relatively independent of body weight.

Although there was a trend toward decreased inhibition in smaller infants and children given similar isoflurane concentrations, differences between the groups were not quite statistically significant. Although statistically significant differences might be identified in a larger study, differences are not likely to be clinically important because the mean thresholds spanned only \( \approx 0.3^\circ \) C. Relatively constant thermoregulatory inhibition in infants and children of different ages is in marked contrast to the potency of isoflurane, which increases to \( \approx 150\% \) of the adult requirement in infants 1–6 months of age. Thus, inhibition

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**Table 1. Morphometric Data and Summary of Results**

<table>
<thead>
<tr>
<th>Group</th>
<th>Weight (kg)</th>
<th>Age (yr)</th>
<th>No. male/f</th>
<th>TM (°C)</th>
<th>MBT (°C)</th>
<th>Time (min)</th>
<th>[Isoflurane]</th>
</tr>
</thead>
<tbody>
<tr>
<td>5–10</td>
<td>7.9 ± 1.6</td>
<td>0.6 ± 0.47</td>
<td>4/6</td>
<td>34.9 ± 0.3</td>
<td>33.9 ± 0.3</td>
<td>127 ± 15</td>
<td>0.8 ± 0.2</td>
</tr>
<tr>
<td>10–20</td>
<td>13.7 ± 2.4</td>
<td>2.6 ± 1.3</td>
<td>13/15</td>
<td>34.8 ± 0.3</td>
<td>34.0 ± 0.4</td>
<td>137 ± 13</td>
<td>0.9 ± 0.2</td>
</tr>
<tr>
<td>20–30</td>
<td>23.4 ± 2.1</td>
<td>6.9 ± 1.6</td>
<td>5/7</td>
<td>34.8 ± 0.2</td>
<td>33.9 ± 0.3</td>
<td>127 ± 8</td>
<td>0.9 ± 0.2</td>
</tr>
<tr>
<td>30–50</td>
<td>38.9 ± 8.8</td>
<td>9.7 ± 2.9</td>
<td>4/5</td>
<td>34.6 ± 0.2</td>
<td>33.7 ± 0.2</td>
<td>136 ± 11</td>
<td>0.8 ± 0.1</td>
</tr>
</tbody>
</table>

**Fig. 1.** The central thermoregulatory threshold in 32 healthy children and infants undergoing abdominal surgery. Although there was a trend towards increased threshold temperatures in smaller patients, differences between the groups were not statistically significant.

**Fig. 2.** The mean body thermoregulatory threshold in 30 healthy children and infants undergoing abdominal surgery. There were no significant differences between the groups.

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of thermoregulatory vasoconstriction in infants is greater than in older children when administered anesthetic concentrations are age-adjusted.

In previous studies evaluating thermoregulatory inhibition by halothane \(^1\) and \(\text{N}_2\text{O}/\text{fentanyl} \) anesthesia, \(^2\) we included normothermic control groups to assure that vasoconstriction resulted from thermoregulation, not hypovolemia or surgical stress. However, significant vasoconstriction never occurred without hypothermia, suggesting that nonthermoregulatory factors did not routinely confound the results. We did not include normothermic control groups in this study because vasoconstriction was rarely observed in two recent studies in which most infants and children were maintained at relatively high temperatures by airway humidification. (Three of these patients, who became colder than most, did vasoconstrict at a mean rectal temperature of 34.8 ± 0.4°C and a mean end-tidal isoflurane concentration of 1.03 ± 0.06%.) \(^3\)!\(^4\)

Central thermoregulatory responses are based on integrated thermal input from receptors throughout the body, including the skin surface. \(^5\) The extent to which various tissues contribute to thermoregulatory responses remains unclear. Even the relatively well-understood cutaneous contributions are complicated: facial skin is five times more sensitive than other surfaces, rapid temperature changes produce up to five times the effect of slow perturbations, and responses to warm and cold stimuli are not symmetrical. \(^6\) Estimating mean body temperature in humans is further complicated by the inability to directly measure temperature at numerous critical sites.

Nonetheless, a variety of formulas for calculating mean body temperature have been proposed. \(^7\) Most combine a single central temperature with an index of average skin surface temperature. Using a single temperature to estimate contribution of central tissues is reasonable because tympanic membrane, esophageal, and rectal temperatures are similar in infants and children who are undergoing cardiopulmonary bypass. \(^8\) Average skin temperature is relatively easy to measure: the popular four-sites formula devised by Ramanathan \(^9\) correlates well with a ten-site area-weighted average during a wide variety of anesthetic situations. \(^9\)

The difficulty with all mean body temperature formulas is the implicit assumption that measured values reflect central thermal input. Which formulas are valid, and under what circumstances, has yet to be determined. The mean body temperature at which the infants and children in this study vasoconstricted was calculated using a formula designed to estimate the average physical temperature of the body (rather than mean thermoregulatory input). Although this formula probably overestimates cutaneous contributions (and has not been validated for use in anesthetized patients), we used it to maximize differences between the thresholds calculated using only central temperature and those calculated using both central and skin temperatures. Nonetheless, it is apparent from figures 1 and 2, that using mean body temperature minimally changes the shape of the response curve. Shape of the thresholds (mean body) curve may have differed more had skin temperatures changed considerably during the study period.

The infants and children in this study were given caudal analgesia and thus differed from the adults in our previous evaluation of thermoregulation during isoflurane anesthesia. \(^10\) (In our experience, this dose of bupivacaine produces a sympathetic blockade extending no higher than the 12th thoracic dermatome.) Although caudal anesthesia may influence thermoregulatory responses in several ways, none is likely to have significantly changed the thresholds in these infants and children. We previously demonstrated that thermoregulatory responses to central hypothermia are well preserved during epidural anesthesia. \(^11\) Because sympathetic blockade levels were presumably low in these infants and children, cutaneous thermal input was prevented from only a small portion of the skin surface. In any case, cutaneous thermal input is probably not very important in anesthetized humans in a typical operating room environment. Finally, there were no significant threshold differences between the infants and the oldest children (who were very nearly adult-sized).

In adults, forearm–fingertip skin surface temperature gradients correlate well with laser Doppler flowmetry, \(^2\) cutaneous heat flux, \(^12\) calf–toe gradients, \(^3\) forehead–nose gradients, \(^13\) and volume plethysmography. \(^4\) However, skin temperature gradients have not been validated in infants and children. We thus used laser Doppler flowmetry (which is relatively independent of patient size) as our standard measure of vasoconstriction in this study. Skin temperature gradients correlated well with laser Doppler flowmetry, indicating that gradients reflect peripheral flow in patients of various size. Advantages of skin temperature gradients include low cost, simplicity of use, and resistance to movement artifact.

In summary, we observed active thermoregulatory vasoconstriction in infants and children given isoflurane anesthesia (≈0.9% end-tidal concentration, not age corrected) and caudal analgesia. Central temperature thresholds did not differ significantly as a function of age or weight and were similar to those observed previously in adults. Thresholds calculated using an index of mean body temperature also did not differ in infants and children of different weights. There was a good correlation between laser Doppler flowmetry and forearm–fingertip skin temperature gradients.
The authors would like to thank Mon-a-Therm Inc. who donated the thermometers and thermocouples we used. We also greatly appreciate the loan of a Datex Capnomac from Datex Medical Instrumentation, Inc.

References