Rewarming, Ultraprofound Hypothermia and Cardiopulmonary Bypass

Amr M. Elrifai, MD, Julian E. Bailes, MD, Shou-Ren Shih, MD, Joseph C. Maroon, MD, Marc L. Leavitt, PhD, Edward Teeple, MD, Daniel V. Loesch1, MD, Eric M. Cottington, PhD, Michael J. Taylor, PhD, Babak Bazmi, BS, Cecilia Devenyi, BS, Kimberly A. Ciongoli, BS

Departments of Neurosurgery and Anesthesiology, Allegheny-Singer Research Institute, Allegheny General Hospital and The Medical College of Pennsylvania, Pittsburgh, Pennsylvania,
1Department of Neurosurgery, Henry Ford Hospital, Detroit, Michigan

Keywords: rewarming rates, hypothermia, cardiopulmonary bypass, blood substitute

Abstract

Rewarming, a key event in resuscitation from accidental, experimental and clinical hypothermia, is sometimes followed by neurologic, cardiac, and respiratory sequelae and may lead to death. The rate of rewarming has been implicated but not quantified as etiologic in these sequelae. Under anesthesia fifteen dogs were cannulated and connected to an extracorporeal circuit for oxygenation, core cooling and rewarming. They were subjected to ultra-profound hypothermia with a core (esophageal) temperature as low as 1.3°C, cardiac arrest, blood substitution, and continuous low flow perfusion. After 2-3 hours of cardiac arrest, rewarming began. Mechanical activity of the heart was seen between 10° and 28°C and respiration resumed at 29°C. The rewarming rates of the 15 dogs were retrospectively studied. They were placed into three categories (G) based on the outcome. G-I (N = 2): no neurological complications, G-II (N=8): transient neurological problems, and G-III (N=5): death, mainly from cardiovascular and respiratory complications confirmed at death by autopsy. Heat gain by each animal was recorded as a function of time for all experiments. The time it took each dog to reach 35°C was determined and a mean was calculated (rewarming rate). Normal body temperature for a dog is 37.8°C. Statistical analysis (ANOVA) was performed ex post facto to determine the relationship between rewarming rate and outcome. Our data contradicts the notion that slow core rewarming from nadir to normal temperature offers better outcome. During rewarming metabolic needs change at different temperatures and our laboratory observations appear to provide an explanation for complications that may occur upon rewarming from profound hypothermia.

Introduction

The rewarming rate in severely hypothermic patients with body core temperatures below 10°C, to our knowledge, has never been quantified. Profound accidental hypothermia with or without water submersion was identified twenty years ago with a mortality rate of 55% to 80%, and sometimes as high as 100% (1-7). Slower external passive rewarming prevented vascular collapse from peripheral vasodilation, but did not improve survival rate (8). Knowledge that proper cardiovascular function was critical in recovery from severe hypothermia had no effect upon early patient experience (2). Subsequent publications described a lower mortality rate with some form of internal or core rewarming such as gastric or rectal lavage, hemo- or peritoneal dialysis, central venous warm crystalloid infusion, respiration with humidified air, or partial cardiopulmonary bypass (9-15). The effect of these rewarming methods on the different body functions has been studied and
reported repeatedly (16-19). Cardiopulmonary bypass has now been widely accepted as the primary choice of rewarming from accidental hypothermia in many institutions. Also, it is used in most surgical applications of hypothermia. Recent advances have improved survival rate but mortality is still reported as high as 30% (8). Most previous studies are lacking in information on the effect of the rewarming rate on survival and neurological outcome. In addition to the lack of information about rewarming rates, there are two generally described approaches referred to as "rapid" and "slow" rewarming. It is difficult, however, to debate the advantage of each without removing the ambiguity of the meaning of "slow" and "fast" rewarming. The purpose of this report is to examine and quantify "slow" vs. "fast" rewarming from ultra-profound hypothermia. Also, by defining and identifying the rates that are followed by good outcomes we may perhaps improve survival from accidental and clinical exposure to hypothermia.

**Materials and Methods**

This analysis describes results from an experimental protocol, the hypothesis and rational of which were described and published, to study the effect of ultra-profound hypothermia as low as 1°C, in a totally exsanguinated and blood substituted canine model (20). More details followed in a more recent publication in 1992 (21).

This animal study was conducted utilizing the standards of the Animal Welfare Act and the guidelines of the United States Public Health Services for the use and care of laboratory animals, and was approved by the Institutional Animal Care and Use Committee of Allegheny-Singer Research Institute. Under anesthesia, fifteen adult mongrel dogs were cannulated to establish extracorporeal cardiac bypass. The right external jugular vein and the carotid artery were cannulated and connected to the bypass circuit. The circuit consisted of a Sarns roller pump, a pediatric bubble oxygenator and a heat exchanger. Animals were cooled externally via a water bath and internally via the bypass circuit. The blood substitute was circulated during the profoundly cold phase <10°C (Table 1). After 2.5-3 hours of cardiac arrest, rewarming was started. Initially, core rewarming was implemented by warming the blood substitute. The animals were then placed in warm water bath that had a temperature gradient from their esophageal temperature of less than 5°C. When esophageal temperature reached 10°C, the animal's own blood was added to the circuit. The heart was allowed to start; otherwise electroversion was used. Core rewarming continued, using the extracorporeal pump, until temperature reached 30°C and the animals were able to maintain adequate cardiovascular functions.

They were then weaned from the pump, removed from the bath and surface warmed using heated pads set at 37°C. Upon reaching normal temperature the animals were decannulated and allowed to recover.

The rewarming rate for the 15 consecutive non-selected experiments was recorded versus time.

**Results**

Dogs were grouped in three categories (G) according to the outcome. G-I (n=2): no neurological complications, G-II (n=8): transient neurological problems: hind limb weakness, circling behavior, or decreased vision and G-III (n=5): death, mainly from respiratory and cardiovascular complications, confirmed at autopsy. Retrospective statistical analysis and data review were conducted to determine the effect of and/or the relationship between core and external rewarming and survival from experimentally induced ultra-profound hypothermic cardiac arrest. ANOVA was used to test for difference among groups in survival and on outcome and the Scheffe test was considered to examine pair wise differences between groups, p<0.05 was considered significant.

**Initial analysis:** The average heat gain/min or rewarming rate from nadir temperature (N) to 35°C for each group was calculated. An initial determination showed that animals that died were rewarmed faster (0.3°C/min) than animals that survived (0.1°C/min). This difference was even statistically significant p<.002 (Table 2b). There was also a significant difference in rewarming rates among G-I, G-II and G-III, p<.02 suggesting that slower rewarming is more beneficial (Table 2a). The Scheffe procedure showed a difference be-

<table>
<thead>
<tr>
<th>Na⁺</th>
<th>K⁺</th>
<th>Cl⁻</th>
<th>Ca²⁺</th>
<th>Mg²⁺</th>
<th>SO₄⁻</th>
<th>Glucose</th>
<th>HEPES</th>
<th>Dextran 40 (%)</th>
<th>pH (25°C)</th>
<th>Heparin # (IU/L)</th>
<th>Osmolality (mOsm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>140</td>
<td>5.0</td>
<td>102</td>
<td>1.5</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>25</td>
<td>6</td>
<td>7.80</td>
<td>2000</td>
<td>308</td>
</tr>
</tbody>
</table>

Table 1
The composition of the blood substitute (K15) in mM/L.

The blood substitute circulated during the 3 hour cardiac arrest period.

---

a Sarns, 3M, Ann Arbor, MI  
b William Harvey, Santa Ana, CA  
c Electromedics, Inc., Engelwood, CO  
d Cryomedical Sciences Inc., Rockville, MD
Table 2a. Comparison between the three groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>Time (min)</th>
<th>Mean heat gain (S.E.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>260.5</td>
<td>26.5 (.1)</td>
</tr>
<tr>
<td>Group II</td>
<td>224.1</td>
<td>22.8 (.2)</td>
</tr>
<tr>
<td>Group III</td>
<td>126.0</td>
<td>20.9 (.3)</td>
</tr>
</tbody>
</table>

Table 2b. Comparison between survivors and non-survivors.

<table>
<thead>
<tr>
<th>Group</th>
<th>Time (min)</th>
<th>Mean heat gain (S.E.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survivors</td>
<td>231.4</td>
<td>19.1 (.1)</td>
</tr>
<tr>
<td>Non-survivors</td>
<td>126.0</td>
<td>20.9 (.3)</td>
</tr>
</tbody>
</table>

Between G-I and G-III, and G-II and G-III.

Observation: Observations of rewarming behavior of the successfully resuscitated animals cooled to near the freezing point, contradict the notion that the average heat gain/min is conformably linear (Figure 1). After examining the statistical data and knowing that the metabolic requirement changes with temperature, it was felt that a single rewarming rate from the nadir temperature when tested previously in a smaller sample of 12 animals is an oversimplification (22). The previous analysis also led to the same conclusion.

Current analysis: Rewarming curves of 15 animals were analyzed using a cut off point at 28°C based on the temperature coefficient known as the Q10 (23). The results of this calculation were more informative than the initial determination expressed above. The average heat gain/min was then computed for the two segments: nadir to 28°C and 28+°C.

In the nadir-28°C segment, statistical difference was found among the three groups using ANOVA, p=0.05. The animals that had no neurological complications were initially rewarmed faster than those with transient neurological problems or those that died (Table 3a). However, pair-wise differences did not achieve statistical significance at the 0.05 level when Scheffe was applied. The G-I and G-II animals were grouped together (survivors) and compared with G-III (non-survivors). The results were also significantly different, p=0.01. These results are suggesting that faster rewarming is desirable before a temperature of 28°C is achieved.

In the 28°+ segments, the animals that had no neurological complications were rewarmed slower than those with complications or those that died. The differences in rewarming rates among the three groups were statistically significant using ANOVA p=0.002. The Scheffe procedure showed that differences existed between G-I and G-III and between G-II and G-III. No significant difference was found between G-I and G-II. Also, when testing survivors vs. non-survivors statistical significance was observed (p=.0004).

Discussion

Historically, there were sporadic anecdotal reports on the effects of profound hypothermia. It ranged from reporting an instance of hypothermia in 1757 (18,23), to the effect on troops in 1812 (18). It was not until 1961 when 23 accidental hypothermia cases of body temperature less than 28°C were reviewed. This report demonstrated that passive external rewarming, with a survival rate of 21%, had a better outcome than active external rewarming, with 0% survival rate, suggesting that slower rewarming is advantageous. The majority of accidental hypothermia victims are found with a core temperature of near 30°C, and in summary the consensus derived from treating these patients is that slower rewarming is more advantageous. Furthermore, many reports on
rewarming after exposure to hypothermia, whether accidental or clinical, do not detail the rewarming process by failing to describe the rewarming rate. This shortcoming in the literature left rewarming rates unavailable as a review source.

The ambiguities of the non-quantitative adjectives, “fast” and “slow,” which are perceived differently, still lead to controversy. Fast rewarming meant between 40 and 68 minutes to Patterson and Ray in 1962 (25), while slow rewarming meant over 12 hours to Esmilie-Smith in 1958 (3). Bloch suggested the use of 0.5°C/hr (0.008°C/min) as a guideline for rewarming when the duration of hypothermia is brief (26). He reported a rate of 0.02°C/min when patients were hypothermic for 30 hours at 30°C and 0.003°C/min when patients were hypothermic for 192 hours (8 days) at 30°C.

Hall and Syverud in 1990 reported two cases of severe hypothermia and described a rapid rewarming technique of closed thoracic cavity lavage. Patients were rewarmed at a rate of 0.3°C/min and 0.35°C/min and both patients died (27). Recently, mortality decreased after the introduction of core rewarming as a viable method of treating accidental hypothermia cases (9-16,18).

The collective wisdom for clinical use of the hypothermia technique was to warm the patients using a rate of 0.5°C/min or less which is perceived by the majority to be slow. This acceptance came about after Egerton et al (28) reported that the rewarming of patients from 10°C to 30°C in 13 minutes (0.65°C/min) led to grand mal seizure. However, there is no mention on how rewarming proceeded over 30°C (28).

In 1983, Baumgartner reported rewarming from 20°C to 35°C in 67 minutes (on average 0.2°C/min.) in 15 cases without mortality (29). Five years later Spetzler recommended rewarming at a rate of 0.2°C to 0.5°C/min (30). This rate has generally been well accepted in current use. The need to quantify the rewarming rate for clinical hypothermia has not been compelling, because all cases to date required cardiopulmonary bypass which can affect core rewarming fairly quickly. When the pump is disconnected only surface or spontaneous rewarming which is relatively slow continues. However, there
are reported instances when complications develop and although the reason could not be identified, rewarming is implicated.

Our study shows that rewarming rates vary according to temperature. Since we cooled all animals to near the freezing point, we were able to examine the rewarming pattern of these animals recovering from very low temperatures. It showed that G-III animals that were rewarmed nearly uniformly within the acceptable rate of 0.2-0.3°C/min did not survive.

All animals that survived were initially rewarmed at a rate of 0.4°C/min to 0.5°C/min (fast) until temperature reached 28°C, then the rate was substantially slowed to 0.03°C/min to 0.04°C/min (slow). There was a substantial difference between the rewarming rates above and below 28°C (p=.000008). It has been very fallacious to think of rewarming as a single rate applicable at all temperatures. The data showed strong trends even in the case of morbidity when it did not achieve statistically significant difference. The statistics become more rigorous in distinguishing survivors from non-survivors. This weakness of statistics could be due to the small sample size.

This study focused on attempting to provide a better rewarming equation. It showed that there is a need to further study the rewarming process and to standardize the reporting of rewarming rates. This animal study demonstrates that there are different metabolic needs at segmented rewarming rates and at different temperatures. Our statistical analysis indicates that there is a significant difference in rewarming rates between survivors with good and intermediate outcome and non survivors.

References
25. Paterson RH, Ray BS. Profound hypothermia for intracranial surgery: Laboratory and clinical experiences with


Note

Parts of this information were presented at the Cardiovascular Science and Technology Conference, Louisville, KY, 1990.

This study was supported by a grant from Cryomedical Sciences, Inc., Rockville, MD