Delayed, spontaneous hypothermia reduces neuronal damage after asphyxial cardiac arrest in rats

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Objective: **Core temperature is reduced spontaneously after asphyxial cardiac arrest in rats. To determine whether spontaneous hypothermia influences neurologic damage after asphyxial arrest, we compared neurologic outcome in rats permitted to develop spontaneous hypothermia vs. rats managed with controlled normothermia.**

Interventions: **Male Sprague-Dawley rats were asphyxiated for 8 mins and resuscitated. After extubation, a cohort of rats was managed with controlled normothermia (CN) by placement in a servo-controlled incubator set to maintain rectal temperature at 37.4°C for 48 hrs. CN rats were compared with permissive hypothermia (PH) rats that were returned to an ambient temperature environment after extubation. Rats were killed at either 72 hrs (PH72hr, n = 14; CN72hr, n = 9) or 6 wks (PH6wk, n = 6, CN6wk, n = 6) after resuscitation. PH72 rats were historic controls for the CN72 rats, whereas PH6 and CN6 rats were randomized and studied contemporaneously.**

Measurements: **A clinical neurodeficit score (NDS) was determined daily. A pathologist blinded to group scored 40 hematoxylin and eosin -stained brain regions for damage by using a 5-point scale (0 = none, 5 = severe). Quantitative analysis of CA1 hippocampus injury was performed by counting normal-appearing neurons in a defined subsection of CA1.**

Main Results: **Mean rectal temperatures measured in the PH6wk rats (n = 6) were 36.9, 34.8, 35.5, 36.7, and 37.4°C at 2, 8, 12, 24, and 36 hrs, respectively. Mortality rate (before termination) was lower in PH compared with CN (0/20 vs. 7/15; $p < .005$). PH demonstrated a more favorable progression of NDS ($p = .04$) and less weight loss ($p < .005$) compared with CN. Median histopathology scores were lower (less damage) in PH72hr vs. CN72hr for temporal cortex (0 vs. 2.5), parietal cortex (0 vs. 2), thalamus (0 vs. 3), CA1 hippocampus (1.5 vs. 4.5), CA2 hippocampus (0 vs. 3.5), subiculum (0 vs. 4), and cerebellar Purkinje cell layer (2 vs. 4) (all $p < .05$). There was almost complete loss of normal-appearing CA1 neurons in CN72hr rats (6 ± 2 [mean ± SD] normal neurons compared with 109 ± 12 in naïve controls). In contrast, PH72hr rats demonstrated marked protection (97 ± 23 normal-appearing neurons) that was still evident, although attenuated, at 6 wks (42 ± 24 normal-appearing neurons, PH6wk).**

Conclusion: **Rats resuscitated from asphyxial cardiac arrest develop delayed, mild to moderate, prolonged hypothermia that is neuroprotective. (Crit Care Med 2000; 28:3511–3516)**

KEY WORDS: cerebral ischemia; temperature; hypothermia; rat; cardiac arrest; postischemic hypothermia; resuscitation; neuronal damage; cardiopulmonary resuscitation; neuroprotection

Asphyxia is the most common mechanism of cardiac arrest in patients who suffer arrest secondary to coma caused by severe head injury, drowning, foreign body obstruction, or intoxication (1). Asphyxia is particularly relevant to the pediatric population, in which 75% of cardiac arrests are respiratory in origin. Asphyxial cardiac arrest differs from other models of brain injury in several important respects. Compared with traditional cerebral arterial occlusion models of forebrain ischemia, cardiac arrest completely stops blood flow to the entire organism, producing a concurrent insult to the hindbrain and the development of extracerebral multisystem dysfunction (postresuscitation syndrome). The qualitative differences in the injuries are best demonstrated by the observation that rats are moribund for the first 24–48 hrs after asphyxial arrest compared with a relatively rapid recovery (within 1–2 hrs) for rats subjected to transient forebrain ischemia by vascular occlusion. Another important feature of asphyxial cardiac arrest is the progression from incomplete ischemia to complete ischemia before cardiovascular collapse. Compared with sudden complete ischemia, as occurs with ventricular fibrillation, asphyxial arrest produces lower tissue pH, higher tissue Pco_2, greater parenchymal damage, and increased disruption of the blood-brain barrier (2–4). The result is a different and more severe pattern of central nervous injury in asphyxial arrest compared with the other oxygen deprivation states (4–6).

Asphyxial cardiac arrest in rats is an established model for the investigation of brain injury after cardiac arrest (7–11). During work with this model, we serendipitously observed that rats spontaneously developed hypothermia after the injury. Recognizing that hypothermia can be neuroprotective (11–13), we performed the two experiments described in this article. The initial experiment examined the effects of eliminating spontaneous hypothermia. In this experiment, the

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elimination of spontaneous hypothermia markedly worsened neurologic outcome at 72 hrs compared with historical controls managed with permissive hypothermia. We then prospectively confirmed and characterized the depth and duration of the hypothermia that occurs spontaneously after resuscitation and demonstrated that permissive hypothermia resulted in long-term (6 wks) neurologic protection.

MATERIALS AND METHODS

The protocol was approved by the Institutional Animal Care and Use Committee at the University of Pittsburgh School of Medicine. The model was described previously in detail (7).

Male Sprague-Dawley rats (Harlan, Indianapolis, IN) weighing approximately 350 g were housed ≥5 days on a 12-hr diurnal schedule and were allowed food and water *ad libitum* before the insult. Anesthesia was achieved by using halothane and N_2O/oxygen. Animals were intubated with a 14-gauge angiocatheter and were ventilated with a Harvard Rodent Ventilator (Harvard Apparatus, Holliston, MA). After intubation, an intraperitoneal injection of vecuronium (2 mg/kg) was administered. The left femoral artery and vein were cannulated. The ventilator was adjusted to maintain a $Paco_2$ of 30–45 torr (4–6 kPa) and a pH of 7.32–7.50. Temperature was measured via a tympanic probe and was maintained at 37°C ± 0.5°C throughout the preparation, insult, and first hour of recovery. Before asphyxia, the anesthetic gases were washed out with 3 mins of ventilation with 100% oxygen followed by 2 mins of room air. At the beginning of the washout period and 4 mins later, 1-mg/kg doses of vecuronium were administered. Vecuronium was administered before asphyxia to prevent reflex respiratory efforts during asphyxia. However, previous experience with this model demonstrates that when rats are asphyxiated without paralysis, they remain anesthetized and do not struggle during asphyxia (14). After the washout period, animals were asphyxiated by disconnecting the respiratory tubing from the ventilator for a duration of 8 mins (resulting in approximately 5.5 mins of cardiac arrest). Rats were resuscitated with resumed ventilation (100% oxygen), chest compressions, epinephrine (0.005 mg/kg iv), and sodium bicarbonate (1 mEq/kg iv).

Rats were weaned from the ventilator at 1 hr after resuscitation and were returned to either their housing in a temperature-regulated room maintained at 23.3°C (permissive hypothermia condition, in which rats killed after 72 hrs were labeled PH72hr, n = 14, and rats killed after 6 wks were labeled PH6wk, n = 6) or a servo-controlled incubator (Narco C86 infant isolette, Warminster PA) set to maintain rectal temperature at 37.4 ± 0.5°C (controlled normothermia condition, CN72hr, n = 9, CN6wk, n = 6). CN rats were housed in the incubators for 48 hrs, after which time they were removed and placed into their previous housing. Rats were given D5 isotonic saline (20 mL/kg) subcutaneously each day until they were feeding and drinking without assistance.

A neurologic deficit score (NDS) was determined daily, as described previously (7). The score includes an assessment of consciousness, respiration, cranial nerves, motor and sensory function, and coordination. Normal rats have an NDS of zero. Daily weights were quantified in each rat.

Rats were killed with halothane anesthesia and were perfused with 3% paraformaldehyde. Brains were removed and fixed in paraformaldehyde for ≥24 hrs before being imbedded in paraffin and sliced into 6-μ sections for hematoxylin and eosin staining. All brains were examined by a pathologist who was blinded to group. Damage was scored in 40 brain regions by using a 5-point ordinal scale (0 = none, 1 = minimal, 2 = mild, 3 = moderate, 4 = marked, and 5 = severe). The semiquantitative scores reflect the approximate number of neurons manifesting ischemic changes in the population examined (1 = <5%, 2 = 6% to 20%, 3 = 21% to 50%, 4 = 51% to 75%; 5 = 76% to 100%). Quantitative analysis of a subsection of neurons in CA1 hippocampus was performed by counting the number of normal-appearing neurons in a 20× field directly superior to the lateral blade of the dentate. Counts were performed by two blinded observers who used color photomicrographs.

Data were entered into SPSS (Version 7.5 for Windows; SPSS, Chicago, IL) for statistical analysis. Survival was analyzed by using the Fisher exact probability test. Continuous data, including initial weight, temperature, glucose, hematocrit, pH, and Pco_2, were analyzed by Student's *t*-test. The Huynh-Feldt repeated measures analysis of variance was applied to the serial measurements of weight and neurodeficit score. This was used because of the scales of measurement of the outcomes and the violation of the assumptions necessary for the parametric test. The ordinal rankings of histologic damage were analyzed with both the Mann-Whitney U test for continuous and the Fisher exact test for categorical outcomes. All reported *p* values are two-tailed.

RESULTS

Three of nine CN72hr and four of six CN6wk rats died before termination, whereas none of the 20 PH rats died ($p < .005$ Fisher exact test). Although necropsies were performed on all of these rats, the causes of death remain unclear. Baseline physiologic values are presented in Table 1. The mean baseline hematocrit for CN rats was statistically higher than that in PH rats. However, hematocrit was in a normal range in all rats, and the small difference (1.7%) is unlikely to be clinically significant. The time to arrest (defined as the duration from initiation of asphyxia to a mean arterial pressure of <10 mm Hg without evidence of pulsations) was ~2.5 mins, resulting in a total arrest time (no flow) of 5.5 mins.

The characteristics of rectal temperature changes occurring during the first 48 hrs for rats managed with PH were obtained from the six PH6wk rats and are depicted in Figure 1. All rats developed hypothermia, but the degree and duration of hypothermia varied somewhat between animals. Rectal temperature remained >37°C for the first hour after asphyxia but by 3 hrs had decreased to <36°C. In all but one rat, rectal temperature recovered to 37°C by 24 hrs after the insult. The measured rectal temperature of CN rats (37.6°C ± 0.6°C) closely approximated the protocol target temperature (37.4°C ± 0.5°C).

Daily weights and NDS for PH and CN rats are presented in Table 2. Because

Table 1. Preinsult physiologic values

	Permissive Hypothermia (n = 20)	Controlled Normothermia (n = 15)	*p* Value
Weight (g)	373 ± 26	365 ± 20	.35
Temperature (°C)	37.4 ± 0.19	37.4 ± 0.16	.23
Glucose (mg/dL)	150 ± 36	150 ± 18	.99
Hematocrit	37.5 ± 1.7	39.2 ± 1.4	.004
pH	7.41 ± 0.04	7.42 ± 0.04	.5
Pco_2 (torr)	38.5 ± 3.2	37.3 ± 3.6	.3
Time to arrest (secs)	167 ± 27	164 ± 22	.71
Cardiopulmonary resuscitation time (secs)	31.3 ± 5.5	31.1 ± 5.5	.91

To convert torr to kPa, multiply the value by 0.1333.

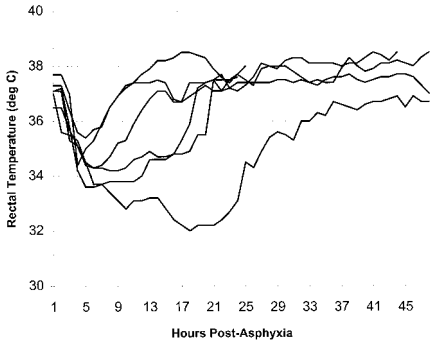

Figure 1. Rectal temperature of permissive hypothermia rats killed after 6 wks (n = 6).

Table 2. Neurodeficit scores (NDS) and weights

	Permissive Hypothermia (n = 20)	Controlled Normothermia (n = 15)
NDS		
24 hrs postinjury	37 ± 10	47 ± 7
48 hrs postinjury	20 ± 12	33 ± 11
72 hrs postinjury	9 ± 7	30 ± 19
Weight (g)		
Preinjury	373 ± 26	365 ± 20
24 hrs postinjury	343 ± 28	326 ± 21
48 hrs postinjury	329 ± 28	306 ± 19
72 hrs postinjury	322 ± 28	293 ± 19

both distributions violated the assumption of sphericity (Mauchly's test of sphericity $p < .05$), we performed the Huynh-Feldt repeated measures analysis of variance. The analysis revealed a significant group effect on the change in NDS over time ($p = .04$). Similarly, there was a significant group effect on the change in weight over time ($p = .006$). The greater weight loss and higher (worse) NDS in CN vs. PH rats are consistent with the greater degree of neuronal injury, as shown subsequently.

Structures exhibiting injury in one or more rats (from either CN72hr or PH72hr groups) include the cortex (piriform, frontal, entorhinal, cingulate, retrosplenial, parietal, temporal, and occipital), caudoputamen, septal nuclei, subiculum, hippocampus (CA1, CA2, CA3), dentate gyrus, indusium griseum, lateral reticular nucleus, thalamus, midbrain, cerebellar cortex, pons, vestibular nucleus, and medulla oblongata. This distribution is similar to that published by other investigators examining histopathologic damage after asphyxial cardiac arrest (4, 7, 9). Histologic damage was scored on a 6-point scale and analyzed with the Mann-Whitney U test. The analysis revealed that for 14 of the 24 brain regions with injury, there was a statistically significant difference between groups (Mann-Whitney U test, all $p < .05$). However, the entire range of ordinal values was not used, which resulted in a high percentage of ties. Given this, the scoring was collapsed into none to minimal injury vs. mild to severe injury, and a Fisher exact test was performed. Four of the 14 regions did not reach statistical significance with the Fisher exact test (frontal lobe cortex = 0.08, CA1 = 0.05, dentate = 0.06, cerebellum = 1.0), whereas the remaining regions had $p < .05$. Data for all 14 regions are presented in Figure 2. For each region, the injury was more severe in CN72hr. Regions that have been demonstrated, in a variety of models, to be particularly vulnerable to ischemic brain injury (CA1 hippocampus, lateral reticular nucleus, and cerebellar Purkinje cells) were the most severely injured. Structures without injury included the globus pallidus, amygdala, olfactory bulb, hypothalamus, and substantia nigra. No injury was seen in any white matter tracts. The numbers of normal-appearing neurons in the selected region of CA1 hippocampus in all groups are presented in Figure 3. Spontaneous hypothermia resulted in marked protection of CA1 at 72 hrs that was still evident, although attenuated, at 6 wks.

The high mortality rate in CN rats and absence of mortality in PH rats influence the comparisons between groups. Because CN rats with the most severe injuries were more likely to die, the outcome measures in the remaining CN rats may be inflated. Therefore, comparisons of NDS, weight, and histopathology are biased against the PH groups. Even with this disadvantage, PH resulted in significant improvements in all three of these outcome measures.

DISCUSSION

The results of this study demonstrate that rats develop spontaneous, mild to moderate hypothermia of variable onset and duration after asphyxial cardiac arrest. To our knowledge, this is the first study to document delayed, prolonged, spontaneously occurring hypothermia in an animal model of cardiac arrest. Furthermore, although the hypothermia was delayed and was at most moderate in degree, it significantly decreased both mortality rate and brain injury as assessed by neurologic deficit score and histology at 72 hrs after resuscitation. Neuroprotection was attenuated but still evident when evaluated 6 wks after the insult. These data in the rat model of asphyxial cardiac arrest, when taken in context with a growing body of evidence supporting a beneficial affect of hypothermia on neurologic injury, suggest that postresuscitative hypothermia is a potential treatment strategy after asphyxial arrest.

We chose to examine rectal temperature in this series of experiments. However, some investigators advocate direct measurement of parenchymal brain temperature because brain and body temperature can become dissociated after brain injury and therapeutic interventions might differentially affect brain and body temperature (15). Measurement of brain temperature is not performed routinely in clinical settings, and invasive measurement of brain temperature in the laboratory often requires additional exposure to anesthetics and results in local tissue stress and injury. In support of our decision to examine rectal temperature, we performed separate experiments to compare brain temperature with rectal and tympanic membrane temperature in 22 rats recovering from asphyxial arrest and found the mean difference to range from 0.01 to 0.40 over time with 95% confidence intervals for the mean difference ranging from 0.01 to 0.6. It is possible that asphyxial arrest is less likely to result in an uncoupling of brain and body temperature compared with models of isolated brain injury because asphyxia injures the entire organism. Therefore, perturbations that might affect local temperature, such as changes in metabolism, blood flow, inflammatory cascades, and so forth, are likely to occur in both brain and body.

It is difficult to continuously measure rectal temperature on awake naïve rats to determine the range of normothermic rectal temperature. Obtaining even inter-

Area	No Injury	Injury Minimal	Injury Mild	Injury Moderate	Injury Marked	Injury Severe	Mann-Whitney U Test P Value
Frontal Cortex	○○○○○○○ ●● ○○○○○○	○ ●●		●	●		.03
Parietal Cortex	○○○○○○○ ○○○○○○○	●	●●●	●	●		<.01
Temporal Cortex	○○○○○○○ ○○○○○○	○ ●	●●	●●	●		<.01
Occipital Cortex	○○○○○○○ ● ○○○○○○○		●	●●●	●		<.01
Subiculum	○○○○○○○ ○○○○	○	○○		●●● ●●●		<.01
Hippocampus CA 1	○○○○	○○○	○○○○○○		○ ●●●	●●●	<.01
Hippocampus CA 2	○○○○○○○ ○○○○○	○○	●	●●	●●	●	<.01
Hippocampus CA 3	○○○○○○○ ●● ○○○	○○○○	●	●●		●	.05
Dentate Gyrus	○○○○○○○ ●● ○○○○○○	●	○ ●●	●			.04
Lateral Reticular Nucleus	○○○○○○○ ○○○○	○○	○	●●●	●●	●	<.01
Thalamus	○○○○○○○ ○○○○○○○		●	●●● ●●			<.01
Midbrain	○○○○○○○ ●● ○○○○○○○		●●●	●			.02
Cerebellar Cortex		○○	○○○○○○○ ○	○	○○○ ●●● ●●	●	<.01
Medulla Oblongata	○○○○○○○ ● ○○○○○○○		●●● ●	●			<.01

Figure 2. Data for 14 brain regions with injury in which there was a statistically significant difference between groups. *Open circles*, rats in permissive hypothermia group killed after 72 hrs; *solid circles*, rats in controlled normothermia group killed after 72 hrs.

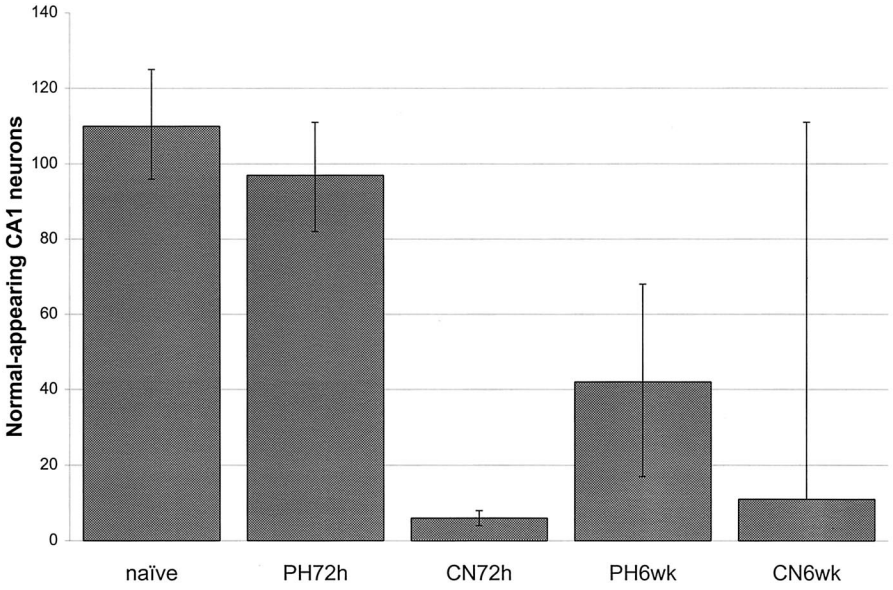

Figure 3. Mean counts of normal-appearing CA1 neurons. *Error bars* represent the 95% confidence intervals. *PH72h*, rats in permissive hypothermia group killed after 72 hrs; *CN72h*, rats in controlled normothermia group killed after 72 hrs; *PH6wk*, rats in permissive hypothermia group killed after 6 wks; *CN6wk*, rats in controlled normothermia group killed after 6 wks.

This study reinforces the importance of monitoring and/or controlling postinjury temperature in animal models of brain injury. The results complement the growing body of evidence supporting resuscitative hypothermia as a treatment strategy after cardiac arrest and suggest that even delayed application of mild to moderate hypothermia can be beneficial.

mittent rectal temperature recordings can be stressful and not well tolerated. However, we have recently accumulated continuous radiofrequency telemetry data (Minimitter, Sunriver, OR) by using indwelling, intraperitoneal, temperature probes in naïve and asphyxiated rats. Intraperitoneal temperature correlates well with rectal temperature (difference <0.5°C) and fluctuates in naïve rats between 36.7°C and 38.0°C with a mean of 37.8°C. Therefore, the rectal target temperature of 37.4°C, chosen as the target temperature for CN rats, is within the limits of normothermia.

A limitation of this study is that the PH72hr group was a historic control. However, the controlled normothermia group killed at 72 hrs (CN72hr) was run simultaneously with several other groups not included in the article (data available on request). The purpose of these groups was to explore methods for increasing the severity of neurologic injury in the model. The additional groups were managed with the same temperature protocol used for historic controls (permissive hypothermia) plus modifications intended to increase neurologic injury. Specifically, we eliminated the sodium bicarbonate in the resuscitation ($n = 5$), extended the asphyxia time to 8.5 mins ($n = 2$), and extended the sacrifice time to 5 days ($n = 2$). In each of these nine rats managed with permissive hypothermia plus an intervention designed to increase injury, the amount of injury was markedly less than that seen in the concurrently run CN72hr rats. Therefore, contemporaneous experiments confirm the robust protection afforded by permissive hypothermia. Although the model has been used in the Safar Center for Resuscitation Research for >10 yrs, all of the PH72hr and CN72hr experiments described in this article (including "historic" controls) were performed by the same technician over an interval of nine sequential months. We have recently acquired a computer-based, radiofrequency, telemetry system (Minimitter) that allows continuous acquisition and manipulation (via heating and cooling devices) of core (intraperitoneal) body temperature. Experiments with this device have reaffirmed the occurrence of spontaneous hy-

pothermia and the association between active warming and increased mortality rate and neurologic injury. Finally, the pathologist was blinded throughout to the experimental design. It is thus unlikely that unrecognized variables changed over time and contaminated the experiment. This is substantiated by the prospectively collected data demonstrating increased mortality and injury in the CN6wk group compared with the concurrent PH6wk group.

The results of this experiment complement a growing body of literature demonstrating a neuroprotective effect of hypothermia in a variety of circumstances. Interest in hypothermia as a treatment modality for brain injury was rekindled in the late 1980s and early 1990s, when experiments performed in carefully controlled rodent models of brain ischemia (using cerebral vascular occlusion techniques) (16, 17) and dog experiments of cardiac arrest (18) demonstrated that even mild intraischemic hypothermia could be neuroprotective. These reports were immediately followed by studies demonstrating the effectiveness of resuscitative (postischemic) hypothermia in dog cardiac arrest models (19–23) and rodent incomplete forebrain ischemia models (24–28). These latter studies were encouraging for two reasons: First, the hypothermia was mild and therefore unlikely to cause physiologic derangements, and second, the protection was remarkably robust. Favorable results also have been documented in cardiac arrest models using cats (29) and rats (11, 30, 31). Our study adds to the literature by documenting spontaneous development of hypothermia after cardiac arrest which, if permitted (left untreated), is neuroprotective.

There appears to be a window within which resuscitative hypothermia will be most effective. Delay in initiating hypothermia (22, 26, 28) and premature cessation of hypothermia (25) both have been demonstrated to diminish its effectiveness. The parameters of the therapeutic window are likely to vary depending on the animal model used and the severity of the injury employed (24). Remarkably, in our model of rat asphyxial cardiac arrest, a neuroprotective effect of a spontaneously occurring hypothermia was observed even when hypothermia developed over several hours and was followed by a slow recovery to normothermia within 24–36 hrs.

In addition to a lack of benefit in scenarios where the injury is too severe or the hypothermia is not applied within the therapeutic window, it is possible that hypothermia could be harmful. Coagulopathy, life-threatening dysrythmias, impaired cardiac function, and (if prolonged) increased risk of infection all have been documented with moderate to profound hypothermia (<32°C) (32). In addition, hypothermia may prevent or delay important reparative processes such as production of neurotrophins (33). In our study, hypothermia developed spontaneously in a delayed manner and was mild to moderate in depth. It is possible that potentially deleterious effects of hypothermia were avoided with this approach, because cardiovascular function has recovered and is stable at 1–2 hrs after asphyxia, and mild to moderate hypothermia has not been demonstrated to have detrimental cardiovascular effects.

Another potential limitation of resuscitative hypothermia is that it may delay rather than prevent neuronal cell death. Dietrich et al. (34) found that resuscitative hypothermia of 30°C for 3 hrs after global brain ischemia in rats protected CA1 hippocampal cells at 3 and 7 days postischemia. However, 2 months after the injury, the hypothermia-treated rats had the same amount of CA1 cell loss as normothermic controls. In contrast, Colbourne et al. (25, 27) demonstrated long-lasting protection (functional and histologic outcomes out to 6 months) in gerbils treated with resuscitative hypothermia (32°C) when the duration of hypothermia was extended from 12 to 24 hrs and in rats kept 32°C to 34°C for 48 hrs (histopathology at 28 days) (35). In our model, permissive hypothermia merely delayed the evolution of death for some neurons, whereas for other neurons the benefit was long lasting. The discordance between these studies suggests that the degree and duration of hypothermic protection may be importantly influenced by the details of the hypothermia paradigm. Regardless, if a treatment modality merely delays the evolution of cell death, it may remain of value because it will extend the window of opportunity for other therapeutic modalities (36).

Clinical Relevance. The spontaneous hypothermia after cardiac arrest observed in this study also has been described in adult humans after cardiac arrest (37). We recently documented the occurrence of spontaneous mild to moderate hypothermia in more than half of a cohort of children resuscitated from cardiac arrest (38). More importantly, all the hypothermic children were treated with the application of heating lamps. The evidence from our asphyxial arrest model (and other models of brain injury) suggests that the clinical practice of actively warming patients who are tolerating mild to moderate hypothermia may worsen brain injury.

The ability to safely cool brain-injured patients and to improve neurologic outcome recently was demonstrated by Marion et al. (39) in a randomized, controlled trial comparing the effects of moderate hypothermia (32°C to 33°C for 24 hrs) to normothermia in 82 patients with severe closed head injuries. Simultaneously, Holzer et al. (40) in Vienna and Bernard et al. (41) in Australia published their preliminary experiences in treating adult victims of prehospital cardiac arrest with resuscitative hypothermia. Holzer et al. (40) treated 27 patients at 33°C for 24 hrs after cardiac arrest and demonstrated an increase in the number of patients achieving good neurologic outcome (52% of treated patients vs. 27% of historical controls). Bernard et al. (41) treated 22 patients and found improved neurologic outcome (11 of 22 treated patients vs. 3 of 22 historical controls achieved good neurologic outcome) and decreased mortality rate (10 of 22 treated vs. 17 of 22 control patients died). There is now an ongoing randomized, European multicenter trial of resuscitative hypothermia after cardiac arrest with an anticipated enrollment of 500 patients. Our data support a potential value of mild or moderate hypothermia in asphyxial arrest, even when it is spontaneous and delayed.

CONCLUSIONS

We have documented significant neuroprotection as a result of postresuscitative hypothermia in a model of asphyxial cardiac arrest in rats. To the best of our knowledge, this is the first study to document spontaneously occurring hypothermia in an animal model of cardiac arrest. Notwithstanding the delayed onset and variable duration, the hypothermia was markedly protective. This study reinforces the importance of monitoring and/or controlling postinjury temperature in animal models of brain injury. The results complement the growing body of evidence supporting resuscitative hypothermia as a treatment strategy after cardiac arrest and suggest that even delayed application of mild to moderate hypothermia can be beneficial. Until clinical trials are completed, it seems prudent to avoid attempts at correcting spontaneous, mild hypothermia in hemodynamically stable patients after asphyxial arrest. Rather, hemodynamically stable patients should be managed with permissive hypothermia.

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