Lack of Nonshivering Thermogenesis in Infants
Anesthetized with Fentanyl and Propofol

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Background: Sweating, vasoconstriction, and shivering have been observed during general anesthesia. Among these, vasoconstriction is especially important because—once triggered—it minimizes further hypothermia. Surprisingly, the core temperature plateau associated with vasoconstriction appears to preserve core temperature better in infants and children than adults. This observation suggests that vasoconstriction in anesthetized infants may be accompanied by hypermetabolism. Consistent with this theory, unanesthetized infants rely on nonshivering thermogenesis to double heat production when vasoconstriction alone is insufficient. Accordingly, the authors tested the hypothesis that intraoperative core hypothermia triggers nonshivering thermogenesis in infants.

Methods: With Ethics Committee approval and written parental consent, the authors studied six infants undergoing abdominal surgery. All were aged 1 day to 9 months and weighed 2.4−9 kg. Anesthesia was maintained with propofol and fentanyl. The infants were mechanically ventilated and allowed to cool passively until core (distal esophageal) temperatures reached 34−34.5°C. Oxygen consumption—the authors’ index of metabolic rate—was recorded throughout cooling. Because nonshivering thermogenesis triples circulating norepinephrine concentrations, arterial blood was analyzed for plasma catecholamines at = 0.5°C intervals. Thermoregulatory vasoconstriction was evaluated using forearm−fingertip, skin-surface gradients, with gradients exceeding 4°C, indicating intense vasoconstriction. The patients were subsequently rapidly rewarmed to 37°C. Regression analysis was used to correlate changes in oxygen consumption and plasma catecholamine concentrations with core temperature.

Results: All patients were vasoconstricted by the time core temperature reached 36°C. Further reduction in core temperature to 34−34.5°C did not increase oxygen consumption. Instead, oxygen consumption decreased linearly. Hypothermia also failed to increase plasma catecholamine concentrations.

Conclusions: Even at core temperatures <2°C below the vasoconstriction threshold, there was no evidence of nonshivering thermogenesis. This finding is surprising because all other major thermoregulatory responses have been detected during anesthesia. Infants and children thus appear similar to adults in being unable to increase metabolic rate in response to mild intraoperative hypothermia. (Key words: Anesthesia; pediatric. Temperature. Thermoregulation: nonshivering thermogenesis.)

THE primary autonomic defenses against hypothermia in adults are arteriovenous shunt vasoconstriction and shivering. Although vasoconstriction is well preserved in unanesthetized infants, shivering is not. Instead, infants, like many mammals, rely on nonshivering thermogenesis to increase metabolic heat production when vasoconstriction alone is insufficient to maintain core body temperature. In cold-exposed unanesthetized infants, nonshivering thermogenesis doubles metabolic rate. Even premature infants substantially increase metabolic heat production during cold exposure. Nonshivering thermogenesis is accompanied by plasma nor-
Nonshivering thermogenesis in anesthetized infants

Epinephrine concentrations three times normal, whereas epinephrine concentrations remain normal. 11 All major autonomic thermoregulatory defenses have been observed during general anesthesia, including sweating, 12,13 active vasodilation, 12 arteriovenous shunt vasoconstriction, 14,15 and shivering. 14,15 Vasoconstriction and shivering thresholds (triggering core temperatures) are reduced in anesthetized adults. 14,15 General anesthetics similarly reduce the vasoconstriction threshold in pediatric patients. 16,17 Thermoregulatory vasoconstriction is clinically important because it minimizes further core hypothermia by decreasing cutaneous heat loss and constraining metabolic heat to the core thermal compartment. 18 Interestingly, the core-temperature plateau associated with vasoconstriction appears to preserve core temperature better in infants and children than in adults, 17 although pediatric patients often are considered more susceptible to cold environments.

How thermoregulatory defenses in infants so effectively prevent additional core hypothermia remains unknown. A potential explanation is that vasoconstriction is accompanied by hypermetabolism. Accordingly, we tested the hypothesis that core hypothermia triggers nonshivering thermogenesis in anesthetized infants. Because animal and in vitro studies indicate that volatile anesthetics peripherally impair nonshivering thermogenesis at the level of brown adipose tissue, 19 we administered total intravenous anesthesia.

Methods

This study was conducted with approval of the Ethics Committee at the University of Vienna and with written consent from parents who were fully informed of the potential risks. We studied six American Society of Anesthesiologists' (ASA) physical status 1 or 2 infants undergoing abdominal surgery. They were aged 1 day to 9 months and weighed 2.4–9 kg. Patients participated only when their attending surgeons believed the risk of infectious or bleeding complications to be remote and when insertion of a radial artery catheter was clinically appropriate. Patients with known metabolic disorders were excluded, as were those given medications likely to influence thermoregulatory control or sympathetic nervous system function.

Protocol

Anesthesia was induced with propofol, 3 mg/kg, fentanyl, 5 μg/kg, and vecuronium bromide, 0.1 mg/kg, and maintained with propofol, 10 mg·kg⁻¹·h⁻¹, and fentanyl, 3 mg·kg⁻¹·h⁻¹. Additional vecuronium was administered as necessary to maintain one or two mechanical twitches in response to supramaximal electrical stimulation of the ulnar nerve at the wrist. The infants were intubated with uncuffed endotracheal tubes sufficiently large to keep the tracheal leak pressure >20 cm H₂O.

The infants' lungs were mechanically ventilated with a volume-controlled, pressure-limited respirator. The respirator was set to a 10-ml/kg tidal volume with a respiratory rate sufficient to maintain end-tidal arterial carbon dioxide tension (Paco₂) near 35 mmHg. This always produced peak-inspiratory pressures well below 20 cm H₂O. Inspiratory gases were passively conditioned with a heat- and moisture-exchanger positioned between the Y-piece of the circle system and the endotracheal tube. After tracheal intubation, inspired oxygen concentrations were generally kept below 50% but were increased when necessary to maintain arterial oxygen saturation (Pao₂) ≥95%. A radial arterial catheter was inserted. Surgery was not delayed for study purposes; consequently, the measurements to be described were obtained after skin incision.

Operating rooms were kept near 22°C, and patients were minimally draped; no active cutaneous or fluid warming was used during the initial portion of the study. Consequently, the infants cooled passively until distal esophageal (core) temperatures reached 34–34.5°C. Subsequently, forced-air warming rapidly returned skin and core temperatures to normal. 20 The same high surface area-to-mass ratio that allows infants to cool quickly makes it easy to rapidly rewarm them using surface heating.

Measurements

Systemic oxygen consumption was evaluated with a DeltaTrac® II, MBM-200 metabolic monitor designed specifically for use in infants and small children (Datex Inc., Helsinki, Finland). The system determines oxygen consumption by multiplying minute ventilation by the difference in inspired and mean expired oxygen concentration. Oxygen consumption was determined at 1-min intervals and a running 5-min average was applied to these data. Oxygen consumption (in ml/min) was normalized by body weight to account for differences in patient size. Measurements started when the anesthetic management and metabolic monitor stabilized and continued throughout core cooling. The temperature range was ≈1.5°C in four patients and ≈2°C in the others.

Blood from an arterial catheter was analyzed for
plasma norepinephrine, epinephrine, and dopamine concentration at 0.5°C intervals. Plasma samples were prepared with a reagent kit from Chromsystem, Inc. (Munich, Germany), extracted with alumina oxide, and then separated by high-pressure, liquid chromatography on a reverse-phase column using electrochemical detection. The method used is sensitive to 20 pg/ml plasma and has a coefficient of variation near 15%.

Thermoregulatory vasoconstriction in the arms was evaluated using forcarim – fingertip, skin-surface gradients. Vasoconstriction in the legs was similarly evaluated with calf – toes gradients. Skin-temperature gradients exceeding 1°C were considered to indicate intense vasoconstriction.

Only data obtained during core cooling were considered in the analysis. Linear regression was used to correlate individual oxygen consumption core temperature data. Additionally, available oxygen consumption and catecholamine concentrations in each patient were averaged within each 0.5°C range of core temperatures between 36 - 36°C. The group mean within each range was subsequently determined from the individual averages. Regression analysis was used to correlate changes in mean oxygen consumption and plasma catecholamine concentrations with core temperature. Results are presented as means ± SD.

Results

There were no complications associated with the study. Half the patients were aged 1 month or less (table 1). Operating room temperatures averaged 22 ± 2.4°C. Intravenous fluids were administered at a rate of 8 ± 2 ml·kg⁻¹·h⁻¹. All patients were intensely vasoconstricted in the arms and legs by the time esophageal temperature reached 36°C; vasoconstriction was subsequently maintained until well after rewarming started.

Individual oxygen consumption data failed to reveal any consistent effect of cooling on systemic oxygen consumption (fig. 1). Regression analysis of the group data revealed that oxygen consumption decreased 12%/°C throughout the 36 - 34°C core temperature range. Hypothermia did not alter plasma norepinephrine concentrations (fig. 2). Concentrations of epinephrine and dopamine also remained unchanged during core cooling.

Discussion

The thermodynamic efficiency of shivering and nonshivering thermogenesis (heat produced by metabolism of a given substrate) is identical. Nonshivering thermogenesis is more effective because shivering generates heat peripherally where it is more easily dissipated to the environment. Further, the muscular activity should be supported by augmented peripheral blood flow, which also facilitates loss of core heat to the environment. The efficacy of nonshivering thermogenesis may be one reason that most small animals activate this defense before shivering. Classic studies indicate that nonshivering thermogenesis in unanesthetized human infants doubles metabolic rate and that the combination of vasoconstriction and nonshivering thermogenesis allows infants to maintain normothermia even in cool environments. Nonshivering thermogenesis occurs in a specialized tissue, brown fat (the macroscopic brown coloration is a result of enormous mitochondrial density in the adipocytes). Thermogenesis is mediated neuronal release of norepinephrine that binds to β3 adrenoreceptors on brown adipocytes. Binding activates adenylate cyclase, which increases cytosolic cyclic adenosine monophosphate (cAMP), phosphorylates protein kinase, and activates hormone-sensitive lipase. Free fatty acids released by lipolysis are transported to the mito-
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Table 1. Morphometric and Demographic Characteristics and Hemodynamic Responses

<table>
<thead>
<tr>
<th>Subject</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>Average</th>
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</thead>
<tbody>
<tr>
<td>Age (d)</td>
<td>3</td>
<td>2</td>
<td>0.03</td>
<td>1</td>
<td>9</td>
<td>0.03</td>
<td>2.5 ± 3.1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>4.5</td>
<td>3.1</td>
<td>2.6</td>
<td>3.8</td>
<td>8</td>
<td>2.4</td>
<td>4.1 ± 1.9</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>60</td>
<td>54</td>
<td>48</td>
<td>51</td>
<td>73</td>
<td>49</td>
<td>56 ± 9</td>
</tr>
<tr>
<td>Mean BP (mmHg)</td>
<td>49</td>
<td>74</td>
<td>55</td>
<td>29</td>
<td>58</td>
<td>35</td>
<td>50 ± 15</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>124</td>
<td>121</td>
<td>115</td>
<td>157</td>
<td>95</td>
<td>115</td>
<td>121 ± 18</td>
</tr>
</tbody>
</table>

Individual heart rates and blood pressures are average values during core cooling; there were no statistically significant or clinically important temperature-dependent changes in either.

BP = blood pressure. HR = heart rate.

Chondria, where they are metabolized initially by \( \beta \) oxidation and subsequently in the citric acid cycle.

Norepinephrine stimulation also increases transcription of a unique protein, thermogenin.\textsuperscript{26} Thermogenin is a proton-anion transporter that disperses the mitochondrial proton gradient by short-circuiting the adenosine diphosphate (ADP)-phosphorylation system, thus uncoupling substrate oxygenation from adenosine triphosphate (ATP) synthesis.\textsuperscript{27} This allows metabolic energy generated by lipid oxidation to be dissipated as heat rather than preserved in high-energy chemical species.

Physiologic control of brown fat thermogenesis, like most thermoregulatory responses, is largely central.\textsuperscript{28,29} Autoradiographic \([\textsuperscript{14}C]\)deoxyglucose techniques further localize the control site to the anterior hypothalamus.\textsuperscript{30} In general, efficient responses such a behavioral modification and vasomotor changes are activated first.

Responses such as sweating and shivering, which are metabolically costly or use substantial resources, are only activated when efficient responses fail to maintain body temperature. The threshold for shivering, for example, is \( \approx 1^\circ C \) less than that for vasoconstriction,\textsuperscript{31} a difference that is preserved during general anesthesia.\textsuperscript{13,15} The relation between the vasoconstriction and nonshivering thermogenesis thresholds has yet to be quantified in unanesthetized infants. However, nonshivering thermogenesis is among the "costly" responses and would thus not be anticipated until vasoconstriction was fully activated. Because nonshivering thermogenesis is the physiologic analog of shivering, it is reasonable to expect the thresholds to differ by \( \approx 1^\circ C \).

Our patients (who were given relatively little anesthesia) were fully vasoconstricted by the time core temperature decreased to \( 36^\circ C \). Thus we had an \( \approx 2^\circ C \) range of core temperatures over which nonshivering thermogenesis might be observed, although we failed to detect the hypothermia-induced increase in metabolic rate that characterized nonshivering thermogenesis. Instead, systemic metabolic rate decreased linearly, just as it does in anesthetized adults.\textsuperscript{32} Further, we failed to detect the typical large increase in the plasma norepinephrine concentration associated with nonshivering thermogenesis. Infants and children appear similar to adults in being unable to increase metabolic rate in response to mild intraoperative hypothermia.

Our inability to identify intraoperative nonshivering thermogenesis is surprising because hypermetabolism would have helped explain the unexpected efficacy of the core-temperature plateau in pediatric patients. The apparent special ability of infants and children to protect intraoperative core temperature must result from another mechanism. Thermoregulatory vasoconstriction, for example, may be especially intense in pediatric patients. Alternatively, body morphology may contrib-
ute; their globular trunks combined with relatively small arms and legs likely increase the efficacy of vasoconstriction.

Our failure to identify nonshivering thermogenesis also is surprising because all other major autonomic thermoregulatory responses have been readily detected during anesthesia. Why propofol and fentanyl might specifically block nonshivering thermogenesis remains unclear, but these data suggest that this type of general anesthesia alters control of nonshivering thermogenesis differently from vasoconstriction and shivering. An alternative, but perhaps less likely, explanation is a peripheral anesthetic-induced inhibition of nonshivering thermogenesis.

It also remains possible that intraoperative nonshivering thermogenesis occurs at core temperatures <36°C. Thermogenesis at such temperatures would, however, be of little clinical relevance (except during cardiac surgery) because pediatric patients are rarely allowed to cool even to that temperature. It also remains possible that intraoperative nonshivering thermogenesis is retained in patients given other types of intravenous anesthesia, although there is no obvious biochemical reason to expect propofol or fentanyl to specifically impair this thermoregulatory defense. One study concluded that fentanyl and nitrous oxide impair nonshivering thermogenesis in neonatal rabbits.5 However, the same study concluded that metocurine administration (without concomitant anesthesia) inhibits cold-induced thermogenesis, whereas curare does not. The authors’ explanation for this surprising difference was that “one [curare] is a nondepolarizer, and one [metocurine] is a depolarizer.”

Volatile anesthetics are known to peripherally inhibit nonshivering thermogenesis.9 Given that we were unable to detect nonshivering thermogenesis even during intravenous anesthesia, it thus seems unlikely that this response would be clinically important in patients given volatile anesthetics. Consistent with this theory, no relation between temperature and oxygen consumption was observed in four infants anesthetized with halothane (although vasoconstriction was not evaluated in that study, and the core temperature range was not specified).54

The range age over which nonshivering thermogenesis is clinically important remains unknown in unanesthetized humans. However, it is likely that shivering largely replaces nonshivering thermogenesis at about 1 yr. Some nonshivering thermogenesis may persist even in adults, but its magnitude is small.35–38 The oldest patient in our study was aged 9 months and would thus be expected to retain the potential for nonshivering thermogenesis. Lack of nonshivering thermogenesis in our patients cannot be explained by the inclusion of several patients aged 6–9 months because there also was no evidence of cold-induced thermogenesis in the younger patients.

In summary, even at core temperatures ≥2°C below the vasoconstriction threshold, we were unable to detect a increases in oxygen consumption or circulating norepinephrine that would indicate activation of nonshivering thermogenesis. This finding is surprising because all other major thermoregulatory responses have been detected during anesthesia and because nonshivering thermogenesis would have helped explain the unexpected efficacy of the core-temperature plateau in pediatric patients. Infants and children appear similar to adults in being unable to increase metabolic rate in response to mild intraoperative hypothermia.

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