HOSPITAL CHRONICLES 2010, 5(3): 138–145

REVIEW

Advances in Post-Resuscitation Care: the Role of Therapeutic Hypothermia

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KEY WORDS: *hypothermia; therapeutic hypothermia; cardiac arrest; cooling; resuscitation*

ABBREVIATIONS
PCI = percutaneous coronary intervention
PEA = pulseless electrical activity
ROSC = restoration of spontaneous circulation
STEMI = ST-elevation myocardial infarction
TH = therapeutic hypothermia
VF = ventricular fibrillation

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Manuscript received February 28, 2010; Revised manuscript received May 24, 2010; Accepted June 11, 2010

ABSTRACT

Therapeutic hypothermia (32˚C-34˚C) is the only therapy that improved neurological outcome after cardiac arrest in randomized, controlled trials. It protects the brain after ischemia by reduction of brain metabolism, attenuation of reactive oxygen species formation, inhibition of excitatory amino acid release, attenuation of the immune response during reperfusion and inhibition of apoptosis. Its use is recommended by the American Heart Association and the International Liaison Committee on Resuscitation in unconscious adult patients for 12 to 24 hours following resuscitation from out-of-hospital ventricular fibrillation cardiac arrest. The role of therapeutic hypothermia is uncertain when the initial cardiac rhythm is asystole or pulseless electrical activity, or when the cardiac arrest is primarily due to a noncardiac cause such as asphyxia or drug overdose. The possible neuroprotective effect of hypothermia following resuscitation from non ventricular fibrillation cardiac arrest needs to be balanced against the associated cardiovascular, coagulation, immune, and electrolyte disturbances. Mild hypothermia is generally a safe and effective therapy after cardiac arrest, even in hemodynamically compromised patients and in patients undergoing percutaneous coronary intervention. Because the induction of therapeutic hypothermia has become more feasible with the development of simple intravenous cooling techniques and specialized equipment for improved temperature control in the intensive care unit, it is expected that therapeutic hypothermia will become more widely used in the management of anoxic neurological injury whatever the presenting cardiac rhythm.

THE CLINICAL PROBLEM

About 450,000 Americans have cardiac arrest annually.[1] About 80% of cardiac arrests occur at home, for which the rate of death is at least 90%.[1,2] More than half the survivors have permanent brain damage of varying degrees.[3,4] In–hospital arrests have better outcomes than those that occur outside the hospital, with restoration of circulation exceeding 50% and survival to hospital discharge reaching approximately 20%.[5,6]

Cardiac arrest causes immediate cessation of cerebral blood flow and the subsequent oxygen deprivation leads to neurological ischemic injury after several minutes. If resuscitation results in restoration of spontaneous circulation (ROSC), an additional reperfusion injury occurs. The causes of the anoxia and reperfusion injury are complex and multifactorial but largely relate to metabolic disturbances that exacerbate cellular injury.[7-18] Permanent neurological injury occurs after 5 to 10 minutes of complete ces-

sation of cerebral blood flow at normothermia. There has been considerable research into treatments that may ameliorate this anoxic neurological injury. Although a number of drugs that inhibit the metabolic disturbances have produced encouraging results in animal models,[11-17] their clinical efficacy still remains to be shown. At present, the only treatment with both laboratory and clinical supportive data in this setting is therapeutic hypothermia.[11,12,18,19]

THE ROLE OF HYPOTHERMIA, MECHANISMS OF NEUROPROTECTION

Therapeutic hypothermia (TH) is defined as the controlled lowering of core body temperature to 32˚C to 34˚C.[20] This temperature goal represents the optimal balance between clinical effect and cardiovascular toxicity. In addition this temperature spectrum provides easier clinical management of shivering, one of the more severe complications of hypothermia, which may require substantial amounts of sedation or neuromuscular blockade to be suppressed.[18] Cardiac arrhythmias generally occur at 31˚C (e.g. slow atrial fibrillation), whereas at 28˚C, spontaneous ventricular fibrillation (VF) may ensue.

Protective mechanisms of hypothermia include reduction of brain metabolism (metabolism is reduced by 5% to 8% per degree Celsius reduction of core temperature), attenuation of reactive oxygen species formation, inhibition of excitatory amino acid release, attenuation of the immune response during reperfusion, inhibition of apoptosis, and modulation of nuclear factor kappa B expression.[21,22]

COOLING METHODS

One of the major barriers in the past to the extension of TH has been the feasibility of this treatment. Nowadays numerous cooling methods are available, differing greatly in effectiveness, controllability, invasiveness, and cost. Surface cooling devices are noninvasive and include simple ice packs, alcohol bathing, convective air blankets, and heat exchanger or water matresses.[21,23-25] Ice packs applied to head, neck, torso, and extremities of the patient provide a relatively slow cooling rate of 0.9˚C per hour.[26] Although this technique is inexpensive, the application of ice packs is cumbersome.[21] Invasive cooling methods include the administration of ice-cold fluids intravenously, intravascular cooling catheters, body cavity lavage, extracorporeal circuits, and selective brain cooling.[21,27-31] The infusion of ice-cold fluids has the advantages of low price and ubiquitous availability, but require large infusion volumes. [21] Factors that might influence the effectiveness of cooling with cold fluids are infusion speed and muscle relaxation. The use of an endovascular cooling catheter is limited to the hospital setting. The heat exchanger mattress and endovascular cooling catheters are also expensive, and the latter require insertion by a physician with additional training. Continuous temperature monitoring in patients receiving therapeutic hypothermia is as important as monitoring of arterial blood pressure during vasopressor therapy.[25,26] Passive and slow rewarming is also recommendable.[25] For the intensive care setting, we would recommend the endovascular cooling catheter technique,[21,27] in conjunction with continuous monitor display of bladder temperature.[25] Cooling catheters can achieve whole body cooling rates of 1.5 ˚C per hour. Based on prior randomized controlled trial results,[25] we would suggest maintenance of bladder temperature within 32˚C to 34˚C for at least 24 hours, followed by a passive rewarming period of at least 12 hours. For the emergency department, operating room, and/or hospital ward setting, we would suggest the placement of ice packs around the head, neck, torso, and limbs.[26] This would enable the rapid initiation of cooling until the placement of the cooling catheter in the intensive care unit.

CLINICAL DATA

Therapeutic hypothermia has been in use for centuries.[32] In Figure 1, the so-called "Russian Method of Resuscitation" (1803) consisted of burying the victim of a cardiac arrest in snow[33] (Figure 1).

More than two hundred years later (2005 guidelines), the American Heart Association and the European Resuscitation Council recommended the implementation of mild hypothermia in the post cardiac arrest treatment algorithm of patients

(12-24 hours following resuscitation), when the first documented rhythm was VF or pulseless ventricular tachycardia, and state that hypothermia should be considered for the treatment of non-VF rhythms as well.[34,35] The 2005 guidelines were based on two pivotal randomized, controlled trials.[25,26] The first of these pivotal studies was a large, multicenter randomized, controlled trial that enrolled 275 patients in 9 European hospitals.[25] Patients who were resuscitated from cardiac arrest with an initial cardiac rhythm of VF and transported to the hospital were eligible for participation to the study. Patients allocated to therapeutic hypothermia were cooled after arrival at the hospital using a mattress delivering cold air over the entire body, and cooling from 32˚C to 34˚C was maintained for 24 hours, followed by slow rewarming over 12 hours. In the therapeutic hypothermia group, 75 of 136 patients (55%) had a favorable neurological outcome (i.e. Pittsburgh Cerebral Performance Category 1 or 2), as compared with 54 of 137 (39%) in the normothermia group (P=0.009). Mortality at 6 months was 41% in the hypothermia group compared with 55% in the normothermia group (P=0.02). The complications did not differ significantly between the two groups. Importantly, this trial excluded patients with a presenting rhythm other than VF, older patients (age 75 yrs or more), patients with hypotension (mean arterial pressure 60 mm Hg for more than 30 minutes after ROSC), and patients with hypoxia (arterial oxygen saturation 85% for 15 minutes after ROSC). The second randomized trial was conducted in 4 hospitals in Victoria, Australia.[26] There were 77 patients allocated to either hypothermia (33˚C for 12 hours) or normothermia. The primary outcome measure was survival to hospital discharge with sufficiently good neurological function to be sent home or to a rehabilitation facility. Twenty-one of the 43 patients treated with hypothermia (49%) had a favorable outcome compared with 9 of the 34 (26%) treated with normothermia. After adjustment for small baseline differences in age and time from collapse to the ROSC, the odds ratio for a good outcome with hypothermia as compared with normothermia was 5.25 (95% confidence interval=1.47-18.76; P=0.011). This study also enrolled only patients with VF as the presenting cardiac rhythm and stable hemodynamics, but did not exclude older patients or those with hypoxia.

Sagalyn et al,[36] reviewed findings from recent literature on the post-resuscitation care of cardiac arrest patients having undergone therapeutic hypothermia as part of non-trial treatment. An electronic search of the literature (PubMed; National Library of Medicine, Washington, DC) was conducted to identify potential reports of therapeutic hypothermia after cardiac arrest. The search was conducted in November 2007 and included papers in all languages. Studies were considered for analysis if they evaluated adult victims of sudden cardiac arrest (>18 years old), if they were not randomized controlled trials, and if they were published after 2002, i.e. the year of publication of the Bernard[26] and HACA group[25] trials. Studies with and without historical controls (non-hypothermia subjects) were included. All studies with historical controls included comparisons of survival (Table 1) and of survival with good neurological outcome (Table 2) between the former and therapeutic hypothermia-treated patients. Confirming the rate of survival improvement reported by the randomized trials, the odds ratio reported in each study reflects the marked mortality benefit of therapeutic hypothermia, as well as the associated improvement in neurological recovery. Summary odds ratios are shown at the bottom lines of Tables 1 and 2 and demonstrate an approximately two- to three-fold improvement in both survival and good neurological recovery when therapeutic hypothermia was applied. The survival and favorable neurological outcome data for the studies that did not include historical controls are shown in Table 3. Despite this limitation, it is noteworthy that the overall survival to hospital discharge was 59%, which is similar to the 65% overall survival of the controlled studies cited in Table 1. In addition, the percentage of favorable neurological outcome in the stud-

TABLE 1. Survival in study subset with historical controls[36]

Author	n		Historical control	Therapeutic Hypothermia	OR	95% CI
	HC	TH	n (%)[a]	n (%)		
Arrich et al[37]	123	462	39 (32)	267 (58)	2. 9	1. 9-4. 6
Belliard et al[38]	36	32	13 (36)	18 (56)	2. 3	0. 8-6. 8
Busch et al[39]	34	27	11 (32)	16 (59)	3. 0	0. 9-9. 9
Oddo et al[40]	54	55	20 (37)	28 (51)	1. 8	0. 8-3. 8
Schefold et al[41]	31	31	21 (70)	21 (70)	1. 0	0. 3-2. 9
Sunde et al[42]	58	61	18 (31)	34 (56)	2. 8	1. 2-6. 4
Combined ORs					2. 5	1. 8-3. 3

HC, historical control (non-hypothermia) group; TH, therapeutic hypothermia group; OR, odds ratio; CI, confidence interval.
[a]All percentages rounded to nearest integer.

TABLE 2. Favorable outcomes in study subset with historical controls[36]

Author	n		Historical control n (%)[a]	Therapeutic Hypothermia n (%)	OR	95% CI
	HC	TH				
Arrich et al[37]	123	462	39 (32)	212 (46)	1. 8	1. 2-2. 8
Belliard et al[38]	36	32	6 (17)	13 (41)	3. 4	0. 99-12. 8
Busch et al[39]	34	27	9 (26)	11 (41)	1. 9	0. 6-6. 5
Oddo et al[40]	54	55	11 (20)	26 (47)	3. 5	1. 4-9. 1
Schefold et al[41]	31	31	6 (19)	19 (61)	6. 6	2. 1-20. 8
Sunde et al[42]	58	61	15 (26)	34 (56)	3. 6	1. 6-8. 5
Combined ORs					2. 5	1. 9-3. 4

HC, historical control (non-hypothermia) group; TH, therapeutic hypothermia group; OR, odds ratio; CI, confidence interval.
[a]All percentages rounded to nearest integer.
Favorable outcome is defined as Cerebral Performance Category at discharge of 1 or 2.

TABLE 3. Survival and favorable outcome in studies without historical controls[36]

Author	TH, n	Survival, n (%)[a]	Favorable Neurologic Outcome, n (%)
Al-Senani et al[43]	13	9 (69)	5 (38)
Feuchtl et al[44]	19	11 (58)	9 (47)
Haugk et al[45]	28	14 (50)	9 (32)
Hovdenes et al[46]	50	41 (82)	34 (68)
Kliegel et al[47]	26	14 (54)	13 (50)
Laish-Farkash et al[48]	51	32 (63)	31 (61)
Scott et al[49]	49	19 (39)	16 (33)

TH, therapeutic hypothermia.
[a]All percentages rounded to nearest integer.
Favorable neurologic outcome is defined as Cerebral Performance Category at discharge of 1 or 2.

ies without historical controls was 45%, again similar to the 47% of the controlled studies cited in Table 1.

NON-VF ARREST

Patients with an initial cardiac rhythm of asystole have a lower rate of survival than patients with VF, presumably because the longer period of cardiac arrest has caused VF to degenerate into asystole.[18] This longer cardiac arrest time would lead to a more severe neurological injury. Given this increased severity of neurological injury, the possible role of therapeutic hypothermia after non-VF arrest remains uncertain. There have been three clinical studies that provide data relevant to this patient group. In a pilot trial, Hachimi-Idrissi et al randomized 30 comatose patients to either therapeutic hypothermia or normothermia after non-VF arrest.[50] Hypothermia was induced with local surface cooling and was maintained for 4 hours. In the hypothermia group of 16 patients, 2 patients (13%) survived with favorable neurological recovery as compared to 0 of 14 (0%) in the normothermia group. This difference was not statistically significant. In a prehospital study, Kim et al,[51] randomized patients with out-of-hospital cardiac arrest to either paramedic cooling using a rapid intravenous bolus of 2 L of ice-cold saline or normothermia. Of 125 resuscitated patients, 74 had an initial cardiac rhythm of asystole or pulseless electrical activity (PEA). In the therapeutic hypothermia group, three of 34 patients (9%) recovered as compared to nine of 40 patients (23%) assigned to normothermia. In this study, numbers were also too small to draw any conclusion concerning the efficacy of therapeutic hypothermia.

In a third study, the results of the implementation of a protocol for therapeutic hypothermia in a Scottish hospital were reported.[52] There were 139 out-of-hospital cardiac arrest patients admitted over a 4-year period. Of these, 27% had a favorable outcome (discharged home or to rehabilitation). Of the favorable outcome patients, 41% were VF patients and only 7% were non-VF patients. Given such low rates of recovery after non-VF arrest (approximately 7%–12%), a prospective study comparing therapeutic hypothermia to normothermia in non-VF patients would require a very large number of patients to show any potentially improved outcomes. Therefore, in patients with anoxic brain injury after non-VF cardiac arrest, clinicians will need to balance the possible benefit of therapeutic hypothermia against the possible side effects of this therapy. However, the latter may be easily managed in the critical care setting.

PATIENTS WITH SHOCK FOLLOWING CARDIAC ARREST RESUSCITATION

Patients resuscitated from cardiac arrest often have hemodynamic instability due to the myocardial dysfunction that is present for some hours to days.[53] These data also suggest that therapeutic hypothermia may be successfully implemented when the post–cardiac arrest patient presents with cardiogenic shock, together with other standard therapeutic measures in this setting such as urgent coronary artery catheterization. However, there is currently insufficient data to confirm that this approach improves outcomes. Knafelj et al,[54] compared 40 patients with ST-segment elevation myocardial infarction (STEMI) undergoing percutaneous coronary intervention (PCI) with cooling after cardiac arrest to 32 patients undergoing PCI without cooling. Cooling was started before, during, or after PCI. Neurological outcome was better in the cooling group (55% favorable outcome vs only 16% of the non-cooling group; P=0.01), and the combination of therapeutic hypothermia and PCI proved to be safe and feasible. While most of the patients in this study were cooled after PCI,[54] Wolfrum et al,[55] induced hypothermia in 16 patients with STEMI after successful resuscitation but before PCI and compared them to 17 historical controls. The combination treatment proved to be safe and feasible and did not increase the "door-to- balloon" time. In another study,[40] five of 17 hypothermia-treated patients with postresuscitation shock survived with good neurological recovery, while all 14 normothermic controls died (P=0.027).

IN-HOSPITAL CARDIAC ARREST

In-hospital cardiac arrest generally has a different etiology compared with out-of-hospital cardiac arrest.[6,56,57] Whereas most out-of hospital cardiac arrest is due to underlying cardiac disease, in-hospital cardiac arrest (outside the emergency room or critical care unit) is generally due to causes such as respiratory failure, pulmonary embolism, electrolyte abnormalities, and/or severe sepsis.[6,56,57] In addition, after the cardiac arrest is recognized and the "blue code" called, cardiopulmonary resuscitation is undertaken and a medical team which provides advanced life support care arrives within less than 3-5 minutes.[6,57] Nevertheless, despite the rapid response, significant neurological injury may occur after resuscitation from in-hospital cardiac arrest. For example, in an observational study from the USA National Registry of Cardiopulmonary Resuscitation, there were 36,902 patients with in-hospital cardiac arrest and the rate of survival to hospital discharge was 18%.[57] Of the survivors, 27% had poor neurological outcome, presumably due to the anoxic neurological injury from prolonged, unrecognized cardiac arrest that occurred in a non-monitored area before recognition of cardiac arrest from the hospital staff. Our results on good neurological recovery rate were similar.[6] Given the feasibility and few side effects of therapeutic hypothermia, it would seem reasonable to systematically implement it following ROSC. In fact, in cases of prolonged cardiopulmonary resuscitation, consideration could be given to induction of hypothermia even before ROSC.

HYPOTHERMIA IN BRAIN INJURY AND STROKE

Several studies suggest that hypothermia or even controlled normothermia reduces brain edema and intracranial pressure in patients with traumatic brain injury.[58,59] By contrast, only a few small pilot studies have evaluated hypothermia as a treatment for acute ischemic stroke, and no controlled trials of hypothermia for hemorrhagic stroke have been performed.[60] Despite the fact that more outcome data are needed to recommend hypothermia for standard practice, there is a strong physiological rationale and ample experimental data supporting its use. The multiple neuroprotective mechanisms of hypothermia are summarized in Table 4.

SIDE EFFECTS OF HYPOTHERMIA

The possible side effects include shivering, changes in the immune system, electrolyte disturbances, coagulation abnormalities, cardiovascular side effects, alterations of drug metabolism. Shivering could counteract the beneficial effects of hypothermia by raising energy and oxygen demands. Therefore, muscle paralysis was used in the randomized controlled trials.[25,26] The detection of infections might be delayed because fever as an indicator of infection is suppressed by the hypothermia. Minor electrolyte changes that can be expected include hypernatremia, hypokalemia, hypomagnesemia, hypophosphatemia, and hypocalcemia. Hypothermia leads to bradycardia and a rise in systemic vascular resistance. The risk of arrhythmias (bradycardia necessitating pacemaker support, atrial fibrillation, or VF) rises with temperatures below 30°C but is very low at 33°C. Serious complications have not been

TABLE 4. Mechanisms of action by which hypothermia can limit ischemic damage.[60]

Reduced metabolic demand
Reduced proteolysis
Cell membrane stabilization
Inhibits spreading depolarizations
Decreased excitotoxic damage
Reduces lactate and tissue acidosis
Reduced free radical and reactive oxygen species formation
Alters apoptotic signals
Reduction in neuronal calcium influx and toxicity
Reduces ischemia-associated gene expression
Inhibits inflammation and cytokine production

observed to a significant extent in the major randomized trials.[25,26] Sagalyn et al[36] analyzed the reported adverse events and a relevant summary is provided in Table 5.

A limitation of the current literature is that the severity of the adverse events is rarely reported although it is of great relevance to practitioners; for example, in the study by Arrich et al,[37] 3% of therapeutic hypothermia patients had bleeding complications, but only 1% required treatment. Future studies will hopefully present more data on the adverse effects of hypothermia, and perhaps, on their effect on outcome. This might then result in the specification of (any) contraindications to hypothermia.

CONCLUSION

Therapeutic hypothermia is a safe and effective therapy after cardiac arrest and is recommended by the American Heart Association and the International Liaison Committee on Resuscitation for unconscious adult patients with spontaneous circulation after out-of-hospital VF cardiac arrest. It should also be considered for out-of-hospital cardiac arrest from a non-shockable rhythm or cardiac arrest in hospital. It is so far the only therapy that improved neurological outcome after cardiac arrest in randomized controlled trials. Hypothermia can be induced safely in hemodynamically compromised patients as well as in patients undergoing PCI. New technology for both surface and intravascular cooling has been developed that enables more rapid cooling and accurate temperature control. Future studies should provide more data on the adverse effects of therapeutic hypothermia, in order to improve the safety of the hypothermia protocols.

TABLE 5. Overview of adverse events[36]

Author	Group	n	Pneumonia (%)[a]	Sepsis (%)	Arrhythmia (%)	Bleeding (%)
Arrich et al[37]	TH	462	NR	NR	28 (6)	15 (3)
Busch et al[39]	TH	27	19 (70)	NR	7 (26)	NR
Busch et al[39]	HC	26	13 (50)	NR	9 (35)	NR
Laish-Farkash et al[48]	TH	51	27 (53)	12 (24)	5 (10)	8 (16)
Oddo et al[40]	TH	55	16 (29)	2 (4)	20 (36)	NR
Oddo et al[40]	HC	54	19 (35)	2 (4)	23 (43)	NR
Sunde et al[42]	TH	61	29 (47)	2 (8)	15 (25)	5 (8)
Sunde et al[42]	HC	58	33 (57)	1 (2)	9 (16)	NR
Total, TH	TH	656	91/194 (47)	16/167 (10)	75/656 (11)	28/574 (5)
Total, HC	HC	138	65/138 (47)	3/112 (3)	41/138 (30)	NA

TH, therapeutic hypothermia group; HC, historical control (non-hypothermia) group;
NR, not reported; NA, not applicable.
a, All percentages rounded to nearest integer.

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