The Effects of Ether, Ethanol, Propanol and Butanol on Tolerance to Deep Hypothermia

Experimental and Clinical Observations*

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Ordinary adult laboratory animals and humans are unable to maintain adequate cardiovascular function under deep levels of hypothermia induced by surface cooling. During a long-term study of the unusual tolerance exhibited by hibernating animals to low body temperatures, it was accidentally discovered that butyl alcohol (butanol-1) increased the tolerance of the non-hibernator to deep hypothermia.

With the knowledge that ethyl alcohol (ethanol) may permit resuscitation of humans accidentally cooled to deep levels of hypothermia, it was felt advisable to study the protective action of the three monovalent alcohols, ethanol, propanol and butanol. During this study, deep ether anesthesia was shown to have a similar protective effect.

Materials and Methods

Mongrel hounds between 1.5 and 3 years of age, weighing between 6.5 and 16 kg., were used.

In these experiments, ether (inhalation) or a monovalent alcohol (intravenous) was administered to dogs during acute, lethal, ice-water immersion hypothermia. Control experiments were also conducted.

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The following anesthetic regimen was employed: induction and intubation were accomplished with 75 to 175 mg. thiopental sodium, following which the dog was put on a semiclosed system using four parts nitrous oxide to one part oxygen. The dog was then immersed to neck level in a specially constructed ice-water bath and allowed to cool (Fig. 1). To eliminate shivering, one to three intravenous doses of 25 mg. thiopental sodium were required during cooling. At 30°C, the dog was connected to a closed system using pure oxygen with an intermittent positive pressure ventilator operating at 20 respirations per minute. At 25°C, 5 per cent CO₂ was added to the anesthetic circuit and the dog was cooled in this manner until the end-point of the experiment (i.e. at the onset of ventricular fibrillation or after two minutes cardiac asystole).

Intravenous infusions were made through a cannulated femoral vein and arterial blood samples were drawn through a cannulated femoral artery. The esophageal temperature (adjacent to the heart) was continuously monitored with an Elektrolaboratoriet Copenhagen thermocouple. Arterial pressure was measured directly by an aneroid manometer, calibrated in millimeters of mercury, connected to a cannulated carotid artery. Readings of esophageal temperature, blood pressure, and pulse were taken at 15 minute intervals during cooling, as well as at the end-point of the experiment. The lead II electrocardiogram was visualized on a Sanborn recorder and...
photographic records were taken at 15-minute intervals during cooling.

Ether

Series A: Constant 10 per cent inhalation ether anesthesia was administered to eight dogs during cooling from 36° C to 16° C, using a Vernetrol ether vaporizer attached to the anesthetic circuit.

Series B: Six dogs were treated as in Series A, except that the concentration of ether was increased to about 15 per cent for 30 to 60 seconds if ventricular premature contractions appeared on the electrocardiogram. The procedure was repeated as necessary to suppress this cardiac irregularity.

Alcohols

Three series of six dogs each received a standard intravenous dose of ethanol, propanol-1, or butanol-1 respectively.

Preliminary experiments using intravenous ethanol to prevent ventricular fibrillation in dogs indicated that approximately 40 per cent of the mean lethal dose offered the greatest protection. Corresponding dosages of propanol-1 and butanol-1 were established on the basis of acute toxicity studies conducted on the three monovalent alcohols. The specifications and doses of the alcohols are shown in Table 1. The alcohol solutions were administered during cooling, 1/20 of the standard dose being given for

Figure 1: This photograph illustrates the cooling technique employed, as well as the anesthetic, recording, and alcohol infusion equipment. (A) Ice-water bath, (B) gas machine, (C) ventilator, (D) recorder, (E) thermocouple, (F) alcohol infusion.
TOLERANCE TO DEEP HYPOTHERMIA

Table 1—Alcohol Specifications and Doses

<table>
<thead>
<tr>
<th></th>
<th>Ethanol*</th>
<th>Propanol-1†</th>
<th>Butanol-1†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mol. wt.</td>
<td>46.07</td>
<td>60.09</td>
<td>74.12</td>
</tr>
<tr>
<td>MLD in dogs (g/kg)‡</td>
<td>4.90</td>
<td>2.42</td>
<td>1.26</td>
</tr>
<tr>
<td>Dose (g/kg)</td>
<td>2.0</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Dose/MLD in dogs</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Per cent v/v employed§</td>
<td>15</td>
<td>10</td>
<td>5</td>
</tr>
</tbody>
</table>

*Consolidated Alcohols Ltd.; †Fisher Scientific Co. Ltd. (certified reagent); ‡mean lethal dose (with artificial ventilation)12; §With 5 per cent glucose in H2O.

each C° fall in temperature from 36° C to 16 C°.

Arterial samples for alcohol determination were taken at 30 minute intervals from the onset of the alcohol infusion, as well as at the end-point of the experiment. Each sample consisted of approximately 5 ml oxalated blood and an additional quantity of blood was drawn and discarded each time to flush out the cannula. Including these amounts, the total volume of blood drawn was equal to the total volume of alcohol solution infused. Blood alcohol levels were determined by the Widmark desiccation method4 as modified by Smith.6

Control

Twenty-four dogs were treated as in the alcohol series, except that the intravenous infusion consisted of only 5 per cent glucose in distilled water, an equal quantity of blood being drawn and discarded.

RESULTS

In general, inhalation ether anesthesia and all three monovalent alcohols increased the tolerance of the dog to low body temperatures and decreased the incidence of ventricular fibrillation.

Ether

Table 2 summarizes the results of the ether experiments. In both Series A and Series B, the incidence of ventricular fibrillation was significantly decreased by ether anesthesia (P<0.02). However, the increase in tolerance to low body temperatures was much more pronounced in Series B (6.9° C) where concentrations of ether exceeding 10 per cent were employed.

A dramatic disappearance of the ventricular premature contractions, which characteristically precede ventricular fibrillation,1 was noted when the concentration of ether was temporarily raised to about 15 per cent. Following this, a mild, transient, delayed pressor response was observed. Otherwise no significant differences were noted between the experimentals and the controls with respect to rate of cooling or the blood pressure, pulse, and electrocardiogram, provided that ventricular fibrillation had not ensued.

Alcohols

Table 3 summarizes the results of the alcohol experiments. A definite, but less marked degree of protection was afforded by the monovalent alcohols. Ethanol, propanol-1, and butanol-1 increased the tolerance to low body temperatures by 4.2, 3.2, and 1.7 C° respectively, the effect diminishing as the molecular weights of the alcohols increase. Although the incidence of ventricular fibrillation was reduced in each case, the individual series are too small to

Table 2—The Effects of Ether Anesthesia on Tolerance to Deep Hypothermia in Dogs

<table>
<thead>
<tr>
<th>No. dogs cooled</th>
<th>Control</th>
<th>Ether (Series A)</th>
<th>Ether (Series B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ether dosage</td>
<td></td>
<td>10 per cent</td>
<td>Over 10 per cent</td>
</tr>
<tr>
<td>No. of dogs fibrillating</td>
<td>20</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Mean lethal temp. (°C)†</td>
<td>18.7±0.68</td>
<td>14.9±1.44</td>
<td>11.8±1.17</td>
</tr>
<tr>
<td>Increased tolerance (°C)</td>
<td>-</td>
<td>3.8</td>
<td>6.9</td>
</tr>
</tbody>
</table>

*Significantly different at the 2 per cent level; †±SE
Table 3—The Effects of Intravenous Ethanol, Propanol-1, and Butanol-1 on Tolerance to Deep Hypothermia in Dogs

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Ethanol</th>
<th>Propanol-1</th>
<th>Butanol-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. dogs cooled</td>
<td>24</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Alcohol dosage (g/kg)</td>
<td>—</td>
<td>2.0</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>No. of dogs fibrillating</td>
<td>20</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Mean lethal temp. (°C)*</td>
<td>18.7±0.86</td>
<td>14.5±1.38</td>
<td>15.5±2.22</td>
<td>17.0±2.10</td>
</tr>
<tr>
<td>Increased tolerance (°C)</td>
<td>—</td>
<td>4.2</td>
<td>3.2</td>
<td>1.7</td>
</tr>
</tbody>
</table>

*±SE

make the results statistically significant. However, by combining the three alcohol series together (18 dogs), it can be shown that the administration of a monovalent alcohol (40 per cent of the mean lethal dose) significantly decreases the incidence of ventricular fibrillation (P<0.02).

Figure 2 illustrates the rise in blood alcohol levels during cooling from 36° C to 16° C. The levels rose in approximate proportion to the alcohol dosages (2.0, 1.0, and 0.5 g/kg for ethanol, propanol-1, and butanol-1 respectively).

As with ether, a temporary increase in the dose of alcohol would often eliminate ventricular premature contractions, but the effect was less pronounced. Otherwise no significant differences were noted between the experimentals and the controls.

Clinical Application

The body temperature of adult humans cannot be lowered, with safety, below 28 to 30° C because of the risk of ventricular fibrillation. At this temperature, circulatory arrest can be tolerated for only eight to ten minutes. If a patient, protected with adequate blood alcohol levels, could be safely cooled below 28° C, the surgeon would have time to perform more complicated intracardiac procedures under direct vision without the hazards of cardiac bypass techniques.

In this study, intravenous ethanol was used in conjunction with surface cooling in two clinical cases requiring direct vision cardiac surgery. Ethanol was chosen because it proved to be the most effective alcohol in the foregoing experimental series and its toxicity has been well established.

Twenty-nine to 31° C is the usual body temperature range for surface cooling hypothermia. In these cases, modest but significantly lower temperatures were used (i.e. 26° C and 24.8° C) in order to ob-

![Figure 2: The relationship between the mean blood alcohol level and temperature during intravenous infusions regulated to the rate of cooling. Each point represents the mean value (±SE) of 6 dogs.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21441/)
serve heart action and note the tendency to ventricular fibrillation which is significant in adult humans at these temperatures.

In order to adequately control blood ethanol levels in hypothermia, preliminary experiments were carried out in dogs to determine the rate of accumulation and distribution of ethanol in body fluids, and the rate of elimination of ethanol from the body fluids in normothermia and hypothermia following a standard intravenous dose of ethanol. On the basis of this data, both patients were given a total dose of 2.4 g ethanol/kg body weight, administered intravenously throughout a 3 hour cooling period prior to surgery. This produced blood ethanol levels of approximately 400 mg/100 ml at the time of circulatory occlusion.

The first patient was an 18-year-old boy with a diagnosis of congenital pulmonary stenosis. Valvotomy and extensive infundibulectomy were performed under moderate hypothermia achieved by surface cooling to an esophageal temperature of 26° C. There was no evidence of myocardial irritability during cooling and two periods of circulatory occlusion (three and four minutes) were well tolerated. Strong, regular cardiac contractions, accompanied by a return of blood pressure to 100 mmHg without drugs, were observed immediately following reconstitution of the circulation.

The second case was a 12-year-old girl with a diagnosis of atrial septal defect (Fig. 3). Operative correction was performed under moderate hypothermia achieved by surface cooling to an esophageal temperature of 24.8° C. A blood pressure of 75 mmHg was maintained before and after the 11 minute period required for over-sewing the atrial septal defect. Again, the heart action immediately following cardio-tomy, characterized by strong, slow, reg-

**Figure 3:** Closure of an atrial septal defect under moderate surface hypothermia using intravenous ethanol. Changes in blood pressure, esophageal temperature, and blood ethanol level are noted.
ular contractions, was particularly impressive.

There is limited use for surface hypothermia in adult cardiac surgery. No conclusions can be made from observations during two trial clinical procedures, but with a background of experience in surface cooling hypothermia, it was our impression that they demonstrated better than usual cardiac function.

**Discussion**

In 1950, Bigelow et al. reported that extrasystolic action leading to ventricular fibrillation was the electrocardiographic abnormality most commonly seen in their air and coil-cooled dogs. Death by either ventricular fibrillation or cardiac asystole may occur in the hypothermic dog, the latter usually occurring in premature animals or in adult dogs where specific anesthetic techniques are employed. In both instances there is an associated increase in tolerance to deep hypothermia.

It has been reported that, among many other drugs, thiopental sodium and 5 percent dextrose both have an antifibrillatory effect in the hypothermic dog. However, as both the experimental and the controls in this study received approximately the same doses of these two drugs, it can be assumed that the decreased incidence of ventricular fibrillation was related to the administration of ether or a monovalent alcohol.

Japanese cardiovascular surgeons have taken advantage of the antifibrillatory effect of ether anesthesia to safely perform extensive intracardiac procedures under hypothermia, achieved by surface cooling. Using stage III plane III ether anesthesia, Seta et al. have reported 65 cases of open heart surgery performed under deep immersion hypothermia, the lowest temperatures ranging from 24°C to 17°C and the duration of circulatory occlusion ranging from 6 minutes 35 seconds to 47 minutes.

The antifibrillatory effect of ether, as yet, has not been adequately explained. It is a well known fact that ether anesthesia causes a significant increase in the circulating catecholamines. The circus movement theory of Lewis postulates repetitive re-excitation of cardiac tissue by a cardiac impulse re-entering an original area of excitation. Any one or a combination of a relatively long conduction pathway, a slow conduction velocity, or a short refractory period would favor fibrillation by allowing re-entry of the cardiac impulse into the original area of excitation after it is no longer refractory. Covino has shown that, below 25°C, the conduction velocity in cardiac muscle decreases without a proportional increase in the refractory period thus allowing circus movement to occur. He was able to prevent ventricular fibrillation by the administration of certain catecholamines which increased the conduction velocity during this critical period. In view of these observations, ether could possibly exert its antifibrillatory effect by increasing the level of circulating catecholamines which, in turn, increases the conduction velocity in cardiac muscle. However, contrary to a circus movement theory of cardiac fibrillation, the recent work of Angelakos and Torres shows that, in hypothermia, ventricular conduction velocity diminishes to an equal extent in both myocardial and specialized fibers, the extent of slowing (twofold) being less than the increase in refractoriness (threelfold).

The association of alcohol with low body temperatures is not new. There are numerous accounts of drunkards, exposed to the cold night air, or water, with survival from deep levels of hypothermia. In 1956, Senn reported the first use of intravenous alcohol as an antifibrillatory agent in hypothermia. Bertho has recently shown that intravenous alcohol, when administered before cooling, has a protective effect on the myocardium in deep hypothermia.

Many theories have been put forward to explain the effects of alcohol on the myocardium, particularly in relation to its antifibrillatory action in hypothermia. Alcohol itself is a well known myocardial depressant. In 1961, McGuire showed that butyl
alcohol could produce a reversible cardio-
plegia.

The urinary excretion of epinephrine and norepinephrine in the dog is markedly 
increased during acute, sublethal alcohol 
intoxication. Perhaps this release of cate-
cholamines increases the conduction velocity in cardiac muscle, as described with ether, thus preventing ventricular fibrillation.

Klingman suggests that the hyperglycemia observed in alcohol intoxicated dogs is related to an increased release of epi-

nephrine and norepinephrine. A similar hyperglycemic response to ether anesthesia has been noted by Brewster. Winbury points out that the maintenance of contractile activity during anoxia is dependent on the reserves of phosphate bond energy, on exogenous and endogenous substrates, and on the capacity for anaerobic glycolysis. Therefore, the ether or alcohol induced hyperglycemia may provide the phosphate bond energy necessary to account, at least in part, for the enhanced myocardial performance observed in deep hypothermia.

In conclusion, it is evident that ether affords a significant protection against ventricular fibrillation, and its use by cardio-
vascular surgeons in Japan has greatly ex-

panded the scope of surface cooling for intracardiac procedures. Both clinical and experimental evidence suggest that the monovalent alcohols may also be a useful adjunct to surface hypothermia.

SUMMARY

In the course of investigation into the natural hibernation of mammals and its possible application to clinical hypothermia, it was suspected that ether, ethanol, pro-

panol-1, and butanol-1 protected the hypo-

thermic heart from ventricular fibrillation. Fifty-six dogs were subjected to lethal, ice-

water immersion hypothermia and the ef-

fects of these various protective agents, ad-

ministered during cooling, were observed. Ether anesthesia significantly decreased the incidence of ventricular fibrillation and increased the tolerance to low body temperatures. Intravenous ethanol, propanol-1, and butanol-1 were also effective. These results suggest that ether and the monovalent alcohols may be useful adjuncts to direct vi-

sion cardiac surgery performed under mod-

erate to deep levels of surface hypothermia. Two clinical cases using intravenous ethanol are reported.

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Complete reference list will appear in reprints.

HYPERTROPHIC LOBAR EMPHYSEMA

The authors describe a case of bronchogenic (para-

tracheal) cyst with subsequent development of a hyperto-

phic emphysematous right lower lobe. Pre-

operative aspiration and subsequent excision of the right lower lobe were done as emergency procedures and were followed by a remission. At a second op-

eration, removal of a paratracheal cyst resulted in complete recovery.