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Hypothermia Eliminates Isoflurane Requirements at 20° C

*Joseph F. Antognini, M.D.**

Background: **Hypothermia decreases anesthetic requirements, but the temperature that completely eliminates anesthetic needs has not been previously determined.**

Methods: **Eight female goats were anesthetized with isoflurane and catheters were placed in the femoral artery and cranial vena cava, after which the right carotid artery and external jugular vein were dissected free. Peripheral temperature was monitored in the rectum and core temperature in the vena cava. A thermistor was placed in the epidural space *via* a small burr hole to monitor brain temperature. Minimum alveolar concentration (MAC) for isoflurane was determined by eliciting gross, purposeful movement with a tail clamp. Cardiopulmonary bypass (CPB) was established using bubble oxygenators with venous blood drained from a jugular vein and arterial blood infused with a roller pump into the carotid artery. The animals were cooled to approximately 29° C, and MAC redetermined, after which further cooling to 20° C was accomplished. Isoflurane was eliminated, core and brain temperature adjusted in 2–3° C increments, and the tail clamp applied until two temperatures were found that just permitted and just prevented movement. The animals were rewarmed, isoflurane added, and post-CPB MAC determined.**

Results: **At 38.5° C, pre-CPB MAC was 1.3 ± 0.1% (mean ± SEM). At 29.0° C, MAC was 0.7 ± 0.1%, and the anesthetizing temperature was 20.1 ± 0.6° C. At 37.3° C, post-CPB MAC was 1.0 ± 0.1% ($P < 0.05$ *vs.* pre-CPB).**

Conclusions: **These results confirm the rectilinear decrease in MAC seen in previous studies and establishes the anesthetizing temperature at 20° C. (Key words: Anesthetics, volatile: isoflurane. Hypothermia: anesthesia. Potency, anesthetic: MAC. Surgery, cardiovascular: cardiopulmonary bypass.)**

PROFOUND hypothermia is used during certain surgical procedures, such as complex cardiac repairs[1–4] and giant intracerebral aneurysms.[5] Anesthesia is reduced during the period of hypothermia because of the well known effect of temperature on anesthetic requirements.[6–11] Hypothermia decreases anesthetic needs in a rectilinear fashion, such that a 10° C decrease from 38° C results in an approximately 50% decrease in halothane[6,7] and isoflurane[6] requirements. Extrapolation of this relationship indicates that hypothermia itself would act as a complete anesthetic at 18–21° C.[8] Cyclopropane requirements, however, diminish less with hypothermia, and extrapolation of these data suggest an anesthetizing temperature of 0–6° C. Previous attempts to document this have been thwarted by ventricular fibrillation, which occurs at 22–25° C.[7,8] We sought to determine at what temperature anesthetic requirements are completely eliminated. Cardiovascular support during the period of profound hypothermia was provided by extracorporeal circulation.

Materials and Methods

This study was approved by the animal care and use committee. Eight female goats of different breeds, age approximately 1.5 yr and weight 38 ± 2 kg (mean ± SEM), were used. Anesthesia was induced *via* mask with isoflurane 5% in oxygen. The trachea was intubated and a stomach tube placed to drain rumen contents. A femoral arterial catheter was placed for mean arterial pressure (MAP) and blood gas determinations. Core temperature was measured with a thermistor placed in the cranial vena cava *via* the external jugular vein, brain temperature was monitored with an epidural thermistor placed *via* a small burr hole, and a rectal thermistor was used for peripheral temperature determinations. All of the temperature probes were calibrated with a mercury thermometer in the 20–40° C range. Heart rate (HR) was monitored with the electrocardiogram. The right carotid artery and external jugular vein were dissected for cannulation.

Minimum alveolar concentration (MAC) for isoflurane was determined with a tail clamp.[12] Briefly, a calibrated agent analyzer (Model 254; Datex, Tewksbury, MA) sampled alveolar gas from a catheter placed in the distal endotracheal tube. The isoflurane concentration was held constant for 15–20 min and a 12-inch hemostat

* Assistant Professor.

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Address reprint requests to Dr. Antognini: Department of Anesthesiology, University of California, Davis, TB-170, Davis, California 95616.

applied to full rachet lock to the tail and moved vigorously for 1 min. A positive response was considered to be gross, purposeful movement, usually a pawing motion or turning of the head. Chewing, stiffening, or coughing were considered negative. Depending on the initial response, the isoflurane was increased or decreased 0.2%, the new concentration maintained for 15–20 min, and the tail clamp reapplied. (In a few instances, spontaneous, purposeful movement occurred at the lower concentration; this was taken as a positive response.) This process was continued until two concentrations were found that just prevented and just permitted movement. MAC is the average of these.

After control MAC determination, heparin 4 mg/kg was administered in preparation for cardiopulmonary bypass (CPB). Blood was drained from a cannula placed in the vena cava *via* the external jugular vein; for arterial inflow, a centrally directed cannula was placed in the carotid artery. (The goat has an extensive rete mirabile that maintains cerebral circulation if a carotid artery is occluded.[13])

For CPB, bubble oxygenators were used (Bentley B-10, Irvine, CA) and flow provided by a calibrated roller pump, with temperature controlled with a water bath. The unit was primed with isotonic crystalloid, and arterial filtration was not used. Oxygen flows of 3–5 l/min were used for the oxygenator, with an isoflurane vaporizer placed in line. Blood flow from the roller pump was kept at approximately 40 $ml \cdot kg^{-1} \cdot min^{-1}$. Additional heparin, 1–2 mg/kg, was given every 1–1.5 hr of bypass.

The animals were cooled to about 29° C, and the core and brain temperatures closely matched (within 1° C). The rectal temperature lagged somewhat, but was usually within 2° C. Minimum alveolar concentration was then redetermined. During bypass, the lungs were ventilated and isoflurane concentration from the oxygenator exhaust (measured in an airtight fashion) was always matched to the end-tidal alveolar isoflurane concentration. (Anesthetic partial pressure in the exhaust closely approximates arterial anesthetic partial pressure.[14]) Once MAC was determined, the animals were cooled to about 20° C, and the isoflurane was eliminated during this period. The isoflurane was off for 36 ± 4 min (range: 23–50 min), the oxygenator and lung isoflurane concentration were 0.0–0.1% for 19 ± 7 min (range: 10–40 min), and the tail clamp was applied. Depending on the response, the temperature was increased or decreased 2–3° C, stabilized for 10–15 min, and the tail clamp reapplied. This process was repeated until two temperatures were found that just prevented and just permitted movement; these were averaged to obtain the anesthetizing temperature. Isoflurane was added, the animals rewarmed to normothermia, and MAC measured after termination of CPB. Isoflurane was present for 65 ± 6 min before the post-CPB MAC determination.

Arterial blood gases and hematocrit (Hct) were obtained for the pre-CPB, CPB, and post-CPB periods. Blood gas analysis was performed with electrodes at 37° C; the reported values are not corrected for temperature.

Results are reported as mean ± SEM. The reported temperatures are the average of the core and brain temperatures. Repeated measures ANOVA was used to determine significant changes in MAC, MAP, HR, Hct, and blood gases. A probability of < 0.05 was considered significant.

Results

Minimum alveolar concentration was not determined in one animal at 29° C; post-CPB MAC was not determined in another animal because of inability to separate from bypass. At 38.5 ± 0.4° C, pre-CPB MAC was 1.3 ± 0.1%; at 29.0 ± 0.5° C, MAC was 0.7 ± 0.1%. The anesthetizing temperature was 20.1 ± 0.6° C (fig. 1). Thus, isoflurane MAC decreased approximately 5% for every 1° C decrease. Post-CPB MAC at 37.3 ± 0.5° was 1.0 ± 0.1% ($P < 0.05$ *vs.* pre-CPB). Because the animals were approximately 1.2° C cooler post-CPB, when corrected for temperature, post-CPB MAC was 80% of control.

The anesthetizing temperature was not significantly different when comparing those goats who had the most deterioration in MAC (average 27% decrease) with those with the least deterioration (average 17% decrease): 21.0 ± 0.2° C *vs.* 20.3 ± 0.7° C. Likewise, the time interval between discontinuing the isoflurane and the tail-clamp application did not correlate with the anesthetizing temperature: 19.6 ± 1.1° C in four goats with an interval of 30 ± 3 min, and 20.6 ± 0.7° C in four goats with an interval of 42 ± 2 min.

Mean arterial pressure significantly decreased as temperature decreased: 86 ± 3 mmHg at 38.5° C, 58 ± 4 mmHg at 29° C, 47 ± 2 mmHg at 20° C, and 83 ± 7 mmHg post-CPB. Heart rate also slowed: 121 ± 6 at 38.5° C *vs.* 21 ± 8 at 20° C. Hct decreased and a metabolic acidosis occurred with bypass, but these trends were not progressive (table 1). Arterial oxygen tension

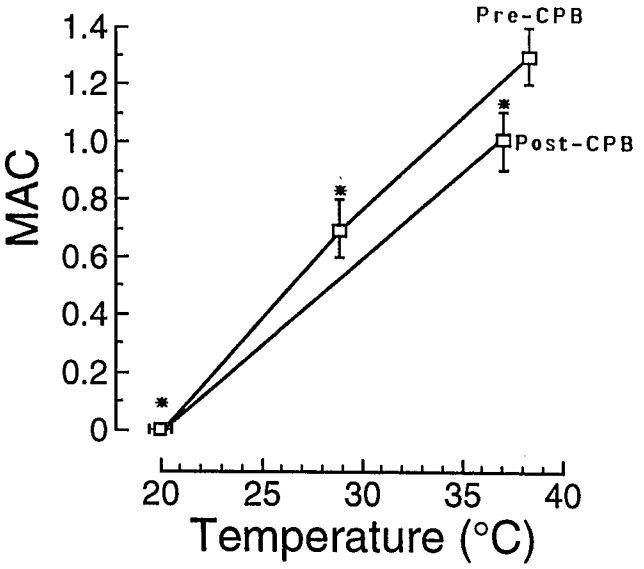

Fig. 1. Hypothermia decreases isoflurane minimum alveolar concentration (MAC, volume %). Minimum alveolar concentration did not return to control with rewarming. Pre-CPB = before cardiopulmonary bypass; post-CPB = after cardiopulmonary bypass. Data are expressed as mean ± SEM. *$P < 0.05$ *vs.* pre-CPB.

was increased at 20° C, probably because of decreased solubility of oxygen at the measurement temperature of 37° C. Total fluids (including CPB prime) were 4.2 ± 0.2 l. Bypass time was 3.6 ± 0.2 h, and total experimental time was 8.5 ± 0.5 h.

Discussion

We found that hypothermia eliminates anesthetic needs at 20° C, confirming that MAC decreases rectilinearly over the 20–39° C range.[6–11] The exact mechanism by which hypothermia decreases MAC is not clear. Solubility of inhaled anesthetics in lipid materials increases with decreasing temperature.[15] If anesthetics act at the lipid membrane, then the number of molecules dissolved will increase with decreasing temperature, and this would cause an apparent lowering of MAC.[8] Hypothermia itself alters physiological functions, *e.g.*, diminished metabolic rate, so this factor could also decrease MAC.

The change in lipid solubility with temperature depends on the anesthetic agent. For example, cyclopropane solubility in olive oil increases 2% for every 1° C decrease; halothane and isoflurane solubility increase 4%.[15] These correlate with the approximately 25% and 50% decrease in MAC, respectively, seen with cyclopropane and halothane over the 38–28° C range. This suggests that solubility changes associated with hypothermia, and not physiologic ones, account for these temperature effects on MAC. Others, however, have argued that the decrease in MAC is greater than the exponential decrease one would expect from solubility changes alone.[8] Although the current study does not specifically address these dual effects of hypothermia on MAC, it clearly establishes the anesthetizing temperature. Interestingly, desflurane has a lipid solubility similar to that of cyclopropane, but the decrease in desflurane MAC (42%)[10] over 10° C is similar to those of halothane and isoflurane. Lipid solubility at 37° C roughly correlates with the effect of temperature on solubility;[15] deviation from this relationship might explain the above discrepancy. However, there are no solubility data for desflurane at hypothermic temperatures.

In humans, mild hypothermia (32–34° C) does not alter the electroencephalogram (EEG), and is associated with patient arousal.[16] Deeper hypothermia leads to progressive lethargy until unconsciousness ensues at around 25–27° C.[16] This initial activation indicates that any physiologic effects of hypothermia do not oc-

Table 1. Acid–Base and Hematocrit Changes in Goats Undergoing Hypothermic Cardiopulmonary Bypass

	*p*H	Pa_{CO_2} (mmHg)	BE (mM)	Pa_{O_2} (mmHg)	Hct (%)
Pre-CPB	7.38 ± 0.02	39 ± 2	−1 ± 3	405 ± 39	34 ± 2
MH CPB	7.24 ± 0.01*	44 ± 3	−9 ± 1*	433 ± 80	24 ± 1*
DH CPB	7.22 ± 0.06*	42 ± 3	−10 ± 3*	699 ± 30*	21 ± 1*
Post-CPB	7.29 ± 0.03*	35 ± 2	−8 ± 2*	358 ± 77	23 ± 1*

Values are mean ± SEM; n = 8 except for MH CPB and post-CPB, where n = 7.

Pre-CPB = before cardiopulmonary bypass, temperature = 38.5 ± 0.4° C; MH CPB = moderate hypothermic cardiopulmonary bypass, temperature = 29.0 ±0.5° C; DH CPB = deep hypothermic cardiopulmonary bypass, temperature = 20.1 ± 0.6° C; Post-CPB = after cardiopulmonary bypass, temperature = 37.3 ± 0.5° C; Hct = hematocrit.

* $P < 0.05$ *versus* pre-CPB.

cur until moderate or deep hypothermia. Thus, the initial decrease in MAC may be caused by physical reasons (*e.g.*, solubility) and the latter decrease may be caused by the physiologic effects of hypothermia itself. In dogs, over the 38–28° C range, there is a 50% decrease in cerebral metabolism;[17] the functional and cellular integrity components of cerebral metabolism are equally affected. In the 28–18° range, however, function is altered much more. These findings indicate that hypothermia might decrease anesthetic requirements on a physiologic basis primarily at the profoundly lower temperatures. In goldfish, anesthetic requirements fall exponentially over the 40–10° C range, but suddenly decrease to near zero at 5° C.[11] Thus, at least in this species, hypothermia itself does not appear to have important anesthetic effects until a critical temperature is reached. No such sudden decrease was seen in our study.

Anesthetics and hypothermia have disparate effects on the cerebral metabolic rate for oxygen ($CMRO_2$), which is depressed about 20% at 1 MAC for halothane[18] and isoflurane,[19] but is unchanged with nitrous oxide.[20] Hypothermia, however, depresses $CMRO_2$ 85% at 20° C.[17] These effects parallel those seen with the EEG. Although there is considerable variability, the EEG slows with hypothermia and becomes isoelectric at around 20° C,[21,22] indicating that EEG isoelectricity and "anesthesia" occur at about the same temperature. This conflicts with the EEG effects of halothane and isoflurane at normothermia, where isoelectricity does not occur until 4 MAC[23] and 2 MAC,[24] respectively. Thus, during hypothermia, it is theoretically possible that an animal may have purposeful movement when the EEG is silent, or nearly so. We initially attempted to document the EEG in the animals, but, despite placing electrodes directly into the skull, shivering prevented us from obtaining valid results.

Minimum alveolar concentration did not return to the pre-CPB level. This deterioration could have affected the observed anesthetizing temperature, but this is not likely. The approximately 50% decrease in MAC from 39 to 29° C is consistent with the findings of Vitez *et al.*,[6] indicating that any deterioration occurred after this. In addition, profound hypothermia would be protective against any emboli-induced ischemia that occurred during this period. Rewarming, however, would eliminate this protection, and also expand gaseous emboli, thus worsening any neurological damage. Furthermore, if this deterioration did alter the anesthetizing temperature, then the variable effect seen in post-CPB MAC would be expected to have caused similar variability in the anesthetizing temperature, which was not seen. While all of these factors indirectly suggest that this deterioration occurred during rewarming, we have no evidence to refute the possibility that it falsely raised the anesthetizing temperature. If MAC does change approximately 5% for every 1° C temperature change, then this deterioration would have increased the anesthetizing temperature by approximately 4° C.

Isoflurane was undoubtedly still present in small amounts at the profoundly hypothermic temperatures, despite efforts to eliminate it completely. This would not significantly alter the results, however. The time for 95% equilibration of isoflurane in the brain (t_{95}) = $\lambda_{br/bl} \cdot V \cdot \ln(1/0.05) \cdot CBF^{-1}$; where $\lambda_{br/bl}$ = brain/blood solubility co-efficient, V = brain volume, and CBF = cerebral blood flow.[25] The $\lambda_{br/bl}$ is the ratio of $\lambda_{br/gas}$ and $\lambda_{bl/gas}$; these two coefficients would be expected to increase approximately the same with changes in temperature,[15] based on aqueous and lipid solubility data. Thus, $\lambda_{br/bl}$ changes little with a decrease in temperature. Cerebral blood flow does decrease with hypothermia, but not nearly as much as cerebral metabolic rate. At 20° C, CBF is about 50% of its control value at normothermia.[17] Although we did not measure CBF, in goats it is normally 80 $ml \cdot 100g^{-1} \cdot min^{-1}$,[26] so at 20° C CBF would be 40 $ml \cdot 100g^{-1} \cdot min^{-1}$. Assuming $\lambda_{br/bl} = 2.5$,[27] t_{95} for the brain is about 20 min. Even with a brain isoflurane concentration of 0.1%, this would not be expected to alter the anesthetizing temperature by more than 1.5° C.

Hypotension, acidosis, anemia, and the length of the experiment are unlikely to have affected the results. While MAP was decreased during hypothermia, these pressures have minimal effect on MAC at normothermia[28] and should be sufficient at 20° C,[29,30] at least judged by the lack of increased neurologic dysfunction in humans who have undergone low-pressure CPB. Also, the relatively low CPB flow rates are adequate to maintain cerebral blood flow.[29,30] The crystalloid prime undoubtedly contributed to the anemia and acidosis. The decreased Hct is still close to the normal value (28–30%) for goats.[31] In addition, anemia does not alter MAC until Hct = 10%.[32] Likewise, a metabolic acidosis does not alter MAC,[33] and there is abundant evidence that MAC does not change over time.[10,12,34] Last, CPB and heparinization, with subsequent increased tissue damage at the clamping site, do not appear to alter MAC.[35]

In summary, hypothermia decreases MAC, and a temperature of approximately 20° C completely eliminates the need for anesthesia. This confirms that the fall in MAC is rectilinear over the 20–39° C range.

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