Moderate Hypothermia After Cardiac Arrest of 17 Minutes in Dogs
Effect on Cerebral and Cardiac Outcome
Yuval Leonov, MD, Fritz Sterz, MD, Peter Safar, MD, and Ann Radovsky, DVM, PhD

Moderate hypothermia (30°C) induced before circulatory arrest is known to improve neurologic outcome. We explored, for the first time in a reproducible dog outcome model, moderate hypothermia induced during reperfusion after cardiac arrest (resuscitation). In three groups of six dogs each (N=18), normothermic ventricular fibrillation cardiac arrest (no blood flow) of 17 minutes was reversed by cardiopulmonary bypass—normothermic in control group I (37.5°C) and hypothermic to 3 hours in groups II (32°C) and III (28°C). Defibrillation was achieved in ≤5 minutes and partial bypass was continued to 4 hours, controlled ventilation to 20 hours, and intensive care to 96 hours. All 18 dogs survived. Electroencephalographic activity returned significantly earlier in groups II and III. Mean±SD best neurologic deficit between 48 and 96 hours was 44±8% in group I, 38±12% in group II, and 35±7% in group III (differences not significant). Best overall performance category 2 (good outcome) between 48 and 96 hours was achieved in none of the six dogs in group I and in four of the 12 dogs in the combined hypothermic groups II and III (difference not significant). Mean±SD brain total histologic damage score was 130±22 in group I, 93±28 in group II (p=0.05), and 80±26 in group III (p=0.03). Gross myocardial damage was greater in groups II and III than in group I—numerically higher overall and significantly higher in group III for the right ventricle alone (p=0.02). Moderate hypothermia after prolonged cardiac arrest may or may not improve cerebral outcome slightly and can worsen myocardial damage. (Stroke 1990;21:1600–1606)

Since about 1950, it has been known that moderate systemic hypothermia (30°C) induced before elective cardiac arrest of 15–30 minutes protects the brain.1,2 Moderate hypothermia induced after cardiac arrest (temporary global ischemia) to resuscitate the brain was explored 30 years ago in uncontrolled clinical trials3–5 and uncontrolled animal experiments.6,7 Resuscitative hypothermia was given up because of unconvincing results, side effects, and management problems.2,8,9

We hypothesize10 that 1) cerebral resuscitation after prolonged cardiac arrest requires prevention or mitigation of the multiorgan-system postresuscitation syndrome,11 2) effective treatments must be multifaceted since the cerebral postresuscitation syndrome is multifactorial,10 and 3) the cerebral postresuscitation syndrome includes multifocal hypoperfusion that fails to meet metabolic needs12–14 and complex chemical cascades toward cell necrosis.10,15 Postarrest hypothermia might reduce metabolism more than blood flow, in synergism with other potentially beneficial mechanisms.16,17

In one of our previous studies,18 moderate resuscitative hypothermia gave unconvincing results. Our present study,19 conducted in 1987, explored for the first time in a reproducible dog cardiac arrest outcome model, the effect of moderate (30°C) resuscitative hypothermia. We controlled reperfusion blood pressure, flow, composition, and temperature with closed-chest cardiopulmonary bypass (CPB).20 We subsequently discovered in models with briefer insults the beneficial effects of mild (34°C) prearrest16,20 and postarrest16,17 hypothermia.

Materials and Methods
This project was approved by the Animal Care and Use Committee of the University of Pittsburgh School of Medicine. All experiments were performed, in randomized sequence, by the same team over 3
months. We used 22 healthy, custom-bred male hunting dogs (coon hounds) from the same breeding colony, mean age 10 (range 8–12) months and mean weight 22 (range 18–25) kg. The model21–23 included ventricular fibrillation (VF) cardiac arrest (no blood flow) of 17 minutes, controlled reperfusion by CPB,20 early defibrillation, assisted CPB to 4 hours, controlled intermittent positive-pressure ventilation (IPPV) to 20 hours, and intensive care to 96 hours. A VF no-flow time of 17 minutes was chosen on the basis of earlier results.10,20

We studied three groups. In the normothermic control group I (n=7), a mean±SD core (pulmonary artery) temperature (Tpa) of 37.5±1.0°C was maintained with surface warming and cooling throughout. In hypothermic groups II (n=7) and III (n=8), the CPB heat exchanger was prepared at 7–10°C below the Tpa to be achieved. The circuit temperature was adjusted after the start of CPB to rapidly achieve a mean±SD Tpa of 34±1°C and immediately after defibrillation (at CPB 2–5 minutes) to achieve a Tpa of 32°C in group II and 28°C in group III by CPB ≤15 minutes. These Tpa values were maintained for 3 hours after arrest. During the fourth hour of CPB, mean±SD Tpa was increased to 36±1°C by adjusting the heat exchanger to ≤5°C above Tpa (maximum 40°C). After weaning from CPB at 4 hours, Tpa was maintained at 37.5°C by surface warming and cooling. During blood cooling and warming with the CPB heat exchanger we had found that Tpa almost equaled tympanic membrane temperature (Tm) and—in invasive pilot experiments16,17—that deep brain (hippocampal) and epidural (“cortical”) temperatures almost equaled Tpa and Tm.

Anesthesia was induced with intravenous diazepam 0.5 mg/kg and fentanyl 5 µg/kg and maintained before arrest with 50:50% N2O:O2 plus light halothane via endotracheal tube. Sterile cutdowns were performed for monitoring and for CPB.20 Continuously monitored variables were electrocardiogram; mean arterial blood pressure (MABP); venous pressures; end-tidal CO2; electroencephalogram (EEG) (scalp clips); Tpa; Tm; and rectal, esophageal, and cutaneous temperatures. Variables controlled before and after arrest were Tpa (see above), MABP at 100±10 mm Hg (by adjusting the halothane concentration before arrest and by using norepinephrine or trimethaphan after arrest), venous pressures at 5–15 mm Hg, PaO2 at >100 mm Hg, PaCO2 at 30–35 mm Hg, base excess at ±7 meq/l, and blood glucose concentration at 90–175 mg/dl before arrest. Blood gases were controlled according to the determinations at 37°C.24,25 Hydration was maintained with intravenous Ringer’s solution without glucose before and for 20 hours after arrest.

Cardiac arrest was achieved under paralysis with pancuronium 0.2 mg/kg. For the insult, N2O and halothane were discontinued and ventilation was continued with 100% O2 for 1 minute and air for 4 minutes. VF (i.e., no blood flow, with constant MABP near 0)10 was induced by external transtho-}

racic electric shock. VF was maintained for 17 minutes, after which reperfusion with CPB was begun (resuscitation time 0).

Reperfusion was controlled with CPB by closed-chest venoarterial pumping via a membrane oxygenator, which had been primed with dextran 40 plus Ringer’s solution, heparin 1.5 mg/kg (150 units/kg), and NaHCO3 2 meq/kg.20 Ventilation was restarted with 100% O2. Immediately before the start of CPB, the dogs received 0.025 mg/kg i.a. epinephrine, which intensified VF and increased MABP upon the start of CPB (maximum blood flow of >100 ml/kg/min). This dose of epinephrine was repeated as needed to achieve a MABP of >100 mm Hg (briefly ≥140 mm Hg). At CPB 2 minutes, an external defibrillating 100-J countershock was given; countershocks were repeated as needed at 200, 300, and 400 J. After the restoration of a spontaneous heart beat, assisted CPB was continued at maximum flow for 15 minutes and then was gradually decreased over 4 hours. During CPB, activated clotting time was maintained at ≥4 minutes with additional heparin as needed. CPB decreased the hematocrit (Hct) to 25–30% due to the priming volume. After 4 hours Hct was corrected by gradual infusion of blood from the CPB circuit. At 4 hours all dogs were weaned to spontaneous circulation.

Intensive care in all three groups included immobilization with pancuronium as needed and IPPV with 100% O2 from 0 to 2 hours and IPPV with 50%:50% N2O:O2 (for analgesia) from 2 to 20 hours. Between 6 and 16 hours 100 µg i.v. fentanyl was given as needed to control “stress” (hypertension or mydriasis). Lidocaine 1 mg/kg boluses (very rarely needed) were given to control ventricular tachycardia. At 20 hours, the effect of pancuronium was reversed with intravenous neostigmine-atropine (1 mg–0.4 mg), and all dogs were weaned to spontaneous breathing by 24 hours. Intensive care to 96 hours was standard for all three groups.21,22

We evaluated early neurologic recovery on the basis of time to sustained EEG activity. Outcome was evaluated every 8 hours between 24 hours (end of IPPV) and 96 hours in terms of neurologic deficit (ND) (0%=no deficit, normal; 100%=brain death)21–23 and overall performance category (OPC) (1=normal, 5=death).21–23 No central nervous system depressants were given after 72 hours so as not to influence the final evaluation at 96 hours. ND and OPC were determined by at least two investigators. In addition, final performance at 96 hours was determined by an observer not involved in life support who was unaware of the dog’s treatment condition. Final OPC was the consensus of at least three observers.

At 96 hours under endotracheal anesthesia with N2O-halothane the dogs were killed by perfusion with paraformaldehyde, and a total necropsy with brain fixation and preparation of specimens was performed.21–23 Sixteen brain regions were examined by light microscopy, and the lesions were scored separately for the number of ischemic neuronal
TABLE 1. Variables Before and Early After Arrest in Dogs

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Mean±SD</th>
<th>Range</th>
<th>Mean±SD</th>
<th>Range</th>
<th>Mean±SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>II</td>
<td>III</td>
<td>I</td>
<td>II</td>
<td>III</td>
<td></td>
</tr>
<tr>
<td>Mean arterial blood pressure (mm Hg)</td>
<td>I (control) (n=6)</td>
<td>II (32°C) (n=6)</td>
<td>III (28°C) (n=6)</td>
<td>I</td>
<td>II</td>
<td>III</td>
<td></td>
</tr>
<tr>
<td>Before arrest</td>
<td>90±15</td>
<td>99±14</td>
<td>98±11</td>
<td>90±15</td>
<td>99±14</td>
<td>98±11</td>
<td></td>
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<tr>
<td>Maximum after arrest</td>
<td>160±12</td>
<td>156±40</td>
<td>150±12</td>
<td>160±12</td>
<td>156±40</td>
<td>150±12</td>
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<tr>
<td>At restoration of spontaneous circulation</td>
<td>99±15</td>
<td>92±12</td>
<td>109±19</td>
<td>99±15</td>
<td>92±12</td>
<td>109±19</td>
<td></td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td></td>
<td></td>
<td></td>
<td>Before arrest</td>
<td>40±3</td>
<td>40±4</td>
<td>39±3</td>
</tr>
<tr>
<td>3 hours after arrest</td>
<td>28±2</td>
<td>30±2</td>
<td>30±5</td>
<td>28±2</td>
<td>30±2</td>
<td>30±5</td>
<td></td>
</tr>
<tr>
<td>Blood glucose (mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td>Before arrest</td>
<td>145±21</td>
<td>161±47</td>
<td>155±16</td>
</tr>
<tr>
<td>30 minutes after arrest</td>
<td>229±30</td>
<td>280±6</td>
<td>205±47</td>
<td>229±30</td>
<td>280±6</td>
<td>205±47</td>
<td></td>
</tr>
<tr>
<td>Countershocks (no.)</td>
<td></td>
<td></td>
<td></td>
<td>Mean±SD</td>
<td>2.6±1.6</td>
<td>4.4±2.9*</td>
<td>3.5±3.1</td>
</tr>
<tr>
<td>Range</td>
<td>1–6</td>
<td>1–7</td>
<td>1–10</td>
<td>1–6</td>
<td>1–7</td>
<td>1–10</td>
<td></td>
</tr>
<tr>
<td>Time to restoration of spontaneous circulation (min)</td>
<td></td>
<td></td>
<td></td>
<td>Mean±SD</td>
<td>4±1</td>
<td>6±2*</td>
<td>5±3</td>
</tr>
<tr>
<td>Range</td>
<td>3–6</td>
<td>3–8*</td>
<td>2–10</td>
<td>3–6</td>
<td>3–8*</td>
<td>2–10</td>
<td></td>
</tr>
<tr>
<td>Time to return of electroencephalographic activity (min)</td>
<td></td>
<td></td>
<td></td>
<td>130±50</td>
<td>52±31†</td>
<td>55±46†</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean±SD unless noted.
*Values for five dogs. The sixth dog required 28 countershocks and 32 minutes for restoration of spontaneous circulation.
†p<0.05 different from group 1 by analysis of variance.

Results

We excluded four dogs; one in group I, one in group II, and two in group III died between 24 and 72 hours of cardiac emergencies (differences not significant). All six dogs that followed protocol in each group could be weaned from IPPV at 24 hours and survived to 96 hours. Before arrest, weight (not shown), anesthesia time (not shown), MABP (Table 1), central venous pressure (not shown), blood gas values (not shown), Hct (Table 1), blood glucose concentration (Table 1), and Tpa (Table 1) did not differ significantly among the groups. Early postarrest variables (Table 1) also did not differ significantly among the groups.

A MABP of >80 mm Hg was achieved in all dogs during total CPB lasting ≤2 minutes. In groups II and III, CPB decreased Tpa and Tso to 34°C (usually) within 2 minutes and to the predetermined Tso in approximately 15 minutes (Table 2). Started at CPB 2 minutes, defibrillating countershocks restored spontaneous normotension by CPB 10 minutes, except in one dog in group II (Table 1). Two dogs in each group were successfully defibrillated with the first countershock. Overall, groups II and III required more countershocks than group I (Table 1), but the differences were not significant. Esophageal temperature (not shown) and Tso (Table 2) closely followed Tpa. Reduction in cutaneous temperature lagged 1–3°C behind Tpa (not shown).

According to protocol, a peak MABP of >140 mm Hg occurred early after arrest in all three groups. The CPB priming volume decreased Hct to approximately 30% at 3 hours in all groups. At 12 hours, after infusion of the circuit blood, Hct was 34±3% in
TABLE 2. Core and Tympanic Membrane Temperatures Before and After Arrest in Dogs

<table>
<thead>
<tr>
<th>Time</th>
<th>Group I (Control) (n=6)</th>
<th>Group II (32°C) (n=6)</th>
<th>Group III (28°C) (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T_{pa} ± T_{mp}</td>
<td>T_{mp} ± T_{mp}</td>
<td>T_{mp} ± T_{mp}</td>
</tr>
<tr>
<td>Before arrest</td>
<td>37.5±0.4</td>
<td>37.5±0.4</td>
<td>37.5±0.4</td>
</tr>
<tr>
<td>15 minutes</td>
<td>36.8±0.5</td>
<td>37.0±0.7</td>
<td>37.0±0.4</td>
</tr>
<tr>
<td>30 minutes</td>
<td>37.5±0.4</td>
<td>37.0±0.4</td>
<td>37.5±0.4</td>
</tr>
<tr>
<td>4 hours (after 1 hour rewarming)</td>
<td>37.4±0.5</td>
<td>37.5±0.2</td>
<td>NA</td>
</tr>
<tr>
<td>6 hours</td>
<td>37.1±0.6</td>
<td>NA</td>
<td>36.3±0.8</td>
</tr>
</tbody>
</table>

T_{pa}, core (pulmonary artery) temperature; T_{mp}, tympanic membrane temperature.
Values are mean±SD °C. NA, not available.

group I, 36±5% in group II, and 42±0% in group III (differences not significant). Cardiac output was 2–4 l/min before arrest and did not change significantly after arrest; at 12 hours, cardiac output was 3.1±0.5 l/min in group I, 3.0±0.3 l/min in group II, and 2.3±0.5 l/min in group III (differences not significant). There were no significant differences among groups in requirements for norepinephrine, trimethaphan, NaHCO3, epinephrine, or lidocaine.

Sustained EEG activity returned significantly earlier in groups II and III than in group I (Table 1). After weaning from IPPV at 24 hours, ND (Figure 1) and OPC (Figure 2) decreased to lowest (best) values at around 72 hours. In all three groups ND decreased to approximately 50–60% at 24 hours and to a best value around 72 hours. One dog in each group showed secondary deterioration in ND and OPC between 48 and 96 hours (Figure 2). Best ND and final ND did not differ significantly among groups (Figure 1). Best OPC and final OPC also did not differ significantly among groups (Figure 2). A good outcome (OPC of 2) was achieved in four of the 12 dogs of the combined hypothermic groups II and III and in none of the six dogs of normothermic group I (Figure 2) (differences not significant).

No brain showed macroscopic lesions. Histologic damage scores showed similar distributions of ischemic neuronal changes in the three groups (Figure 3). Total histologic damage scores were 130±22 in group I, 93±28 in group II (p=0.05), and 80±26 in group III (p=0.03) (Figure 3). Most regional histologic damage scores, including that in the hippocampus, were better (numerically lower) in groups II and III than in group I (Figure 3). No brain region was without ischemic neuronal changes. Microinfarcts and histologic edema were essentially absent in all groups 96 hours after arrest. Individual total histologic damage scores of the 18 dogs correlated with individual final ND (R²=0.62, data not shown).

All hearts had grossly visible pale necrotic foci, primarily subepicardial in the right ventricular free wall.
wall. Necrosis was confirmed histologically. Overall myocardial damage was 0.7±1.6% of surface area in group I, 3±7% in group II, and 4±7% in group III (differences not significant). Myocardial damage in the right ventricle alone was 2±2% in group I, 9±10% in group II (difference not significant), and 12±8% in group III (p=0.02) (Figure 4).

Discussion

In this study with a reproducible dog outcome model, moderate hypothermia (32° or 28°C) induced by CPB after cardiac arrest of 17 minutes did not significantly improve ND or OPC but reduced EEG recovery time and total brain histologic damage score while worsening myocardial damage. In Hossmann’s studies30 with 1 hour of global brain ischemia in cats, precooling increased the proportion of cats in which EEG recovered. We found no correlation between earlier EEG recovery and better neurologic outcome.10'16'17'21-23-31 The dog model used met all our criteria for cardiopulmonary–cerebral resuscitation outcome models16,21 except one; no other postinsult therapy has yet significantly improved functional outcome (ND, OPC) after VF cardiac arrest of 17 minutes. This insult may be too severe. Using a VF of 12.5 minutes in subsequent experiments, mild cooling (34°–36°C) induced before10,20 or immediately after16,17 arrest improved outcome. Mild cooling in the 12.5-minute model did not worsen myocardial damage,16,17 whereas moderate cooling in our current model did. Harmful effects of moderate hypothermia on the heart and cerebral microcirculation8,9 might offset its beneficial effects at the neuronal level.

Controlled $T_{pa}$ and monitored $T_{br}$ (approximating deep brain temperature) changed in parallel. Our dogs’ cerebral temperatures were definitely moderately hypothermic since in pilot experiments invasively monitored brain temperature followed $T_{pa}$ and equaled $T_{br}$.16,17

Ischemic neuronal changes seemed uniformly distributed and correlated with final ND in all 18 dogs. Microinfarcts, predominant after asphyxial arrest,31

![Figure 2. Best overall performance category (OPC) between 24 and 96 hours after ventricular fibrillation cardiac arrest of 17 minutes in dogs. Each dot represents one dog. No significant differences were found between normothermic control group I and hypothermic groups II and III. Arrows represent secondary deterioration to final OPC at 96 hours.](image)

![Figure 3. Bar graph of mean±SD total and regional brain histologic damage (HD) scores following perfusion-fixation 96 hours after ventricular fibrillation cardiac arrest of 17 minutes in dogs (n=6 in each group). Total HD scores were significantly lower in groups II and III than in group I. Most regional HD scores were numerically lower in groups II and III than in group I. Hippocampal HD scores were 13±4 in group I, 10±5 in group II, and 9±2 in group III.](image)
were absent. Hypothermia reduced the severity of ischemic neuronal changes not only in the hippocampus and caudoputamen, but also in other regions. In rat or gerbil models other workers have shown a reduction in the number/severity of histologic lesions, primarily in the hippocampus, after mild to moderate (30°-34° C) preischemic or early posts ischemic hypothermia.

How postarrest hypothermia resuscitates the brain is still unknown. A reduction in cerebral O2 consumption alone cannot explain it; we have speculated on the synergism of multiple mechanisms (see discussions in References 16 and 17). Related pioneering hypothermia research by others concerning protection, focal ischemia, and brain trauma, as well as our pilot experiments on cerebral and extracerebral temperature gradients and clinical cooling methods, have been reviewed. 16,17

Could a negative effect of moderate hypothermia on the heart and cerebral microcirculation offset its beneficial effect on the brain? Necrosis of the right cardiac ventricle was worse in group III, but not severe enough to reduce postarrest cardiac output. Electric injury from defibrillation countershocks is a possibility since the hypothermic dogs required more countershocks. However, this explanation is unlikely since in our past cardiopulmonary resuscitation studies 25,26,31,39 many more countershocks produced no more lesions than in this study, and the electric energy required to cause myocardial necrosis under normothermic conditions seems to be much greater than that received by groups II and III. 40 The countershocks were given at Tpas similar to those in our mild hypothermia studies, 16,17 which showed no increase in myocardial damage.

Our results suggest that after normothermic VF cardiac arrest of 17 minutes in dogs, resuscitation with moderate hypothermia (30°C) by CPB may or may not mitigate posts ischemic brain damage slightly and can worsen myocardial damage. In view of the subsequently obtained significant cerebral benefit of mild prearrest or postarrest cooling, these results call for a systematic evaluation of hypothermia levels and timing in reproducible animal outcome models with milder insults.

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