The Effect of Hypothermia on Isoflurane MAC in Children

Mingzheng Liu, M.D., Xiaqin Hu, M.D.,† Jin Liu, M.D.,‡

Background: Hypothermia has been shown to decrease the requirement for inhaled anesthetics in animals, but information in humans is limited.

Methods: Thirty-three unpremedicated children with congenital left-to-right shunt heart diseases undergoing open heart surgeries were assigned to one of three groups, with nasopharyngeal temperatures at the time of skin incision of 37, 34, or 31°C. Anesthesia was induced and maintained with isoflurane in oxygen. End-tidal isoflurane concentration and nasopharyngeal temperature were kept at stable levels for at least 15 min before the skin incision. Isoflurane minimum alveolar concentration was determined by using the Dixon up-and-down approach.

Results: Isoflurane minimum alveolar concentration values were 1.69 ± 0.14%, 1.47 ± 0.10%, and 1.22 ± 0.15% (mean ± SD) at 37, 34, and 31°C, respectively.

Conclusions: Hypothermia decreases the isoflurane requirement in children by 5.1°C.

HYPOTHERMIA often occurs during surgical anesthesia. Considerable data describing volatile anesthetic requirements in hypothermic animals are available, but information about the effects of hypothermia on the minimum alveolar concentration (MAC) of inhaled anesthetics in humans is limited. Such information is of both clinical and experimental interest. Furthermore, the mechanism of hypothermia decreasing MAC is not clear. We therefore designed the present study to investigate the relation between isoflurane MAC in humans, temperature, and lipid solubility of isoflurane.

Materials and Methods

Determination of Isoflurane Minimum Alveolar Concentration at Different Temperatures

After obtaining Institutional Review Board approval (Fuwai Hospital and Cardiovascular Institute, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China) and informed consent from their parents, 33 children (4–10 yr of age) with congenital left-to-right shunt heart diseases (atrial septal defect or ventricular septal defect) undergoing open heart surgeries with hypothermia cardiopulmonary bypass were included in this study. Patients were randomly assigned to one of three groups, depending on the nasopharyngeal temperature at the time of skin incision: group A (37°C; n = 10), group B (34°C; n = 10), or group C (31°C; n = 13).

Premedication was not used in patients. Electrocardiogram, noninvasive blood pressure, and pulse oxygen saturation (SpO2) were monitored and recorded. During induction, nitrous oxide (4 l/min) and oxygen (1 l/min) were inhaled via a face mask. Isoflurane concentration was adjusted from 0.2% to 5% in approximately 3 to 4 min, and then nitrous oxide was discontinued. Tracheal intubation was facilitated with succinylcholine.

After intubation, oxygen flow rate was adjusted to 1–2 l/min. End-tidal carbon dioxide concentration was monitored with a Nellcor 1500E monitor (Nellcor Puritan Bennett, Inc., St. Louis, MO). End-tidal isoflurane concentration was monitored by a Normac Datex monitor (Datex-Omeda Division, Instrumentarium Corp., Helsinki, Finland). The accuracy of the monitors had been tested, and a calibrated gas standard was provided by Dräger Company (Aktiengesellschaft, Germany). Nasopharyngeal temperature was maintained at 37°C in group A by using a warm water circulating blanket. Surface cooling was applied in groups B and C. Nasopharyngeal temperature was decreased and maintained at 34°C in group B and at 31°C in group C. End-tidal isoflurane concentration, carbon dioxide concentration, and temperature were maintained at stable levels for at least 15 min before the skin incision. The MAC for each temperature group was determined during surgical skin incision by using the standard Dixon up-and-down approach.8 The response to skin incision was observed for 1 min and recorded as “movement” or “no movement.” A movement response was defined as either flexion or withdrawal of one or more extremities in response to skin incision. Breathing, grimacing, and movement of the head were not accepted as a movement response.

In each group, we adjusted inhaled isoflurane concentration to an arbitrary end-tidal concentration in the first patient, so that the end-tidal isoflurane concentration was maintained at that level (group A, 1.70 vol%; group B, 1.50 vol%; and group C, 1.30 vol%). For each succeeding patient in that group, this concentration was decreased or increased by 15%, depending on the adequacy or inadequacy of anesthesia at time of surgical incision in the previous patient. MAC of isoflurane was calculated as the average end-tidal isoflurane concentration between just permitting and preventing movement for stimulus of incision. Anesthesia and surgery for all
the patients was uneventful, and they are discharged within 10 days after the surgery.

**Determination of Olive Oil and Gas Partition Coefficient of Isoflurane**

Olive oil and gas partition coefficient (O/G) of isoflurane at 37, 34, and 31°C were determined with eight samples at each temperature. Isoflurane was purchased from Abbott Company (Shanghai, China) and olive oil from Beijing Medical Company (Beijing, China). A GOW-MAC 580 gas chromatographer (GOW-MAC Instrument Co., Bethlehem, PA) with a 6-m-long stainless steel column composed of 10% SF-96, on Chromasorb WHP, 60/80 mesh, maintained at 75°C, was used. A 15–20 ml/min nitrogen carrier stream flow was delivered through the column to a flame ionization detector at 150°C, supplied by hydrogen at 20–30 ml/min and by air at 200–240 ml/min. Linearity of peak height and isoflurane concentration was confirmed for all measurements. O/G of isoflurane was measured with a method previously reported by Taheri et al. Twenty-milliliter samples of olive oil were placed in 50-ml gas-tight syringes with 20 ml isoflurane, 2.30%. Each syringe was placed in a tonometry in a waterbath of the same temperature as the first equilibration period and shaken vigorously every 15 min for 10–15 s and immediately replaced in the tonometry in a waterbath of 37°C. At the end of the period, 20 ml isoflurane was added before removal of the syringe. Twenty milliliters of gas from within the flask was withdrawn, the concentration of isoflurane was analyzed by gas chromatography. The partition coefficients of isoflurane were determined as follows:

\[
\frac{[(V_f + 20 \, \text{ml} - V_b)/V_b]C_f}{(C_s - C_f)}
\]

where Vf is the volume of the flask, Vb is the solvent volume of the sample transferred, Cf is the concentration of isoflurane in the gas phase of the flask, and Cs is the concentration of isoflurane in the gas phase of the syringe. Twenty milliliters of gas from within the flask was withdrawn, the concentration of isoflurane was analyzed by gas chromatography. The partition coefficients of isoflurane were determined as follows:

\[
\frac{[(V_f + 20 \, \text{ml} - V_b)/V_b]C_f}{(C_s - C_f)}
\]

Results are reported as mean ± SD. Correlation between isoflurane MAC and temperature and between solubility in olive oil and temperature were analyzed using linear regression, with P values less than 0.05 considered statistically significant.

**Results**

Table 1 shows that demographic characteristics were similar in each group. Isoflurane MAC was 1.69 ± 0.14%, 1.47 ± 0.10%, and 1.22 ± 0.15% at 37.6 ± 0.3°C, 33.6 ± 0.2°C, and 31.0 ± 0.4°C, respectively. As anticipated, when the temperature decreased from 37°C to 31°C, the O/G of isoflurane increased linearly.

Table 2 shows the end-tidal isoflurane concentration and temperature at the skin incision and the response to the skin incision from each patient.

**Discussion**

Pediatric patients with congenital left-to-right shunts were chosen for this study based on the following reasoning. First, the surgery was to be performed under hypothermia. Second, inhalational anesthesia induction is well accepted by children with congenital heart diseases, and this leads to an easy way for isoflurane MAC determination. Third, intracardiac mixing of systemic blood with higher anesthetic partial pressure and pulmonary blood occurs in the right heart during inhalational anesthesia induction and maintenance in our patients. This reduces the difference in anesthetic partial pressure between alveolar and pulmonary artery blood and between alveolar and artery blood. Hence, the partial pressure of isoflurane in the brain is well represented by end-tidal concentration of isoflurane. A computer model has demonstrated that during inhalational anesthesia induction, the rate of transfer of anesthetics from alveolar to the central nervous system is unchanged by pure left-to-right shunts.

Isoflurane MAC at 37°C determined in the present study is similar to that reported for children of similar age by Cameron et al. (1.69% vs. 1.60%). Temperature is said to affect anesthetic requirement markedly in humans. The evidence for this is found mainly from animal studies.
HYPOTHERMIA AND ISOFLURANE MAC

Table 2. Individual Data of ET

<table>
<thead>
<tr>
<th>Patient</th>
<th>ETiso (vol%)</th>
<th>T (°C)</th>
<th>Response</th>
<th>ETiso (vol%)</th>
<th>T (°C)</th>
<th>Response</th>
<th>ETiso (vol%)</th>
<th>T (°C)</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.75</td>
<td>36.7</td>
<td>–</td>
<td>1.53</td>
<td>33.3</td>
<td>+</td>
<td>1.34</td>
<td>30.6</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>1.55</td>
<td>36.5</td>
<td>–</td>
<td>1.68</td>
<td>33.6</td>
<td>–</td>
<td>1.16</td>
<td>30.9</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>1.36</td>
<td>36.4</td>
<td>+</td>
<td>1.51</td>
<td>33.6</td>
<td>–</td>
<td>0.98</td>
<td>30.4</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>1.51</td>
<td>36.8</td>
<td>+</td>
<td>1.31</td>
<td>33.5</td>
<td>–</td>
<td>1.14</td>
<td>31.1</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>1.73</td>
<td>36.5</td>
<td>–</td>
<td>1.50</td>
<td>34.0</td>
<td>+</td>
<td>1.32</td>
<td>31.1</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>1.54</td>
<td>36.6</td>
<td>+</td>
<td>1.69</td>
<td>33.6</td>
<td>–</td>
<td>1.51</td>
<td>31.6</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>1.74</td>
<td>35.5</td>
<td>+</td>
<td>1.51</td>
<td>33.7</td>
<td>–</td>
<td>1.30</td>
<td>30.6</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>1.91</td>
<td>36.6</td>
<td>–</td>
<td>1.31</td>
<td>33.5</td>
<td>+</td>
<td>1.18</td>
<td>31.2</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>1.70</td>
<td>36.7</td>
<td>+</td>
<td>1.51</td>
<td>33.4</td>
<td>–</td>
<td>1.00</td>
<td>30.8</td>
<td>–</td>
</tr>
<tr>
<td>10</td>
<td>1.88</td>
<td>37.4</td>
<td>–</td>
<td>1.30</td>
<td>33.6</td>
<td>+</td>
<td>1.18</td>
<td>31.5</td>
<td>+</td>
</tr>
<tr>
<td>11</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1.31</td>
<td>31.0</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1.13</td>
<td>31.1</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1.30</td>
<td>31.2</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Response: + = movement; – = no movement.
ETiso = end-tidal isoflurane concentration.

The effect of hypothermia on MAC of volatile anesthetics in humans has never been reported. In this prospective study, we found that a rectilinear decrease in isoflurane MAC in children of 4–10 yr of age as body temperature decreased. Isoflurane MAC reduced approximately 5.1% for 1°C reduction in body temperature, which is almost identical to a decline of 5%/°C previously reported for isoflurane in rats by Vitez et al.4 and in goats by Antognini,6 suggesting that hypothermia affects isoflurane MAC by a similar mechanism of action for humans and other mammals.

The mechanism by which hypothermia decreases MAC is not clear. Based on the Meyer-Overton hypothesis,12,13 anesthesia occurs when a specific number of anesthetic molecules occupy a crucial hydrophobic site in the central nervous system. This is described by the following formula: anesthetizing partial pressure (e.g., MAC) × lipid solubility (e.g., O/G partition coefficient) = constant. It is well known that hypothermia increases O/G partition coefficients of inhaled anesthetics.1,2,14 Therefore, reduction of MAC of inhaled anesthetics accompanying a decrease in temperature may be explained by increasing solubility of anesthetics in olive oil, which mimic the hydrophobic site in the central nervous system. If this hypothesis is still true under hypothermia, the product of MAC × O/G should be a constant over the decreased temperature range and the same as at normal body temperature. In this study, we found that isoflurane O/G increased with a decrease in temperature in a rectilinear fashion. The increase rate is −3.9%/°C, identical to our unpublished data for brain:gas partition coefficients (−3.9 ± 0.7%/°C) in Chinese male adults (27 ± 8 yr of age), also in accordance with the results calculated by Allott et al.14 (−3.50%). However, as seen in table 1, these data are smaller than the reduction rate of MAC under hypothermia obtained from this study (5.1%/°C) and MAC × O/G decreases with decreasing temperature, instead of a constant. The results suggest that hypothermia per se decreases the requirement for volatile anesthetics in humans, which may lead to no anesthetic required at all at a low enough temperature. Extrapolation of the relation between temperature and isoflurane MAC from the present study (MACiso 0.0784T(°C) − 1.203; r = −0.99; P < 0.01) indicates that anesthetizing temperature (MACiso = 0) would be 16.2°C, which is close to the anesthetizing temperature (20°C) measured directly under cardiopulmonary bypass and the extrapolated values (16–21°C) based on mammal studies.1–3 The electroencephalogram becomes isoelectric at approximately 20°C,15,16 suggesting that both electroencephalogram isoelectricity and ‘hypothermic anesthesia’ occur at approximately the same temperature.

In summary, we have shown that hypothermia decreases the isoflurane anesthetic requirement in children by 5.1%/°C and increases isoflurane O/G in a temperature-related fashion. MAC × O/G decreases with hypothermia. The effect of hypothermia on isoflurane MAC can not be explained only by increasing solubility of inhaled anesthetics in the lipid phase of the central nervous system.

References

1. Eger EI II, Saidman LJ, Brandstater B: Temperature dependence of halothane and cyclopropane anesthesia in dogs: Correlation with some theories of anesthetic action. ANESTHESIOLOGY 1965; 26:764–70
4. Vitez TS, White PF, Eger EI II: Effects of hypothermia on halothane MAC and isoflurane MAC in the rat. ANESTHESIOLOGY 1974; 41:80–1
6. Antognini JF. Hypothermia eliminates isoflurane requirements at 20°C. ANESTHESIOLOGY 1993; 78:1152–6