Beneficial Effect of Mild Hypothermia and Detrimental Effect of Deep Hypothermia After Cardiac Arrest in Dogs

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Background and Purpose: Mild cerebral hypothermia (34°C) induced immediately after cardiac arrest improves outcome. Deep postarrest hypothermia (15°C) has not been studied.

Methods: We used our dog model of normothermic ventricular fibrillation (no blood flow) of 12.5 minutes, reperfusion by brief cardiopulmonary bypass, controlled ventilation to 20 hours, and intensive care to 72 hours. Head surface cooling and bypass cooling were performed from start of reperfusion to 1 hour. Five groups of six dogs each were compared: group I, normothermic controls; group II, deep hypothermia (15°C); group III, moderate hypothermia (30°C); group IV, mild hypothermia (34°C); and group V, mild hypothermia with head surface cooling begun during no flow.

Results: In control group I, five dogs remained comatose (overall performance category [OPC] 4) and one severely disabled (OPC 3). In group II, four dogs achieved OPC 4 and two dogs OPC 3 (NS versus group I). Compared with group I, OPCs were better in group III (p<0.05), group IV (p<0.05), and group V (p<0.05). Neurological deficit scores were also better in groups III, IV, and V than in groups I or II (p<0.05). Total brain histological damage scores were better in group III (p=0.02), group IV (p=0.06), and group V (p<0.05) than in group I. In group II, OPC and neurological deficit scores were the same and histological damage scores numerically worse than in group I and all were worse than in groups III, IV, and V (p<0.05). Cardiovascular complications and myocardial morphological damage in groups II and III were worse than in groups I, IV, and V (p<0.05).

Conclusions: Mild or moderate cerebral hypothermia induced immediately after cardiac arrest improves cerebral outcome, more likely when initiated during arrest, whereas deep postarrest hypothermia can worsen cerebral and cardiac outcome. (Stroke 1992;23:1454-1462)

KEY WORDS • anoxia • cerebral ischemia • hypothermia • dogs

We hypothesize that cerebral outcome after cardiac arrest (complete temporary global brain ischemia) can be improved by optimized therapeutic hypothermia immediately after reperfusion, which mitigates postarrest perfusion failure, reoxygenation injury cascades, self-intoxication from viscera, and derangements of blood elements.1-2

When hypothermia is induced before cardiac arrest (protection) and maintained during cardiac arrest (preservation), deep (10-20°C) cerebral hypothermia is more protective against long arrest than is moderate (28-32°C) hypothermia.4 In the late 1980s, dog cardiac arrest outcome studies by us5 and rat global brain ischemia histological studies by others5-6 independently discovered that even mild (34°C) protective-preservation hypothermia is beneficial. When moderate hypothermia was induced after cardiac arrest (resuscitation), uncontrolled studies in the 1950s by others and controlled studies in the 1980s by us6-10 gave inconclusive cerebral results; we found myocardial damage to be worse in the cooled dogs.10 In 1988 we conducted the first documentations in our dog cardiac arrest outcome models that mild (34°C) resuscitative hypothermia in...

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Materials and Methods

This project was approved by the Animal Use Committee of the University of Pittsburgh (Pa.). We used 36 healthy, custom-bred male coonhounds, mean age 10...
preCA CA2 CA12 10' 20' 30' 1h 1h30' 2h 3h 6h 12h 20h
TIME

GROUP I 37.5°C
GROUP V 34°C
GROUP III 30°C
GROUP IV 34°C
GROUP II 18°C

FIGURE 1. Graphs show actual core (pulmonary artery) temperatures ($T_{pa}$) and brain (tympanic membrane) temperatures ($T_{ty}$, in text) before and after ventricular fibrillation cardiac arrest (VFCA) of 12.5 minutes (no blood flow) in dogs. Methods include cooling with cardiopulmonary bypass (CPB) plus head immersed in ice water ($T_{ty}$ probe in ear sealed with wax) and brief, total CPB for reperfusion, followed by low-flow bypass for $T_{pa}$ control. $n=6$ per group; five groups (Table 1).

(range, 8–12) months and mean weight 22 (range, 18–25) kg. They showed no evidence of neurological dysfunction before the experiment.

The model and the methods used for mild, moderate, and deep hypothermia were reported previously. After ventricular fibrillation (no flow) of 12.5 minutes, reperfusion (resuscitation time = 0) with brief cardiopulmonary bypass to defibrillation was followed by control of ventilation (IPPV) and normotension to 20 hours and intensive care to 72 hours postarrest. Our model met all 10 criteria we have posed to evaluate cerebral resuscitation in animal outcome models of cardiac arrest (see "Discussion" of Reference 11).

After three pilot experiments (reported in "Results"), 33 dogs were randomly assigned to achieve five groups of six dogs each following protocol (Figure 1). For the three exclusions, see "Results." Core (pulmonary artery) temperature ($T_{pa}$) was controlled. "Brain" temperature, estimated noninvasively as tympanic membrane temperature ($T_{ty}$), was monitored from one ear sealed with wax. Outcome studies obviate monitoring brain tissue temperature directly. $T_{ty}$ paralleled $T_{pa}$ and equaled directly monitored deep brain temperature; $T_{ty}$ and epidural temperature were 1–2°C lower than $T_{pa}$ during head surface cooling.11,18

Control group I was to be maintained normothermic throughout ($T_{pa}$ 37.5°C) and groups II–V hypothermic to resuscitation time 1 hour. Group II was to be treated with deep hypothermia of $T_{ty}$ 15°C ($T_{pa}$ < 20°C could not be monitored by pulmonary artery catheter); group III with moderate hypothermia ($T_{pa}$ 30°C); group IV with mild hypothermia ($T_{pa}$ 34°C); and group V with mild hypothermia ($T_{pa}$ 34°C) plus head surface cooling already started during no flow. All experiments were performed by the same team in spring 1990.

After sedation with ketamine 10 mg/kg i.m., anesthesia was induced with N₂O/O₂–halothane by mask and maintained via endotracheal tube with N₂O:O₂ 50:50% plus halothane 0.25–1.0% and IPPV. Sterile cutdowns were performed in the groins and the right side of the neck. Continuously monitored variables were electrocardiogram, heart rate, mean arterial blood pressure (MABP), central venous pressure (CVP), electroencephalogram (EEG), end-tidal Pco₂, $T_{pa}$, $T_{ty}$, and...
esophageal and rectal temperatures. Intermittently monitored variables included arterial $\text{PO}_2$, $\text{PCO}_2$, pH, base excess, hematocrit, glucose, and serum electrolytes. Variables controlled before and after arrest were MABP at $110 \pm 15$ mm Hg (with halothane before arrest, and with intravenous norepinephrine or trimethaphan after arrest); CVP at $5 - 15$ mm Hg; $T_{\text{pa}}$ at $37.5 \pm 0.1^\circ\text{C}$ before and $37.5 \pm 0.5^\circ\text{C}$ after arrest; $\text{PaO}_2$ at $>100$ mm Hg; $\text{PaCO}_2$ at $30 - 35$ mm Hg; base excess at $\pm 7$ meq/l; and blood glucose at $90 - 180$ mg/dl prearrest (by not giving glucose). Blood gases were controlled according to determinations at $37^\circ\text{C}$.

Prearrest control (baseline) measurements were obtained under IPPV with $\text{N}_2\text{O}:\text{O}_2$ 50:50% plus halothane 0.25-1.0% (adjusted to control MABP at 110 mm Hg) and immobilization with intravenous pancuronium. For the insult, $\text{N}_2\text{O}$ and halothane were discontinued and IPPV was continued with 100% $\text{O}_2$ for 1 minute, followed by air (21% $\text{O}_2$) for 4 minutes. In previous experiments without paralysis, this procedure did not elicit struggling. Normothermic ventricular fibrillation was induced by external transthoracic electric shock, and IPPV was stopped. The bypass circuit was primed with dextran 40 and Ringer's solution (50:50), and perfused with blood at $37.5^\circ\text{C}$ in group I and initially at $4^\circ\text{C}$ in group II, $10^\circ\text{C}$ in group III, and $20^\circ\text{C}$ in groups IV and V; the fluid temperature was subsequently adjusted to control $T_{\text{pa}}$. In addition, the head surface was cooled by submersion in an ice water-filled plastic box, starting at resuscitation time 0 in groups II, III, and IV, and at ventricular fibrillation 3 minutes in group V. From resuscitation time 1 hour to 3 hours rewarming was achieved with the heat exchanger $5^\circ\text{C}$ above $T_{\text{pa}}$. Bypass blood was reinfused at 3 hours. In group II, total bypass flow was $\geq 100$ ml/kg per minute to $T_{\text{pa}}$ 15°C as ventricular fibrillation continued, then 50 ml/kg per minute (because metabolism was <50%). At 1 hour postarrest, this bypass flow was continued during rewarming to $T_{\text{pa}}$ 32°C, when spontaneous heartbeat was restored with countershocks. Then, with partial bypass flow, normothermia was reached at <3 hours.

In all five groups, the same intensive care with IPPV to 20 hours was followed by reversal of pancuronium with neostigmine and atropine, weaning from IPPV by 24 hours, and continued intensive care to 72 hours. After 64 hours postarrest, system depressants were given.

Outcome was evaluated every 8 hours, from 24 hours to 72 hours postarrest, as overall performance categories (OPC 1 [normal]-5 [death]) (Figure 2); neurological deficit scores (ND 0% [normal]-100% [brain death]) (Figure 3); and brain histopathological damage (HD) scores (Figure 4). No central nervous system depressants were given after 64 hours postarrest. The OPCs and ND scores were the consensus of at least three observers. Blinded evaluation was not feasible.

At 72 hours postarrest, for morphological examination, endotracheal anesthesia was induced, the chest was opened, and euthanasia by perfusion-fixation of the brain was carried out with buffered paraformaldehyde 3%. The brains were examined macroscopically, cut into 3-mm-thick coronal slices, and prepared for histological examination. Brain HD scores were determined by one pathologist (A.R.) who did not know the treatment group, according to the severity of ischemic neuronal changes, infarctions, or edema, in 18 bilateral anatomic areas (Figure 4). Total HD scores of $\geq 100$ were usually associated with severe functional deficit. The heart was evaluated for function and at necropsy.
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examined grossly with all chambers opened. Macroscopically necrotic (pale) or hemorrhagic areas were quantified by planimetry as percentage of total subepicardial plus subendocardial surface areas. Necroses were confirmed by light microscopy.

According to protocol for this brain outcome-focused study, dogs that died before 72 hours from extracerebral complications were to be excluded, but primary brain deaths were to be included. Exclusion criteria included failure to achieve normotensive reperfusion and specific limits for prearrest hyperglycemia and prearrest or postarrest hypotension, hypertension, acidemia, hypoxemia, hypercapnia, hypothermia, hyperthermia, and anuria.

Data analysis includes pairwise comparisons of each group to each other for ND scores and HD scores, using analysis of variance and Scheffe's post hoc comparison
procedure. All statistical assumptions were met. For both OPCs and myocardial damage scores due to the violation of the statistical assumption of normality, the Kruskal-Wallis test was used to investigate between-group comparisons. Arrhythmia scores, MABP, and cardiac output between groups and time differences were analyzed using a repeated measures analysis of variance and Scheffe’s post hoc comparison procedure. All statistical assumptions were met. For blood pressure, ROSC, restoration of spontaneous circulation; EEG, electroencephalogram; RT, resuscitation time.

*p<0.05 compared with control group I.

†ROSC only possible after warming from tympanic membrane temperature 15°C (RT 0 minutes to 1 hour) to pulmonary artery temperature 32°C at RT 1–2 hours.

### Results

One pilot experiment was performed with the same protocol, including bypass of 1 hour, but without arrest or hypothermia (sham); this dog achieved OPC 1, ND 0%, and HD 0 (normality). Two pilot experiments were performed with cardiac arrest of 12.5 minutes but with moderate (30°C) or mild (34°C) hypothermia induced before arrest; both precooled dogs achieved complete functional recovery (OPC 1 and ND 0%) but had mild histological brain damage at 72 hours (the dog cooled to 30°C had HD 22, and the dog cooled to 34°C had HD 38). Of the 33 dogs randomized, three had to be excluded from analysis of cerebral outcome: two in group II developed intractable ventricular tachycardia and died in cardiogenic shock at 38 and 34 hours postarrest; one in group V did not achieve the required reperfusion pressure. All 30 dogs that followed protocol survived to 72 hours postarrest.

Prearrest preparation and anesthesia times and pre-arrest measurements of MABP, Hct, blood glucose, pHa, PaO₂, PaCO₂, base excess, and Tp showed no significant differences between the five groups (Table 1). Early postarrest Hct, blood glucose, and pHa did not differ between groups, except for pHa in group II, which remained lower. Spontaneous heartbeat was restored in all dogs at 2–4 minutes of bypass with one to three countershocks, except in group II in which deep hypothermia (as expected) sustained weak ventricular fibrillation, requiring total bypass until defibrillation during rewarming to Tpa 32°C at 1.5–2 hours of reperfusion; countershock and NaHCO₃ requirements were the same in all five groups (Table 1). The postarrest hypertensive bout was similar in the five groups, and MABP thereafter was controlled according to protocol. Epinephrine requirements were the same in groups I, III, IV, and V (0.2–0.5 mg). Group II required more epinephrine (0.3–2.0 mg), and the subsequent flow-controlled bypass was associated with mild hypotension (MABP mean, 88 mm Hg) at 60 minutes. In all groups, Hct decreased to 24–38% during bypass of 3 hours and after reinfusion of blood at 3–4 hours returned to low-normal or normal values (30–50%). After restoration of spontaneous circulation, norepinephrine (total dose, 0–1 mg per dog) was needed only up to 15 minutes of reperfusion, with no difference between groups. Cardiac output was 3.5±0.8 l/min before cardiac arrest. After weaning from bypass at 3 hours, cardiac output showed no significant group differences; overall values were 3.2±0.9 l/min at 4 hours and 3.6±1.2 l/min at 6 hours postarrest. Arrhythmias killed two dogs in group II, but arrhythmia scores of the survivors were not signifi-

### Table 1. Prearrest and Early Postarrest Variables in Dogs Subjected to Hypothermia

<table>
<thead>
<tr>
<th>Group</th>
<th>Prearrest</th>
<th>Highest early postarrest (bout)</th>
<th>60 Minutes postarrest</th>
<th>Hematocrit (%)</th>
<th>Blood glucose (mg/dl)</th>
<th>pHa</th>
<th>5 Minutes postarrest</th>
<th>15 Minutes postarrest</th>
<th>60 Minutes postarrest</th>
<th>Countershocks (No.)</th>
<th>Time to ROSC (minutes)</th>
<th>EEG return time, any (RT, minutes)</th>
<th>EEG return time, continuous (RT, minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>108±7</td>
<td>152±6</td>
<td>110±7</td>
<td>40±4</td>
<td>146±12</td>
<td>7.35±0.05</td>
<td>7.34±0.05</td>
<td>7.42±0.03</td>
<td>205±37</td>
<td>1</td>
<td>2.4±0.3</td>
<td>10±7</td>
<td>87±34*</td>
</tr>
<tr>
<td>II</td>
<td>114±6</td>
<td>152±6</td>
<td>114±5</td>
<td>43±3</td>
<td>134±5</td>
<td>7.35±0.05</td>
<td>7.35±0.02</td>
<td>7.34±0.05</td>
<td>230±16</td>
<td>1</td>
<td>2.5±0.5</td>
<td>8±5</td>
<td>43±25</td>
</tr>
<tr>
<td>III</td>
<td>112±7</td>
<td>152±8</td>
<td>122±11</td>
<td>40±4</td>
<td>141±6</td>
<td>7.35±0.02</td>
<td>7.32±0.03</td>
<td>7.32±0.05</td>
<td>217±33</td>
<td>1−3</td>
<td>2.6±0.5</td>
<td>5±3</td>
<td>23±22</td>
</tr>
<tr>
<td>IV</td>
<td>109±7</td>
<td>160±12</td>
<td>121±7</td>
<td>32±3</td>
<td>139±13</td>
<td>7.39±0.03</td>
<td>7.39±0.03</td>
<td>7.39±0.04</td>
<td>182±30</td>
<td>1−2</td>
<td>2.3±0.3</td>
<td>4±2</td>
<td>4±2</td>
</tr>
<tr>
<td>V</td>
<td>162±14</td>
<td>238±55</td>
<td>242±51</td>
<td>32±4</td>
<td>156±12</td>
<td>7.39±0.04</td>
<td>7.39±0.03</td>
<td>7.39±0.04</td>
<td>233±35</td>
<td>2−1</td>
<td>2.1±15</td>
<td>4±2</td>
<td>4±2</td>
</tr>
</tbody>
</table>

Values are mean±SD. Group I, normothermic controls; Group II, deep hypothermia (15°C); Group III, moderate hypothermia (30°C); Group IV, mild hypothermia (34°C); Group V, mild hypothermia with head surface cooling begun during no flow; MABP, mean arterial blood pressure; ROSC, restoration of spontaneous circulation; EEG, electroencephalogram; RT, resuscitation time.

*p<0.05 compared with control group I.
cantly different between groups. Intravenous lidocaine was given for ventricular tachycardia (total, 20–80 mg per dog in intermittent boluses) to one dog in group I, four dogs in group II, and one or two dogs in each of the other groups.

Control of $T_p$ followed protocol (Figure 1). At the start of ventricular fibrillation, $T_m$ and $T_p$ in all groups were 37.5°C (range, 37.4–37.6°C). During normothermic ventricular fibrillation, $T_p$ spontaneously increased slightly and $T_m$ decreased slightly (by 0.1–0.3°C), except in group V, in which head cooling of 9.5 minutes reduced mean $T_p$ by 1.7°C during ventricular fibrillation ($p<0.05$). After arrest, $T_p$ in group I was successfully maintained at 37.5°C throughout. In group II, $T_m$ reached 15°C at resuscitation time 18±3 minutes; the lowest $T_m$ values were 14.5±0.4°C (range, 13.7–15°C). In group III, $T_m$ reached 30°C at resuscitation time 3 minutes and was maintained between 29.0 and 31.3°C until 1 hour; the lowest $T_m$ reached was 26.9±2.4°C (range, 24.0–30.1°C). In groups IV and V, $T_m$ reached 34°C at resuscitation time 2 minutes and was maintained between 33.1 and 34.1°C until 1 hour. In group IV, the lowest $T_m$ reached was 33.0±0.8°C (range, 27.4–32.3°C). In group V, the lowest $T_m$ reached was 30.0±1.7°C (range, 26.6–31.9°C). Rewarming, which started at 1 hour, reached by 3 hours a $T_p$ of 34.4–37.2°C in group II and a $T_p$ of 36.0–38.6°C in groups III, IV, and V. Changes in esophageal and rectal temperatures followed changes in $T_p$.

EEG activity (Table 1) in groups I, III, IV, and V began to return between 5 minutes and 45 minutes of reperfusion; continuous EEG activity started between 90 and 120 minutes, without significant group differences. A significantly delayed return of EEG recovery was only in deep hypothermic group II. During paralysis and IPPV to 20 hours, none of the dogs showed EEG seizure activity. After weaning from IPPV, none of the dogs had sustained seizures, but all 10 dogs with OPC 4 showed running movements, opisthotonus, or spontaneous hyperventilation (seven received diazepam). Urine flow returned at 1–2 hours postarrest, and by 6 hours all dogs had normal or high urine flow. At 20–24 hours, all dogs could easily be weaned from IPPV, except one dog in group I (IPPV to 34 hours) and two dogs in group II (IPPV to 48 hours).

Outcome

OPCs at resuscitation time 24–72 hours were significantly better in groups III, IV, and V than in groups I and II ($p<0.05$) (Figure 2). All dogs achieved their best OPCs at 72 hours (except one dog in group III that secondarily deteriorated between 40 hours and 72 hours). In control group I and deep hypothermia group II, all dogs had poor outcome (OPC 3 or 4). Good outcome (OPC 1 or 2) was achieved in group III in three of six ($p<0.05$ versus group I); in group IV in two of six ($p<0.05$ versus group I); and in group V in four of six ($p<0.05$ versus group I) dogs. Deep hypothermia group II had worse OPCs than mild-to-moderate hypothermia groups III, IV, or V ($p<0.01$). Group V had numerically better OPCs than groups III and IV (NS). There was no difference in OPCs between groups III and IV. Dichotomous analyses (OPC 1 or 2 versus 3 or 4) showed a significant difference of groups III, IV, or V versus groups I or II ($p<0.05$).

ND scores improved (decreased) progressively between 24 and 72 hours postarrest. Best ND scores (at 24–72 hours) (Figure 3) when compared with group I were significantly lower in groups III, IV, or V ($p<0.05$). Deep hypothermia group II had worse ND scores than groups III, IV, or V ($p<0.05$). Final ND scores at 72 hours were 49±9% (range, 32–64%) in control group I; 46±18% (range, 24–82%) in group II (NS); 25±5% (range, 17–34%) in group III ($p<0.05$); 32±8% (range, 20–44%) in group IV ($p<0.05$); and 25±5% (range, 11–38%) in group V ($p<0.01$). ND scores of group I were not significantly different from those of group II. Group V had numerically better final ND scores compared with group IV (NS).

Total brain HD scores at resuscitation time 72 hours showed group differences numerically similar to OPCs and ND scores (Figure 4). Overall, total HD scores in all 33 dogs (including sham and pilot experiments) correlated with final ND scores ($r=0.88$; $p<0.001$). The four dogs with final OPC 1 (one of group V, one sham dog, and two precooled dogs) (Figure 2) had HD 28±26 (range, 0–58). The seven dogs with final OPC 2 had HD 58±14 (range, 52–88). The 13 dogs with final OPC 3 had HD 84±11 (range, 68–88). The nine dogs with OPC 4 had HD 122±21 (range, 92–162). In group I, total HD scores were 117±28 (range, 92–146), indicating severe damage. In deep hypothermia group II, total HD scores were 158±104 (range, 94–384), suggesting (numerically) worse damage than in group I (NS). In group III, total HD scores were 81±4 (range, 76–88) ($p<0.05$ versus group I); in group IV were 82±16 (range, 60–108) ($p=0.06$ versus group I); and in group V were 65±11 (range, 52–80) ($p<0.05$ versus group I). The histological lesions in the brain were predominantly ischemic neuronal changes in the neocortex, striatum, hippocampus, and cerebellum. No brain examined of any dog with 12.5 minutes’ arrest was entirely free of damage; only the sham experiment resulted in HD score 0. In the arrested dogs, cerebral infarcts were seen in only three dogs of group I and two dogs of group II. Regional HD scores for the hippocampus and most other regional scores were numerically but not statistically lower in groups III, IV, and V compared with groups I and II. There were no significant differences in regional HD scores between groups I and II, nor between groups IV and V. There was no evidence of selective protection of the hippocampus or caudoputamen (Figure 4).

Myocardial macroscopic morphological damage (primarily pale necroses on the surface of predominantly the right ventricular wall) was observed in 13 of the 30 dogs; the other 17 were free of macroscopic lesions. These lesions were minimal (<1% area) in one of six dogs of group I and four of six of group V, and absent in all of group IV. These lesions, however, were striking in groups II and III with lower $T_m$. In group II, four dogs had macroscopic necroses over 6%, 0.1%, 0.3%, and 2.2% of the surface area (2.0±2.2%); and in group III, three dogs had macroscopic necroses over 6%, 1.4%, and 2% of the surface area (3.1±2.1%) ($p<0.05$ group II or III versus group I, IV, or V). The macroscopically pale regions histologically showed contraction bands and coagulation necroses. There was a variable (minimal to marked) interstitial accumulation of macrophages and fibroblasts between damaged myofibers.
Hemorrhages of the myocardium were minimal. In macroscopic normal areas of right and left ventricles and interventricular septa there were no histological abnormalities.

Discussion

The results of this study confirm those of our preceding studies.10-12 Mild hypothermia (34°C) when induced immediately postarrest with reperfusion (group IV) improved cerebral outcome without harming cardiovascular outcome. Moderate hypothermia (30°C) (group III) immediately postarrest seemed beneficial for cerebral but hazardous for cardiovascular recovery. Head surface cooling started during arrest (preservation) (group V) seemed to provide additional benefit, despite T<sub>p</sub> having been lowered by only 1–2°C before reperfusion. In addition, this study explored for the first time deep hypothermia (15°C) induced immediately after arrest (group II) and found it to be possibly deleterious for cerebral and cardiovascular recovery.

Our model achieved reproducible outcome, as in the past.5,11,12 A key requirement was met, i.e., that all dogs of group I achieved OPC 3 or 4, none OPC 1 or 5. T<sub>p</sub> and T<sub>v</sub> at onset of arrest were accurately controlled at 37.5±0.1°C. Mild hypothermia achieved OPC 1 in only one dog of group V, whereas in our first study with the same insult and similar treatment mild hypothermia achieved OPC 1 at 72 hours in 11 of 20 dogs, perhaps because bypass with mild hemodilution was 3 hours in this study versus 1 hour in the previous study. Moderate (group III) and mild (group IV) hypothermia, with different T<sub>p</sub> levels, resulted statistically in the same outcome probably because both groups achieved similar moderately hypothermic T<sub>v</sub> values (Figure 1).

Hossmann23 showed that EEG recovery rate after 1 hour of global brain ischemia in cats correlates with mild hypothermia at the start of arrest. In this and previous studies we found no consistent correlation between early return of EEG activity and good neurological outcome. Some EEG activity returned postarrest (numerically) earlier after intra-arrest mild hypothermia (group V), and later after moderate (group III) or deep (group II) hypothermia (Table 1). Continuous EEG activity returned significantly later in deep hypothermia group II, as expected, because T<sub>v</sub> of <30°C suppresses EEG activity.

HD scores were reduced by mild or moderate resuscitative hypothermia not only in the hippocampus and caudoputamen (as is usually seen in rat models) but also in the neocortex and basal ganglia. In groups III, IV, and V, lesions consisted almost exclusively of ischemic neuronal changes, without microinfarcts or edema. The few microinfarcts seen were in groups I and II, suggesting that mild to moderate hypothermia did not worsen cerebral microcirculatory failure postarrest.

Myocardial morphological necroses were similar to those seen in our previous studies with similar models after cardiac arrest and normothermia20,21 worsened by moderate hypothermia.10 Their mechanism is not clear. These lesions were not mitigated by any level of hypothermia—indeed, their extent seemed worse after moderate (group III) or deep (group II) hypothermia. There was no evidence of coronary obstruction. Similar lesions have been reported after transthoracic defibrillating shocks in anesthetized dogs without cardiac arrest or hypothermia.24 Requirements for countershocks, epinephrine, and norepinephrine did not differ between groups. The absence of lesions in some hearts in all groups suggests that hypothermia is not an independent factor.

Deep resuscitative hypothermia (group II) (15°C) induced after normothermic cardiac arrest worsened outcome for reasons still to be clarified. It did not improve cerebral functional outcome, worsened brain HD scores (numerically), worsened myocardial damage scores (significantly), and resulted in two of eight dogs in lethal cardiogenic shock and arrhythmias. This is in stark contrast to the great protection achieved for heart and brain with deep hypothermia induced before circulatory arrest.3,25,26 The cardiovascular side effects of moderate to deep hypothermia are well known.4,27,28 Explanations for the discrepancy might include the following: 1) Arrest under deep hypothermia was usually with heparinization and low Hct, both of which might improve outcome. 2) Deep hypothermia increases plasma viscosity and Hct,29 causes leukopenia,30 reduces endogenous catecholamine release,31 and can cause disseminated intravascular coagulation, particularly during rewarming.32 We saw increased bleeding tendency from cutdown wounds. It can also cause systemic tissue edema, which we found to be transient, and there was no evidence of cerebral edema. 3) Although group II of the present study had the same initial hypertensive bout as other groups,22 there were deliberately lower perfusion pressure at <20°C and necessarily longer duration of complete bypass (1.5–2 hours). 4) An early postarrest hypertensive bout improved cerebral reperfusion33 and outcome,22 which could have been offset by the above deleterious microcirculatory effects of deep hypothermia. 5) Protective-preservative hypothermia preserves brain adenosine triphosphate (ATP) during arrest34 and exerts protection upon depletion of ATP.11,35 However, after reperfusion, deep resuscitative hypothermia might delay ATP recovery, which could hamper reparative chemical processes. Cerebral blood flow with deep resuscitative hypothermia remains to be studied. During mild resuscitative hypothermia, cerebral blood flow after cardiac arrest did not worsen cerebral blood flow further and caused a transiently lower cerebral oxygen uptake.36 Mild hypothermia might attenuate the deleterious reoxygenation chemical cascades, without blocking recovery of ATP and metabolic processes.11

Clinical trials of resuscitative mild (i.e., not risky) cerebral hypothermia seem justified, not only for cardiac arrest cases,11,12 in whom cooling must be accomplished within 15–30 minutes of reperfusion,37 but also after experimental focal brain ischemia,38,39 brain trauma,40-42 and hemorrhagic shock.43 Clinical trials of mild resuscitative hypothermia for acutely comatose patients, starting in the prehospital setting, must not only determine clinically feasible and rapidly effective cooling methods12,18 but also must apply routine monitoring in emergency care of brain temperature as T<sub>p</sub>, or nasopharyngeal temperature and core temperature as esophageal temperature, to prevent cardiac temperature of <32°C and cerebral temperature of >38°C; even mild hyperthermia can damage the already damaged brain further.44 We conclude the following: 1) After prolonged cardiac arrest, mild (34°C) resuscitative total body hypothermia induced immediately and maintained for 1 hour...
postarrest mitigates brain damage, without causing deleterious cardiovascular side effects in previously healthy hearts. 2) The start of additional head surface cooling during arrest might give additional benefit. 3) Deep hypothermia (15°C) without hemodilution induced after cardiac arrest does not improve and might worsen cerebral and cardiovascular outcome.

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Reduction in metabolic demand associated with hypothermia has been known for many years to provide neuronal protection during cerebral ischemia. Interest in hypothermia has been rekindled in recent years by two sets of observations. First, reduction in brain temperature of only a few degrees during ischemia exerts remarkable neuroprotection associated with reduced interstitial neurotransmitter levels.1,2,3 Second, application of mild hypothermia during early reperfusion rather than during ischemia also provides some degree of protection4,5 and thereby offers a window for therapeutic intervention.

Previous studies by Safar and colleagues6,7 demonstrate that mild hypothermia during early reperfusion after cardiac arrest improves neurological outcome in dogs. The present study for Weinrauch et al extends this finding by determining the optimal temperature. They report that systemic cooling to 34°C with brief cardiopulmonary bypass after 12.5 minutes of cardiac arrest improves neurological outcome and neuropathology. Cooling to 30°C provides no additional benefit, whereas cooling to 15°C is no better than normothermic reperfusion. These results are significant in that only a modest degree of brain cooling is required to provide neuroprotection. Although bypass was used for systemic cooling, an earlier study by Sterz et al8 using head cooling in ice water with conventional cardiopulmonary resuscitation (CPR) techniques also demonstrated improved neurological outcome. Therefore, this series of studies may have some clinical applicability to the practice of CPR. Although the time constant for cooling the large human brain with external head and neck cooling is presumably longer than that for small animals brains, the technique is attractive as a potential adjunct to standard CPR for both in- and out-of-hospital arrest. Outcome from CPR remains poor, and availability of drugs that offer definitive neuroprotection when administered after arrest is disappointingly limited. Mild hypothermia during CPR and early reperfusion may be the best postischemic therapeutic intervention currently available for complete cerebral ischemia associated with cardiac arrest.

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