Blood Anesthetic Levels during Surface-Induced Deep Hypothermia under Halothane-Diethyl Ether Azeotrope Anesthesia

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Itoh, T., Thomas, R., Foltz, B.D. and Dillard, D.H. Blood Anesthetic Levels during Surface-Induced Deep Hypothermia under Halothane-Diethyl Ether Azeotrope Anesthesia. Tohoku J. exp. Med., 1986, 148 (1), 103-111 — Blood anesthetic concentration and clinical indicators related to anesthetic management during surface-induced deep hypothermia were determined in seven adult mongrel dogs. The azeotrope of halothane and diethyl ether was assayed by gas chromatography. Blood concentration of halothane ranged from a pre-cooling control of 0.74 vol % to 0.11 vol % at 20°C rewarming; ether ranged from 0.06 vol % at 20°C rewarming to 0.22 vol % at 35°C rewarming. Administration of anesthetic was reduced during cooling because of the spontaneous decrease in mean arterial pressure and heart rate. After elective circulatory arrest was induced, anesthetic was not required until after cardiac resuscitation at about 22°C rewarming. Initial clinical signs indicating a need to increase administration of anesthetic included spontaneous respiration and an increase in mean arterial pressure. Blood azeotrope concentration was significantly lower during rewarming than at comparable temperatures during cooling. We conclude that blood concentration of halothane and ether changes as a function of body temperature and that anesthetic demand may be diminished following total circulatory arrest. —— surface-induced hypothermia; blood anesthetic concentration; halothane-diethyl ether azeotrope

Previous studies have demonstrated that the halothane-diethyl ether azeotrope in a gas mixture of 95% O₂ and 5% CO₂ is superior to many other anesthetic agents for use during surface-induced deep hypothermia (Mohri et al. 1966, 1968, 1972; Sato et al. 1974, 1975; Sands et al. 1980; Haneda et al. 1982, 1986, 1988).
1984). However, determination of blood azeotrope concentration during cooling and after 60 min of total circulatory arrest has not been performed. To be of maximum usefulness, blood anesthetic levels must be carefully correlated to parameters available through clinical monitoring. Therefore, most clinical judgements of anesthetic depth during hypothermia are based on: 1) central aortic and venous blood pressures, 2) heart rate and changes in the electrocardiogram (ECG), 3) pupillary reflex and diameter, 4) rate of cooling and 5) biochemical changes reflected in blood gas and blood chemistry analyses. These indicators are readily and continuously available in the operating room and/or laboratory. The purpose of this study was to determine blood anesthetic concentration in the dog using the halothane-diethyl ether azeotrope during surface-induced deep hypothermia and to correlate measured anesthetic levels with useful clinical parameters.

MATERIALS AND METHODS

Seven adult mongrel dogs of both sexes ranging in weight from 18.2 to 22.0 kg (average weight, 19.4 kg) were used. The details of our standard method of surface-induced deep hypothermia and azeotrope administration have been described previously (Mohri et al. 1966, 1968; Sands et al. 1980). In brief, anesthesia was induced with thiamylal sodium (18 mg/kg) and maintained deep enough to prevent shivering. The azeotrope was administered by passing a gas mixture of 95% O₂ and 5% CO₂ through a Fluotec Mark III vaporizer at flow rates of 8 to 10 liter/min in an open (non-rebreathing) circuit. Animals were ventilated with a Harvard respirator at a tidal volume of 20 ml/kg and at a rate of 20 breaths/min. Atropine sulfate (0.03 mg/kg) and antibiotics were given pre-operatively. Cooling was accomplished by direct ice-water immersion and rewarming by flotation on a plastic sheet interposed between the dog and a 40°C water bath. Ten percent low molecular weight dextran (LMWD; 1 gm/kg) was administered between 35° and 25°C during cooling. Circulatory arrest was induced by inflow and outflow occlusion of the major vessels (aorta, inferior and superior vena cavae). Access to the heart was through a right thoracotomy. Cardioplegia was induced with cold Young’s solution* injected directly into the aortic root proximal to the aortic crossclamp. Resuscitation was accomplished by manual massage, intravenous administration of CaCl₂ (300 mg), epinephrine (10–30 μg) and, when necessary, electrical defibrillation.

Polyethylene catheters were inserted into the abdominal aorta and inferior vena cava via the left femoral vessels. Arterial and venous pressures and the electrocardiogram were monitored on a Hewlett-Packard model 7788A physiologic recording system. Arterial samples for blood anesthetic concentration, blood gas and hematocrit determinations were taken at 5°C intervals during cooling and rewarming. Blood anesthetic levels were assayed by gas chromatography (Heavner et al. 1976). pH, PCO₂ and PO₂ were measured at 37°C with a Model 113 Instrumentation Laboratory blood gas analyzer. Temperature correction to the animal’s rectal temperature at the time of sampling and acid-base calculations were done with standard Severinghaus nomograms. Pupil diameter was determined by micrometer. Rectal and esophageal temperatures were monitored with digital thermometers (Electromedics, Inc. Englewood, CO, USA).

Data were tabulated and computer-processed to provide mean ± s.D. Results were compared using the Student’s paired t-test and differences between means were considered to be statistically significant if p < 0.05.
### Table 1. Blood gas, acid-base and hematocrit during cooling and rewarming

<table>
<thead>
<tr>
<th>Rectal temperature(°C)</th>
<th>Control</th>
<th>35</th>
<th>30</th>
<th>25</th>
<th>20</th>
<th>20</th>
<th>25</th>
<th>30</th>
<th>35</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.35 ± 0.09</td>
<td>7.35 ± 0.08</td>
<td>7.37 ± 0.07</td>
<td>7.381* ± 0.069</td>
<td>7.384 ± 0.071</td>
<td>7.33 ± 0.08</td>
<td>7.32 ± 0.06</td>
<td>7.33 ± 0.06</td>
<td>7.32 ± 0.07</td>
</tr>
<tr>
<td>$P_{CO_2}$ (mmHg)</td>
<td>46 ± 3</td>
<td>46 ± 3</td>
<td>44 ± 2</td>
<td>39 ± 2*</td>
<td>38 ± 2*</td>
<td>40 ± 3</td>
<td>44 ± 6</td>
<td>49 ± 3</td>
<td>55 ± 6*</td>
</tr>
<tr>
<td>$P_{O_2}$ (mmHg)</td>
<td>428 ± 35</td>
<td>453 ± 54</td>
<td>471 ± 42</td>
<td>458 ± 67</td>
<td>421 ± 82</td>
<td>253* ± 90</td>
<td>279* ± 100</td>
<td>215* ± 68</td>
<td>195* ± 72</td>
</tr>
<tr>
<td>$HCO_3^-$ (mEq/liter)</td>
<td>24.8 ± 5.4</td>
<td>26.1 ± 4.6</td>
<td>27.9* ± 6.1</td>
<td>27.3* ± 4.9</td>
<td>28.5* ± 4.5</td>
<td>26.3* ± 1.0</td>
<td>26.6 ± 5.6</td>
<td>27.1 ± 4.1</td>
<td>28.2 ± 3.7</td>
</tr>
<tr>
<td>BE (mEq/liter)</td>
<td>-0.6 ± 6.0</td>
<td>-0.2 ± 5.1</td>
<td>0.5 ± 6.0</td>
<td>-1.3 ± 4.9</td>
<td>-2.2 ± 4.4</td>
<td>-1.2 ± 5.9</td>
<td>-3.3 ± 5.1</td>
<td>-0.9 ± 3.9</td>
<td>1.1 ± 3.9</td>
</tr>
<tr>
<td>Hct(%)</td>
<td>34 ± 5</td>
<td>35 ± 5</td>
<td>31 ± 4*</td>
<td>30 ± 4*</td>
<td>37 ± 9</td>
<td>44 ± 5*</td>
<td>42 ± 6*</td>
<td>37 ± 7</td>
<td>40 ± 7</td>
</tr>
</tbody>
</table>

All values are means ± s.d.

*significantly different from controls ($p < 0.05$).

$P_{CO_2}$, partial pressure of carbon dioxide; $P_{O_2}$, partial pressure of oxygen; $HCO_3^-$, bicarbonate radical; BE, base excess; Hct, hematocrit.
RESULTS

Blood gas, acid-base, hematocrit and hemodynamic data are shown in Table I and Fig. 1. These results were consistent with those of previous experiments (Sands et al. 1980; Haneda et al. 1982, 1984) in which the same technique had been used.

Anesthetic course

The azeotrope was initially delivered at an inspired concentration of 2.0% (Fig. 2). Pre-cooling data collection required approximately 40 min. The inspired azeotrope concentration immediately prior to immersion cooling (control) averaged 1.93%±0.19 at a rectal temperature of 37.5°C. As cooling progressed, mean aortic pressure and heart rate decreased indicating a need to reduce anesthetic administration. During cooling, the inspired concentration was reduced from 1.93%±0.19 to 0.79±0.34 between 37.5°C and 25°C. Immersion cooling was terminated at a rectal temperature of 22°C and at this time a right thoracotomy through the fourth intercostal space was performed. The inspired concentration at 20°C cooling averaged 0.11%±0.18. All animals maintained a normal sinus rhythm throughout cooling except one dog in which a transient AV nodal rhythm was seen between 27°C and 24°C. This nodal arrhythmia was easily controlled by temporarily increasing the anesthetic concentration. Anesthesia was not required during resuscitation of early rewarming (20°C). Cardiac massage was initiated at a mean rectal temperature of 18.6°C±0.8 (range 17.0-19.4°C). Resuscitation
required an average of 20 minutes (range, 7-50 min). Clinical signs indicating a need for anesthesia appeared between 22° and 23°C during rewarming. The first sign was the appearance of spontaneous respiration followed by an increase in mean aortic pressure. As rectal temperature increased from 30°C to 35°C, the inspired anesthetic concentration was also increased from 0.93%±0.42 to 1.68%±0.24.

Anesthetic concentration in arterial blood

Mean blood anesthetic concentrations during cooling and rewarming are shown in Fig. 3. Blood halothane concentration gradually decreased during cooling and increased during rewarming. Blood halothane levels between 30°C cooling and 30°C rewarming were significantly lower than control values. Blood

Fig. 2. Inspired concentrations of halothane-diethyl ether azeotrope during cooling and rewarming. Data points represent mean±s.d. * significantly different from control.

Fig. 3. Blood anesthetic concentrations during cooling and rewarming. ○, Halothane; ●, Ether. Data points represent mean±s.d. * significantly different from control; † significantly different from values at identical rectal temperatures during cooling.
ether concentration also gradually decreased during cooling and increased during rewarming. Blood ether values between 25°C cooling to 30°C rewarming were significantly lower than the normothermic control values.

When halothane and ether concentrations were compared at identical temperatures during cooling and rewarming, their mean blood levels at 30°, 25° and 20°C during rewarming were consistently lower than at the same temperature during cooling.

**Pupil diameter**

Pupil diameter (Fig. 4) increased when surface cooling was initiated and remained stable until circulatory arrest was induced. Pupils were fully dilated throughout to the 60 minutes of total circulatory arrest. A decrease in mean pupil diameter was observed between 20° and 30°C rewarming. However, pupil diameter continued to increase between 30°C and 35°C during rewarming.

![Fig. 4. Pupil diameter during cooling and rewarming. Data points represent mean ± s.d. * significantly different from control.](image)

**DISCUSSION**

Since surface-induced hypothermia was first successfully used in 1965 (Dillard et al. 1967), numerous anesthetic regimens have been studied. The criteria used to judge the efficacy of the various methods include: 1) neurological protection, 2) intraoperative and postoperative hemodynamic stability, ease of resuscitation and pharmacological support during rewarming and in the postoperative period, 3) rate of cooling and rewarming, and 4) physical properties of the anesthetic agents such as explosiveness. According to these criteria, we systematically evaluated in dogs the following anesthetic regimens: ether-100% O₂, ether-98% O₂-2% CO₂ and ether-95% O₂-5% CO₂; 80% N₂O-20% O₂ (Mohri et al. 1972), Forane-100% O₂, Forane-98% O₂-2% and Forane-95% O₂-5% CO₂ (Sato et al. 1975), halothane-diethyl ether azeotrope-100% O₂, azeotrope-95% O₂-5% CO₂.
CO₂ and azeotrope-90% O₂-10% CO₂ (Sands et al. 1980; Haneda et al. 1982, 1984). From these studies we concluded that superior intraoperative and postoperative results were achieved with the halothane-diethyl ether azeotrope in 95% O₂-5% CO₂.

The azeotropic mixture of halothane and diethyl ether was originally described in 1958 (Boivin et al. 1958; Hall et al. 1960; Criscuolo and Wilson 1964). It has been used extensively in the clinical setting but primarily for operations performed under normothermia (Wyant et al. 1963; Wilson et al. 1964). The present study was designed to develop useful clinical and laboratory guidelines based on serially assayed blood azeotrope levels and clinically monitored vital signs taken during surface-induced deep hypothermia. Since the minimum alveolar concentration (MAC) of this agent has not been established for dogs or humans, we based depth of anesthesia on proven clinical standards for the conduct of hypothermia and cardiac surgery. Adequate anesthesia was maintained throughout the period of hypothermia despite a decrease in measured blood levels of halothane and ether.

It has been reported that anesthetic requirement (i.e., (MAC) is influenced by a change in body temperature (Eger et al. 1965; Regan and Eger 1967). Regan and Eger (1967) reported that in the canine model MAC is reduced 50% with halothane and 40% with ether under conditions of moderate hypothermia (27-28°C). This decrease in MAC was rectilinear in relationship to body temperature. It was suggested that cooling to 17-21°C would in itself provide adequate anesthesia necessary to induce a surgical plane. Because their studies did not use deep hypothermia, they demonstrated only the relationship between anesthetic concentration (MAC) and moderate hypothermia. Previous studies from this institution documented the relationship between anesthetic concentration and body temperature during surface-induced deep hypothermia using diethyl ether anesthesia (Wong et al. 1974; Su et al. 1979). In this regard, results from the present study are consistent with those reported by others. Blood concentration of halothane and ether decreased disproportionately as body temperature fell. Mean halothane concentration at 20°C cooling was 20% of control whereas ether measured 50% of control. The disproportionate change in blood azeotrope levels may be explained by the difference in solubility constants for the respective components since at normothermia the partition coefficient for blood/gas is 2.3 for halothane (Larson and Eger 1962) and 12.1 for ether (Eger et al. 1963). Therefore, relative to the drop in body temperature, less of the more lipid soluble fraction (halothane) of the azeotrope was required. This is consistent with observations made during moderate hypothermia (Eger et al. 1965; Regan and Eger 1967).

Anesthetic demand appears to decrease as body temperature falls. One possible reason for this is that cold itself acts as an anesthetic. In addition, lowering of body temperature changes the solubility of the inspired agent(s). The solubility of halothane increased by approximately 220% and ether 260%
when body temperature is reduced to 20°C (Giller and Noehren 1965; Han and Helrich 1966). This increase in solubility suggests that less anesthesia is needed to produce the same effect.

There was no requirement for the azeotrope during the period of circulatory arrest. Anesthesia was not administered until after cardiac resuscitation at about 22°C rewarming. However, blood concentration of halothane and ether did not reach zero. It is assumed that some fraction of halothane and ether remained in blood and/or body tissue during this period. Significantly less anesthesia was required in the rewarming phase than at comparable temperatures during cooling. The reason for this difference is unclear but may be related to the effect and duration of the period of total circulatory arrest.

Patterns of clinically monitored vital signs were also evaluated. The course of heart rate and mean arterial pressure were similar to previous studies in which these parameters were measured in both infants and dogs under surface-induced deep hypothermia. We also found that the change in pupil diameter was not a useful clinical indicator for this procedure. Pupil diameter during ether anesthesia correlates well with anesthetic depth but under halothane anesthesia pupil diameter does not correlate. At the pre-cooling control point (inspired concentration; 1.93% ± 0.19), there was no tearing, eyelash movement or corneal reflex nor was pupil reactivity to light present throughout the period of hypothermia.

Results from this study lead us to conclude that blood concentration of halothane and ether change as a function of body temperature and that anesthetic demand may be diminished following total circulatory arrest.

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