Mild hypothermia during prolonged cardiopulmonary cerebral resuscitation increases conscious survival in dogs*

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Objective: **Therapeutic hypothermia during cardiac arrest and after restoration of spontaneous circulation enables intact survival after prolonged cardiopulmonary cerebral resuscitation (CPCR). The effect of cooling during CPCR is not known. We hypothesized that mild to moderate hypothermia during CPCR would increase the rate of neurologically intact survival after prolonged cardiac arrest in dogs.**

Design: **Randomized, controlled study using a clinically relevant cardiac arrest outcome model in dogs.**

Setting: **University research laboratory.**

Subjects: **Twenty-seven custom-bred hunting dogs (19–29 kg; three were excluded from outcome evaluation).**

Interventions: **Dogs were subjected to cardiac arrest no-flow of 3 mins, followed by 7 mins of basic life support and 10 mins of simulated unsuccessful advanced life support attempts. Another 20 mins of advanced life support continued with four treatments: In control group 1 (n = 7), CPCR was with normothermia; in group 2 (n = 6, 1 of 7 excluded), with moderate hypothermia via venovenous extracorporeal shunt cooling to tympanic temperature 27°C; in group 3 (n = 6, 2 of 8 excluded), the same as group 2 but with mild hypothermia, that is, tympanic temperature 34°C; and in group 4 (n = 5), with normothermic venovenous shunt. After 40 mins of ventricular fibrillation, reperfusion was with cardiopulmonary bypass for 4 hrs, including defibrillation to achieve spontaneous circulation. All dogs were maintained at mild hypothermia (tympanic temperature 34°C) to 12 hrs. Intensive care was to 96 hrs.**

Measurements and Main Results: **Overall performance categories and neurologic deficit scores were assessed from 24 to 96 hrs. Regional and total brain histologic damage scores and extracerebral organ damage were assessed at 96 hrs.**

In normothermic groups 1 and 4, all 12 dogs achieved spontaneous circulation but remained comatose and (except one) died within 58 hrs with multiple organ failure. In hypothermia groups 2 and 3, all 12 dogs survived to 96 hrs without gross extracerebral organ damage ($p < .0001$). In group 2, all but one dog achieved overall performance category 1 (normal); four of six dogs had no neurologic deficit and normal brain histology. In group 3, all dogs achieved good functional outcome with normal or near-normal brain histology. Myocardial damage scores were worse in the normothermic groups compared with both hypothermic groups ($p < .01$).

Conclusion: **Mild or moderate hypothermia during prolonged CPCR in dogs preserves viability of extracerebral organs and improves outcome. (Crit Care Med 2004; 32:2110–2116)**

KEY WORDS: cardiac arrest; resuscitation; hypothermia; extracorporeal circulation; survival; neurologic deficit; dog

Sudden cardiac death remains the principal killer in industrialized countries (1, 2). The potential physiologic potency of standard external cardiopulmonary-cerebral resuscitation (CPCR) far exceeds the current rates of achieving conscious survival after out-of-hospital CPCR attempts. In about 50% of cases, restoration of spontaneous circulation (ROSC; i.e., spontaneous heartbeat) is not achieved in the field and resuscitation efforts are abandoned (1–3). Among patients who reach the hospital intensive care unit, about one half die in the intensive care unit, primarily from cardiac, cerebral, or multiple organ failure (1–3). Among long-term survivors, 10–30% have permanent brain damage. Rapidly induced mild hypothermia after ROSC from prolonged normothermic ventricular fibrillation (VF) cardiac arrest (CA; i.e., no flow) has improved cerebral outcome in dogs (4–8) and patients (9–11). For cases resistant to ROSC attempts, we searched for a method to preserve the organism during transport to, and preparation for, prolonged circulatory support using cardiopulmonary bypass (CPB), which would allow the heart to recover from ischemic stunning or be evaluated, repaired, or replaced (12–16).

For CPCR-resistant cases of CA, we considered "suspended animation for delayed resuscitation" during no-flow, with tympanic temperature (Tty) of 10°C, which is being explored primarily for preservation of the exsanguinating trauma victim to allow transport and resuscitative surgery during pulselessness (17–19). In clinical cases, however, with hearts resistant to ROSC attempts (perhaps only temporarily), clinicians would hesitate to create no-flow deliberately with aortic cold flush, instead of continuing basic (BLS) and advanced life support (ALS) with steps A (airway), B (breathing), and C (circulation by chest com-

*See also p. 2164.

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pressions) with the hope that the heart may resume beating. Other ways to "buy time" might include mild (33–36°C) or moderate (27–32°C) hypothermia during steps A–B–C until CPB is initiated. Others and we have used these definitions for temperature levels of therapeutic hypothermia.

We hypothesized that a) maintaining viability of brain, heart, and organism during prolonged CPCR basic and advanced life support steps A–B–C (low flow) can be a bridge during transport to initiation of CPB in the hospital; b) induction of mild hypothermia during CPCR can maintain viability for ≥40 mins of VF-CA; and c) mild hypothermia (which is safe) is as effective as moderate hypothermia (which has more risk of complications) in preserving the viability of the heart during CPCR.

MATERIALS AND METHODS

The experimental protocol was approved by the Institutional Animal Care and Use Committee of the University of Pittsburgh. The care and handling of the animals followed guidelines of the National Institutes of Health. All surgery was performed by the same team in our animal intensive care unit, using sterile techniques (20–21).

Protocol. The model's protocol, with life support to 96 hrs after reperfusion, simulated a scenario of prolonged VF resistant to defibrillation attempts using CPCR steps A–B–C over 40 mins to "bridge" from collapse via transport to initiation of CPB in the hospital emergency department. Twenty-seven custom-bred hunting dogs (19–29 kg body weight, age 8–12 months) were used. They were sedated with ketamine 10 mg/kg intramuscularly. Anesthesia was induced with halothane 2–4% in N_2O/oxygen 50/50% via a cone mask. The dogs were then positioned supine, intubated, and mechanically ventilated to maintain an arterial P_{CO_2} at 35–40 mm Hg. A positive end-expiratory pressure of 5 cm H_2O was applied. Anesthesia was maintained during preparation with halothane 0.5–1.5% and N_2O/oxygen 50/50% without neuromuscular blockade. Temperature probes were inserted for measuring tympanic membrane (Tty), esophageal, and rectal temperatures. Tty was controlled at 37.5 ± 0.1°C with heating blankets and heating lamps before the insult. We chose to control Tty since the brain was the primary target organ for our therapy. We recognize that the correlation between Tty and brain temperature is poor, although one recent study suggested good correlation between Tty and brain temperature in neurosurgical patients (22). The correlation between core and brain temperatures is also variable (23). Gastric and bladder catheters were inserted. Dextrose 5% in sodium chloride 0.45% was administered at 5 mL/kg/hr via a peripheral intravenous cannula (18 gauge). A 10-Fr catheter was inserted into the left femoral artery to monitor arterial pressure and for blood sampling. A 7- to 8-gauge cannula was inserted 3 cm into the right femoral artery for later use for CPB. A pulmonary artery catheter (7.5 Fr) was inserted via the left femoral vein and advanced into occlusion position for pressure and temperature monitoring, continuous cardiac output determination, and blood sampling. Arterial and central venous pressures and electrocardiogram were continuously recorded on a polygraph. Due to technical issues, venous pressures were not measured accurately during chest compressions.

To control Tty in groups 2, 3 and 4, via venovenous extracorporeal shunt cooling, a 13-Fr catheter was inserted via the femoral vein 20 cm into the inferior vena cava and connected to 15 m long tubing (3 mm inner diameter; primed with isotonic saline 120 mL and 500 IU heparin) immersed in ice water. This simple system was used instead of conventional heat exchangers specifically because of its simplicity. Only one pump was needed. The system could readily be used outside of the hospital. There was no additional systemic heparinization. A shunt flow of 10 mL/kg/min by a roller pump returned the cooled blood via the right external jugular vein into the superior vena cava using a multiple-holed 19-Fr catheter.

Randomization for group assignments was performed after surgical preparation but before the insult began so that one team member could prepare materials for cooling if necessary. Attempts were made to keep the other team members blinded to group assignments until during the insult.

After stabilization and two baseline measurements, intravenous fluids were discontinued, heating devices were turned off, and the dogs were weaned to spontaneous breathing via a T-tube. VF was induced with a 95-V AC, 60-Hz transthoracic shock of 2 secs, using subcutaneous needles. The shock was repeated as needed. Pulselessness was allowed to persist for 3 mins before initiation of cardiopulmonary resuscitation (CPR). CPR basic life support (BLS) steps A–B–C, with air for ventilation to simulate bystander CPR, was then initiated, using left parasternal chest compressions (dogs turned 45° to the right of supine to exert more direct pressure on the heart) with a mechanical thumper (Michigan Instruments, Grand Rapids, MI), rate of 80/min. The depth of compression was titrated to maximize systolic blood pressure. There was no active decompression of the chest. Tidal volumes of approximately 15 mL/kg (larger than the standard in humans based on greater compliance of the dogs' chest and lungs) at an F_{IO_2} of 0.21 were delivered with a self-inflating bag (Laerdal Medical, Stavanger, Norway) at a ratio of five compressions to one ventilation. In previous experiments with this model, this ratio provided better hemodynamics and ventilation during CPR than the 15:2 ratio. There was no interruption of compressions for ventilation. After 7 mins of BLS (10 mins of VF), to simulate arrival of paramedics and futile ROSC attempts, ALS was continued for another 10 mins of normothermic VF, using three external transthoracic DC countershocks of 50 J in rapid sequence. In pilot experiments, even countershocks of ≥150 J after 3 mins of untreated VF and 7 mins of BLS were unsuccessful. Deliberately weak shocks (50 J) were used in the study to avoid premature defibrillation, which would have made that experiment unusable. These shocks never caused defibrillation; VF persisted. Chest compressions were continued at a rate of 60/min (decreased per protocol to maximize systolic blood pressure based on previous experience with this model) and ventilation with F_{IO_2} 1.0, at a ratio of 5:1, was used. The primary goal was to maximize cerebral perfusion pressure. Epinephrine 20 μg/kg was administered intravenously at 5-min intervals from 10 mins VF to 20 mins, without any additional defibrillation attempts. The dogs were to be maintained in VF for a total of 40 mins. Lidocaine (1–1.5 mg/kg intravenously) was administered for recurrent or refractory ventricular fibrillation or ventricular tachycardia.

At VF 20 mins, the dogs were assigned to one of four treatment groups: Control group 1 (n = 7) received continued normothermic CPR-ALS until VF 40 mins, without venovenous shunt flow, with Tty maintained at 37.5°C using heating blankets as necessary. Moderate hypothermia group 2 (n = 7) received venovenous shunt cooling to Tty 27°C during 20 mins of CPR-ALS. Mild hypothermia group 3 (n = 8) was treated as group 2 but received cooling to Tty 34°C. Cooling in groups 2 and 3 was induced with a bolus of 20 mL/kg normal saline at 2°C into the superior vena cava, followed by venovenous extracorporeal pumping at 200 mL/min (estimated to be 10% of cardiac output). In normothermic group 4 (n = 5), the initiating intravenous flush (at 37°C) and venovenous pumping were similar to groups 2 and 3 but were maintained at normothermia. No additional epinephrine or countershocks were administered during this time.

Reperfusion after VF 40 mins was with CPB as an experimental tool since ROSC attempts with external CPCR would not be reliable after such a severe insult. The use of CPB for resuscitation also simulates a possible clinical scenario for cases of refractory VF. The CPB system used a centrifugal pump to circulate venous blood from the superior vena cava catheter into the femoral artery cannula via a membrane oxygenator (12–16). The CPB system had been primed with lactated Ringer's solution 400 mL with sodium bicarbonate 2 mEq/kg. CPB flow was maintained at 100 mL/kg/min. After 15 mins of recirculation with CPB, defibrillation attempts were initiated with external DC countershocks of 150 J

(which could now be successful since the heart has been reperfused), increased if needed by 50 J for repeated shocks. If ROSC was achieved (defined as the presence of arterial pulsations on the arterial pressure tracing), CPB was continued for assisted circulation. By protocol, Tty should be approximately 34°C at this time point. Epinephrine 5 μg/kg was administered intravenously before countershocks and then repeated as needed every 5 mins until ROSC. After ROSC, norepinephrine was titrated to maintain the mean arterial pressure at 90–120 mm Hg. Flow of 100% oxygen through the oxygenator was adjusted to keep $Paco_2$ at 30–35 mm Hg. The CPB flow rate was kept at 100 mL/kg/min until 120 mins and then reduced to 50 mL/kg/min until weaning from CPB at 4 hrs. Weaning was initiated earlier if the dogs achieved ROSC and were hemodynamically stable without inotropic support. The temperature of the water bath of the CPB heat exchanger was set to 34°C. After CPB, Tty 34°C was maintained by external means until 12 hrs in all four groups.

When CPB was initiated, controlled ventilation was resumed with 100% oxygen, which was maintained until weaning from CPB. The intravenous maintenance fluid was restarted. A base deficit of >6.0 mEq/L was treated with sodium bicarbonate intravenously.

Intensive care was continued until 96 hrs or earlier death by technicians and critical care physicians. Controlled ventilation was continued to ≥48 hrs. Neuromuscular blockade was maintained with intermittent doses of pancuronium (0.1 mg/kg intravenously). Analgesia was with N_2O/oxygen 50/50%. In addition, throughout the experiment of 96 hrs, intravenous boluses of morphine (0.1–0.3 mg/kg) and diazepam (0.1–0.3 mg/kg) were titrated to prevent signs of pain (reactive wide pupils or hypertension). Hypotension (mean arterial pressure <80 mm Hg) was treated with normalization of central venous pressure (5–8 mm Hg) and intravenous titration of norepinephrine. Standard intensive care included airway suctioning, periodic deep lung inflations, and position change (rotation). The dogs received cefazolin (250 mg intravenously) every 8 hrs for infection prophylaxis. At 44–48 hrs, neuromuscular block was reversed with neostigmine (50 μg/kg) plus atropine (25 μg/kg) and the dogs were weaned to spontaneous breathing via T-tube and extubated by previously reported criteria (13–20). Dogs that required continued circulatory support were ventilated for an additional 24 hrs. Successfully weaned dogs were transferred to a stepdown intensive care unit for observation and treatment to 96 hrs, with oxygen by mask, continuous monitoring of pulse rate, and arterial oxygen saturation. The maintenance fluid was dextrose 5% in NaCl 0.45% until 48 hrs and dextrose 10% in NaCl 0.45% thereafter, until the dog either could drink adequately, died, or completed the experiment after being killed at 96 hrs.

Outcome Evaluation. Performance was evaluated according to overall performance categories (OPC): 1, normal (able to walk and eat); 2, moderate disability (able to sit but not stand or walk); 3, severe disability (unaware of surroundings, withdraws to pain); 4, coma (some reflexes or pathologic movements, but no response to pain); and 5, death (13–16, 20). This scoring system is designed to be similar to the Glasgow Outcome Scale used clinically. Neurologic function was evaluated as neurologic deficit scores (NDS 0–10% = normal; 100% = brain death), which includes evaluation of consciousness, breathing, cranial nerves, sensory/motor function, and behavior (13–21). Our group, and others, have used these outcome measures >20 yrs for large animal outcome experiments. OPC and NDS were evaluated every 8 hrs after extubation for best (at any time) and final values (at 96 hrs). Attempts were made to discontinue any sedation ≥4 hrs before final evaluations at 96 hrs. If necessary, sedation was reversed with naloxone (1.5–6.0 μg/kg intravenously) and/or flumazenil (0.1 mg intravenously), repeated if needed. The 96-hr NDS evaluation was the average of four evaluators.

After final evaluation at 96 hrs, the dogs were reanesthetized for morphologic studies. Via a left thoracotomy, brain perfusion fixation, with infusion of paraformaldehyde into the aortic arch, for cutting, staining, and histologic damage scoring, was performed as described previously (17, 20, 21). The same six brain slices were stained with hematoxylin-eosin-phloxine. Using light microscopy, the same pathologist, blinded for treatment assignments, scored 19 distinct anatomical brain regions for severity and extent of ischemic neuronal changes, infarcts, and edema (21). A total histopathologic damage score (HDS) of >40 represents moderate damage, and >100 represents severe damage.

A complete necropsy was performed. Macroscopic lesions in the myocardium were scored as absent, minimal, mild, moderate, marked, or severe and were scored taking into account the pattern, appearance, and anatomical distribution (0 = no damage, 100 = severe damage). Although a score was given, this was a qualitative appraisal of overall myocardial damage, without a true quantitative scoring system.

Statistical Analysis. Repeated-measures analyses of variance were performed followed by Bonferroni-Dunn *post hoc* tests to identify differences in hemodynamic variables and temperature data between groups over time. NDS, HDS, and myocardial damage scores were analyzed using Mann-Whitney U test, with the sequentially rejective Bonferroni test being used to preserve the experiment-wise type-I error rate at 0.05. Fisher's exact test was used to assess differences in OPC proportions (dichotomized to OPC 1 and 2 = good outcome [similar to the Glasgow Outcome Scale with potential for independent functioning] and OPC 3, 4, or death = bad outcome) between groups. A $p < .05$ was considered statistically significant.

RESULTS

Three of the 27 dogs were excluded from analysis. One each in groups 2 and 3 had severe, exsanguinating hemorrhage from major liver lacerations secondary to chest compressions. These were clearly direct, severe liver injuries, not minor injuries complicated by coagulopathy. One in group 3 had subarachnoid hemorrhage and *Dirofilaria immitis* infection.

There were no significant differences between groups in baseline measurements, including hemodynamic variables and blood gas, electrolytes, serum glucose, hemoglobin, and hematocrit values.

Despite three countershocks of 50 J during ALS, all 24 dogs remained in VF until reperfusion was initiated with CPB and countershocks with >150 J were delivered. All dogs then achieved ROSC after 15–120 mins of CPB (Table 1). Temperatures (Fig. 1) and blood pressures (Fig. 2) changed as expected, according to protocol. Coronary perfusion pressures (diastolic arterial pressure-central venous pressure) after ROSC were initially slightly above baseline (Fig. 2) but returned to baseline values by 12 hrs. All 12 normothermic dogs (groups 1 and 4) died with cardiovascular and multiple organ failure during intensive care, with the exception of one dog in group 1 that survived to 96 hrs in coma (Fig. 3). Median survival time was 25 hrs (range, 4–96) in group 1 and 15 hrs (4–24) in group 4 (nonsignificant between these two groups). All 12 hypothermic dogs (groups 2 and 3) were successfully weaned from CPB and controlled ventilation and survived to 96 hrs ($p < .0001$ vs. normothermia groups 1 and 4) with normal or near-normal function and brain histology (Fig. 3). If the excluded animals were included (intention to treat analysis), the survival in the hypothermia groups would still be significantly greater than that in the normothermic groups ($p < .0001$).

During CPCR, mean arterial pressures were 39–63 mm Hg and mean diastolic pressures were 24–39 mm Hg without difference between groups (Fig. 2). In groups 2, 3, and 4, these pressures increased after the intravenous flush of normal saline at VF 20 mins and returned to preinfusion levels within 8 mins, with-

Table 1. Resuscitation variables

Group	Control	Tty 27°C	Tty 34°C	Tty 37.5°C
Countershocks, total no.	2 (1–19)	1	1 (1–16)	14 (1–25)
Countershocks, total energy, J	300 (150–3990)	150	150 (150–3200)	2550 (150–4000)
Time of ROSC, mins after start of CPB	22 (15–120)	15	17 (15–33)	32 (15–105)
Total bicarbonate, mEq	115 (50–215)	95 (50–175)	107 (50–130)	100 (95–275)
Total epinephrine, mg	0.9 (0.4–6.4)	0.5 (0.4–1.1)	0.8 (0.5–1.7)	0.9 (0.4–1.7)
Total norepinephrine, mg	6.68 (2.32–85.46)	2.05 (1.26–5.40)	7.49 (2.01–36.32)	23.09 (10.88–49.58)
Duration of NE infusion, mins	3.5 (1–38)	6 (0.25–44)	2.25 (0.5–80.25)	12 (4–24)
Lidocaine, mg	20 (0–280)	25 (20–184)	30 (20–40)	20 (20–30)
Survival time, hrs	25 (4–96)	96	96	15 (4–24)

Tty, tympanic temperature; ROSC, restoration of spontaneous circulation; CPB, cardiopulmonary bypass; NE, norepinephrine.
Data are given as median (range).

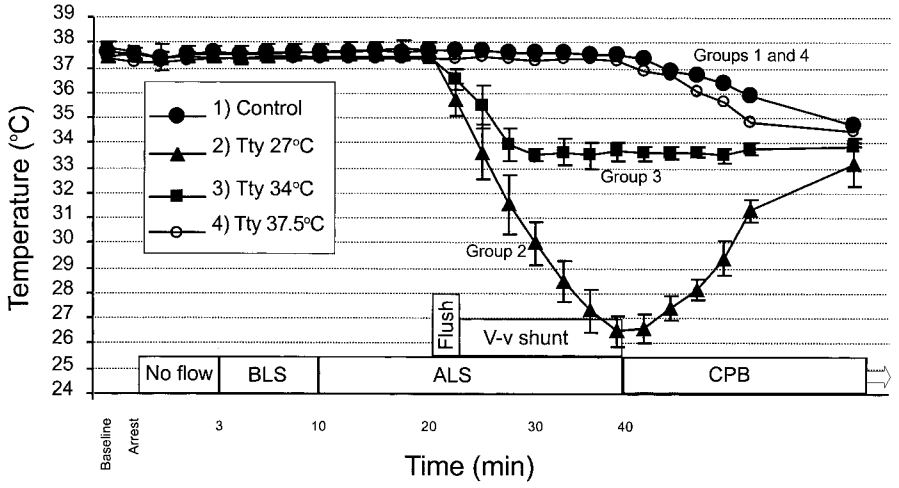

Figure 1. Tympanic temperature (*Tty*) during 3 mins of normovolemic ventricular fibrillation (no flow), followed by 7 mins of basic life support (*BLS*) and 30 mins of advanced life support (*ALS*). *CPB*, cardiopulmonary bypass; *V-v shunt*, venovenous shunt cooling. Data are presented as mean and SD.

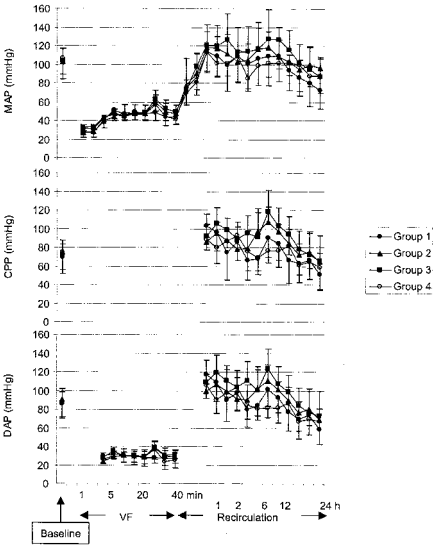

Figure 2. Mean (*MAP*) and diastolic arterial pressures (*DAP*) and coronary perfusion pressure (*CPP*) during and after ventricular fibrillation (*VF*) cardiac arrest. Data are presented as mean and SD.

out statistical differences between groups. After ROSC and after weaning from CPB, heart rate values were significantly higher in normothermic flush group 4 vs. hypothermic flush groups 2 and 3 ($p < .001$ and $p = .006$, respectively), despite adequate analgesia, normalization of central venous pressure, and avoidance of drugs with chronotropic effects. No other differences were observed in the hemodynamic variables between the groups. Mean arterial pressure was controlled per protocol. Cardiac output was not available in several dogs because of difficulty advancing the catheter. After weaning from CPB, cardiac output was quite variable within groups. Values were not statistically different from baseline, nor were they different between groups.

Arterial P_{CO_2} values were also variable. These values were frequently high (50–60 torr) at the time of initiation of CPB but returned to baseline levels per protocol by CPB 15 mins. P_{CO_2} ranged from 30 to 40 torr during CPB and early resuscitation. There were no differences between groups.

Venovenous shunt cooling in groups 2 and 3 was initiated by an intravenous saline flush, which decreased Tty from 37.5°C to 36.1 ± 0.7°C (Fig. 1). Pulmonary artery temperature was 26 ± 0.2°C and esophageal temperature 35.8 ± 1.5°C at the end of the intravenous flush. The time needed for shunt cooling after the flush to achieve Tty 34°C in groups 2 and 3 was only 2 mins (a decrease in Tty of 1°C/min). In group 2, continued venovenous shunt cooling decreased Tty to a nadir of 26.6 ± 0.6°C at the end of CPCR ALS (VF 40 mins). Within 15–20 mins after recirculation with CPB, these temperatures reached 34°C in all groups and were maintained at that level until 12 hrs.

Extracerebral organ failure, after CPB and ROSC, was the main reason for irreversible deterioration in normothermic groups 1 and 4. Arrhythmias appeared within the first hour after ROSC in all four groups. The most frequent form of arrhythmia was multifocal runs of ventricular extrasystoles, appearing intermittently in all dogs, especially during the first day after the insult. During CPB (assisted circulation), after ROSC, ventricular arrhythmias increased gradually in two dogs in each of the normothermia groups 1 and 4. Shortly after these four dogs were weaned from CPB, they died in VF that was resistant to vigorous CPR and up to 25 countershocks. Two dogs in normothermia group 1 and the remaining three dogs in normothermia group 4 died within 38 hrs after recirculation in vasopressor-resistant shock. Two other dogs in normothermic group 1 developed an increasing need for large doses of norepinephrine (despite adequate left ventricular filling pressures), severe metabolic

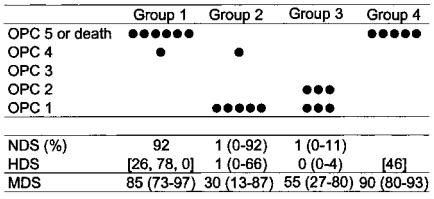

Figure 3. Final 96-hr outcome. Overall performance categories (*OPC*): OPC 1, normal; OPC 2, moderate disability; OPC 3, severe disability; OPC 4, coma; OPC 5, brain death. *NDS*, neurologic deficit score; *HDS*, total brain histologic damage score; *MDS*, gross myocardial damage score. Each dot represents a dog. Values of NDS, HDS, and MDS are expressed as median (range). Brackets represent individual HDS scores at 22–58 hrs of reperfusion.

acidemia, anuria, and respiratory failure. These dogs were killed at 25 and 38 hrs, respectively, when it was recognized that they were not salvageable, to obtain their brains for histologic scoring.

Myocardial injury was present in all four groups, despite patent coronary arteries. Milder lesions were restricted to the subendocardium and subepicardium with a patchy, multicentric pattern that coalesced into larger, focally extensive lesions. Superficial subendocardial hemorrhage and papillary muscle necrosis were more frequently observed in the left than in the right ventricle and more frequently in the normothermia groups than in the hypothermia groups. Microscopically, the areas of myocardial damage were characterized by the loss of fiber cross-striation, decreased nuclear definition, and prominent contraction band necrosis. Intensely eosinophilic transverse bands representing hypercontracted myofibrils span these degenerative cells. In some areas, there was frank associated individual myofiber coagulation necrosis with associated disintegration and loss of fiber integrity. Another finding seen in areas adjacent to frankly degenerative myocardium, especially in subendocardial and subepicardial perivascular locations, was focal myocytolysis (vacuolar degeneration). Some hearts also had large amounts of prominent basophilic stippling of myofibers.

The total myocardial damage scores were significantly lower in the hypothermia groups 2 and 3 than in the normothermic groups 1 and 4 ($p = .0083$) but did not differ between the two hypothermia groups ($p = .1548$, Fig. 3).

Cerebral outcome is illustrated in Figure 3. There was 100% agreement among observers regarding OPC scoring. The only dog in normothermic groups 1 and 4 that survived to 96 hrs remained comatose (OPC 4) and required controlled ventilation. In contrast, all surviving dogs in group 3 and all but one dog in group 2 had good functional outcome (OPC 1 or 2, Fig. 3). Because of early deaths, only four brains of the normothermic groups could be studied histologically: three in group 1 and one in group 4. Histologically, the brains in the normothermic groups were characterized by multifocal infarctions, with vasculitis/encephalitis adjacent to the infarcted areas. These lesions were noted in the frontal, parietal, and occipital cortexes as well as the putamen and caudate nucleus. Multifocal vasculitis was also observed adjacent to an infarcted area in the occipital cortex of one dog in hypothermia group 3. Histopathologic changes in groups 2 and 3 were mild and consisted mainly of isolated ischemic neurons and, in two dogs, focal vasculitis. The only region in which the regional HDS was not zero was the caudate nucleus. Except for these lesions, total brain HDS was normal (0–4%) in all but two dogs in group 2 and in all dogs in group 3 ($p < .001$ for hypothermia groups vs. normothermic groups).

DISCUSSION

This study strongly supports all three hypotheses posed in the introduction. The results show outcome benefit for simulated "refractory" CA cases, in terms of overall organ preservation, survival time, and survival rate, with mild (34°C) or moderate (27°C) hypothermia, induced by venovenous extracorporeal shunt cooling, during prolonged CPCR-ALS steps A–B–C, as a bridge to temporary, prolonged CPB. The benefit derived from mild hypothermia after ROSC for cerebral recovery has been well documented (4–11). All four groups in the present study with VF of 40 mins were treated with mild hypothermia after ROSC; this alone did not prevent organ failure and early death in groups 1 and 4. Demonstration of the added benefit (without negative side effects) of mild (group 3) or moderate (group 2) hypothermia, when introduced during CPR steps A–B–C (low flow), not only for the brain but also for preservation of extracerebral organs, is new. The finding that the impact of hypothermia was so pronounced on extracerebral organ preservation was not expected.

Mild hypothermia initiated before CA in rats was shown to be more beneficial than after CA (24). The results of the present study in a clinically realistic dog model document that therapeutic hypothermia should be initiated as soon as possible, even before ROSC, to provide effective protection from, or to mitigate, post-CA damage to all vital organs. Even though one of us recommended resuscitative moderate hypothermia as a step in the CPCR system as early as 1961 (25), it has not been practiced because of a fear of causing arrhythmias, depressing the myocardium, and causing coagulopathy and infection and because of practical limitations with slow surface cooling (26, 27). Moderate hypothermia (30°C) has been considered detrimental during CPCR, as it may worsen the chance for achieving ROSC, in addition to aggravating the myocardial damage (6, 28). The cardiovascular safety of even 27°C in this study in healthy animals may not apply to patients with diseased hearts.

In the present study we not only documented an effective and feasible technique for the rapid induction of mild (34°C) to moderate hypothermia (27°C) during CPCR steps A–B–C but also demonstrated that hypothermia significantly improves outcome without cardiovascular side effects during prolonged VF in a model of refractory CA. The finding that mild hypothermia is as effective as moderate hypothermia in preserving the viability of the organism obviates the need for lowering the temperature beyond the relatively safe limit of 34°C. We recognize that studies are needed to evaluate the effect of mild hypothermia on the ability to achieve ROSC without CPB in experimental models with diseased hearts. Recent clinical studies suggest that in patients with diseased hearts, postarrest mild hypothermia induced by infusion of large volume (30 mL/kg) of intravenous iced (4°C) crystalloids does not cause arrhythmias and may actually improve hemodynamics (29). Ideally, hypothermia should be induced immediately after CA. However, experience from clinical studies of out-of-hospital CA indicates that 8–10 mins is required in many urban areas for the ambulance to arrive and for paramedics to initiate ROSC attempts (2, 3, 30, 31). Therefore, in the present study the dogs were subjected to 3 mins of no flow, simulating the reaction time for a bystander, followed by 7 mins of BLS, to approximate the time required for the ambulance to arrive. Hypothermia was not induced until after another 10 mins at normothermia, simulating ROSC at-

Mild or moderate hypothermia during prolonged cardiopulmonary cerebral resuscitation in dogs preserves viability of extracerebral organs and improves outcome.

tempts and the time needed to gain vessel access.

Alternative explanations for the results of this study should be considered. The excellent neurologic outcomes in the hypothermia groups may, theoretically, have been the result of better perfusion pressures during CPR. Indeed, the flush administered at the start of the venovenous shunt cooling did increase blood pressure, similar to what has been seen clinically (29). The normothermic shunt group 4, however, had similar blood pressure responses as the hypothermia groups but had significantly worse outcome. Thus, it appears that hypothermia improved outcome. Similarly, the hypothermia groups had less myocardial damage than the normothermia groups. Hypothermia presumably had a protective effect on the heart. Mechanisms of this protection may include decreased heart rate, decreased oxygen demands, decreased apoptosis (32), and increased production of heat shock proteins (33). The resultant improved hemodynamics could have contributed to the improved neurologic outcome.

One potential criticism of the study is that the control (normothermic) group was actually actively warmed during CPCR. This was done to be sure that temperatures were tightly controlled during the insult. Clinically, however, patients tend to cool spontaneously during CA and CPCR. Thus, the protocol may have exaggerated the effects of mild hypothermia since the control group may have actually been hyperthermic compared with patients. The results of this study suggest that perhaps exposure of the victim or other measures should be used during CA to enhance this spontaneous cooling.

Limitations of this study also include the fact that the researcher who evaluated the functional outcome (OPC, NDS) could not be blinded for the treatment groups, although the pathologist who evaluated cerebral histologic outcome was blinded. These experiments require a large team of personnel, who consequently become aware of the group assignments. There were no other personnel available to routinely perform neurologic assessments in every animal. In previous studies, agreement between team members on outcomes scores was good. This is not surprising since the differences between the overall performance categories, the primary functional outcome variable, are not subtle. In addition, the fact that the histopathologic findings correlate with the OPCs suggests a lack of bias in OPC determination.

For clinical use, the catheters used in this study for the venovenous shunt cooling (34) could be replaced by a double-lumen central venous catheter, inserted through a large vein (basilic, cephalic, internal jugular, femoral), with inflow and outflow sites separated. In our pilot experiments we found that the venovenous cooling during CPR is less effective if the tips of the catheters are <20 cm apart. Another alternative is a standard central venous catheter for inflow into the heat exchanger and any peripheral venous catheter for delivery of cooled blood to the patient. Our improvised cooler (heparinized tubing in ice water) (34) might be replaced by a still-to-be-developed, FDA-approved miniaturized pump-cooler for field use. Although the 10 mins allowed in this protocol for achieving venous access and initiation of cooling seems unrealistic with standard techniques, we are working with catheter and imaging companies to develop novel approaches to vessel cannulation that could be more rapid and reliable, even in the hands of physician extenders.

CONCLUSIONS

We conclude that in normovolemic "refractory" VF-CA of 40 mins in dogs, cooling to mild (Tty 34°C) or moderate (Tty 27°C) hypothermia during ROSC attempts of 20 mins with external CPCR steps A–B–C (for BLS and ALS) as a bridge to prolonged CPB can result in survival with full neurologic recovery. This was not achievable in the same scenario with normothermic closed-chest CPCR, despite mild hypothermia after ROSC. A clinically acceptable portable device for blood cooling during CPCR should be developed.

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