

**Therapeutic Hypothermia
For
Cardiac Arrest:
What are we Waiting For?**

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Introduction

It is estimated that 240,000 out-of-hospital cardiac arrests (SCA) occur annually in the United States, 20-38% of which are ventricular fibrillation (VF) or ventricular tachycardia (VT).¹ Prognosis is poor, with a median survival to discharge from any rhythm is 6.4 %.² In Europe, it is estimated that 375,000 people a year suffer SCA.³ Those who do survive to discharge often suffer neurologic impairment due to anoxic brain injury suffered due to the cardiac arrest. One recent study calculates the neurologically intact survival rate after cardiac arrest to be as low as 1.4%.⁴ Few interventions since defibrillation have led to improvement in outcome after SCA.

After years of animal studies, in 2002 two prospective randomized controlled trials were published showing improved outcomes in both mortality and neurologic outcome in comatose survivors of out-of-hospital VF/VT cardiac arrest when treated with therapeutic hypothermia (TH).^{3,5} TH was then internationally recommended to improve outcomes in such patients. Since that time it's use has been increasing as current research continues to reinforce findings of the initial studies as well as explore techniques and further applications.

Prospective Randomized Controlled Trials

In 2002, two prospective randomized controlled trials investigating therapeutic hypothermia for the improvement of neurologic outcomes in comatose patients who suffered an out-of-hospital VF/pulselessVT cardiac arrest were published.

Treatment of Comatose Survivors of Out-of-Hospital Cardiac Arrest with Induced Hypothermia.

This study by Bernard et al. enrolled 77 patients who were brought to 4 Melbourne emergency departments with an initial out-of-hospital rhythm of VF, return of spontaneous circulation (ROSC), and persistent coma after ROSC. Patients were excluded for age <18, age <50 in women (due to risk of possible pregnancy), and cardiogenic shock defined as SBP<90 despite epinephrine. The patients were randomized to group by even or odd day on arrival which resulted in 43 patients in the hypothermia group and 34 patients in the normothermia group. Median age was 66.8 in the treatment group and 65 in the controls. Hypothermia was induced to a goal of 33°C for 12 hours. This was done by application of ice packs to head, neck, torso, and limbs, which was initiated by paramedics in the field and continued by emergency department and ICU staff. Midazolam and vecuronium were given to both groups after initial neurologic evaluation to prevent awareness, hivering and subsequent rewarming in the treatment group. Temperature was measured via bladder or tympanic membrane until a pulmonary-artery catheter was placed for more central measurement. At 18 hours the patients were actively rewarmed with a heated-air blanket. Sedation and neuromuscular blockade were continued throughout this process to prevent shivering. Neurologic outcome was assessed on day of discharge with discharge home or to a rehab facility considered a good outcome and discharge to an extended-stay nursing home or death considered to be poor outcomes. A good outcome was observed in 21 of 43 patients in the hypothermia group and 9 of 34 in the normothermia group (p=0.046). Patient's age and time to ROSC affected outcomes. For each 2 year increase in age, there was a 9% decrease in likelihood of good outcome (p=0.014). For each 1.5 minutes from time of

collapse to ROSC, there was a 14% decrease in likelihood of good outcome ($p=0.001$). Mortality at 30 days was also evaluated and a trend towards decreased mortality, which was not statistically significant, was noted with a mortality rate of 51% in the hypothermia group and 68% in the normothermia group ($p=0.145$). No clinically significant cardiac arrhythmias were identified. Increased glucose with hypothermia and increased potassium with rewarming were noted. The study concluded that TH improves outcomes in patients with ROSC after out-of-hospital VF cardiac arrest.⁵

Mild Therapeutic Hypothermia to Improve the Neurologic Outcome After Cardiac Arrest

This study by the HACA study group was larger, enrolling 275 patients at 9 centers throughout Europe who were non-responsive after an out-of-hospital VF/pulseless VT SCA with ROSC (HACA 2002).³ Though, it was later revealed that 10 patients in this study were resuscitated after in-hospital cardiac arrest.⁶ Patients were excluded for pregnancy, hypotension with MAP <60mmHg for more than 30 minutes, time to ROSC of > 60minutes, or >15 minutes to first attempt at resuscitation by EMS personnel. One hundred and thirty eight patients were randomized to the normothermia group and 137 were randomized to the hypothermia group. Median age was 59 in each group. Patients in both groups received medazolam and fentanyl for 32 hours and patients in the hypothermia group also received pancuronium every 2 hours for 32 hours to prevent shivering. Hypothermia was induced to a goal of 32-34°C for 24 hours. Temperature was measured via tympanic membrane or bladder catheter. A cold air mattress was used to achieve this temperature, though 93 patients also needed ice packs to achieve this goal and 19 patients never reached the goal. The patients were passively rewarmed to a goal of 36°C. Primary outcome was favorable neurologic outcome within 6 months, measured by Pittsburgh Cerebral Performance Category. Secondary outcome was complications during the first 7 days SCA. Seventy five of 136 (55%) patients in the hypothermia group had a favorable neurologic outcome versus 54 of 137 (39%) patients in the normothermia group ($p=0.009$) (Table 1). Number needed to treat was 6. Six month mortality was 41% in the hypothermia group and 55% in the normothermia group ($p=0.02$). Number needed to treat was 7. Complication rates were not statistically significant between the two groups, though there was a trend towards increased incidence of sepsis in the hypothermia group. The study concluded that TH could prevent unfavorable neurologic outcome in patients with out-of-hospital VF/VT cardiac arrest.³

Table 1. Neurologic Outcome and Mortality at Six Months

OUTCOME	NORMOTHERMIA no./total no. (%)	HYPOTHERMIA no./total no. (%)	RISK RATIO (95% CI)*	P VALUE†
Favorable neurologic outcome‡	54/137 (39)	75/136 (55)	1.40 (1.08–1.81)	0.009
Death	76/138 (55)	56/137 (41)	0.74 (0.58–0.95)	0.02

*The risk ratio was calculated as the rate of a favorable neurologic outcome or the rate of death in the hypothermia group divided by the rate in the normothermia group. CI denotes confidence interval.

†Two-sided P values are based on Pearson's chi-square tests.

‡A favorable neurologic outcome was defined as a cerebral-performance category of 1 (good recovery) or 2 (moderate disability). One patient in the normothermia group and one in the hypothermia group were lost to neurologic follow-up.

There are several notable differences between the two trials. The study by Bernard et al. excluded all females <50 years old due to risk of possible pregnancy while the study by the HACA group excluded women only if they were pregnant.^{4,5} This likely affected the median age which was approximately 10 years older in the study by Bernard et al. Age was noted to affect outcome in this study. This may have led to the slightly lower rates of favorable neurologic outcome as compared to the other study, 55% vs. 49%, as well as accounted for the lack of statistical significance of 30 day mortality in the Australian study. Also note that the study by the HACA group was much larger. The studies also used different methods of cooling, with the mattress used by the European group being ineffective in achieving goal temperature in the majority of cases. Also, hypothermia induction was sometimes started by EMS personnel in the Australian study as opposed to in the ED in the European study.^{4,5} As will be discussed later, decreased time to induction of hypothermia may improve outcomes.

In light of the significantly improved neurologic outcomes demonstrated by these two studies, in October 2002 the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation recommended that “unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32-34°C for 12-24 hours when the initial rhythm was ventricular fibrillation,” and “such cooling may also be beneficial for other rhythms or in-hospital cardiac arrest.”⁶ Based on these recommendations, hospitals slowly began using TH.

Mechanism of Neuroprotection:

Therapeutic hypothermia prevents brain injury during two phases, ischemia and subsequent reperfusion. During ischemia, ATP is quickly depleted which leads to failure of sodium-potassium and calcium ion pumps which causes abnormal ion gradients which in turn lead to release of glutamate. Glutamate activates the NMDA receptor, increasing intracellular calcium concentration which positively feeds back on glutamate. The increased intracellular calcium concentration activates proteases which activate a cascade of events that inhibit protein synthesis and result in cell death (see Figure 1.)^{4,13} Hypothermia acts to decrease the cerebral oxygen demand, decreasing the rate of ATP depletion, therefore slowing down this chain of events.⁴ It has been shown that for each 1°C decrease in temperature the cerebral metabolic rate decreases 6-7%.⁷ This was subsequently confirmed in human studies.⁸ Ischemia also leads to inflammation mediated by the invasion of leukocytes and microglia, followed by release of inflammatory cytokines. This inflammation damages surrounding tissue. The cytokines also damage the blood-brain barrier by acting on the vascular endothelium, leading to tissue edema. Hypothermia inhibits neutrophil chemotaxis, and microglia activity, and therefore their damaging consequences.⁴

In the ischemic phase metabolism involves lipolysis resulting in build up of free fatty acids, including arachadonic acid. During the reprofusion phase, metabolism of free fatty acids and arachadonic acid takes place and results in the formation of free radicals. These free radicals then damage the cell membrane resulting in cell damage and activation of intracellular pathways resulting in apoptosis. Hypothermia has been shown to decrease levels of free radicals.⁴ Though the mechanism is not fully elucidated, it likely involves decreased lypolysis due to decreased cerebral metabolism during hypothermia.

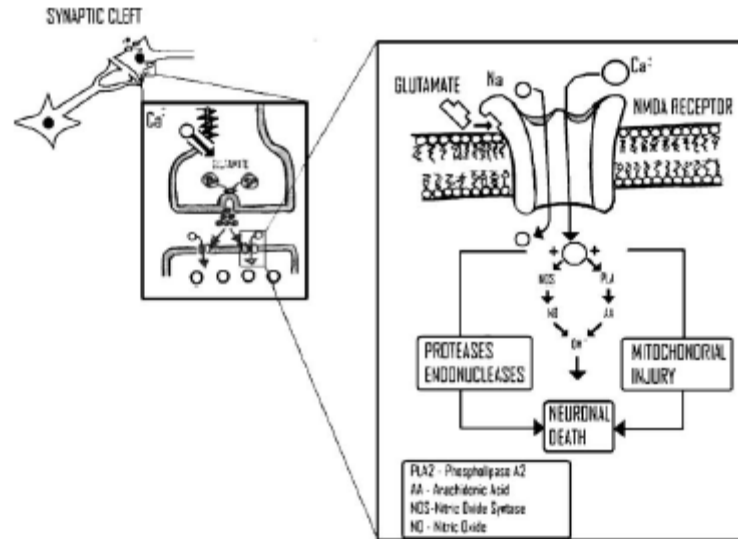


Figure 1- Pathophysiology of brain injury at the cellular level

Side Effects and Contraindications of Therapeutic Hypothermia:

Cardiovascular:

The study by Bernard et al. measured various hemodynamic parameters and found that when shivering was prevented, therapeutic hypothermia decreased heart rate, increases systemic vascular resistance, and showed no difference in stroke volume and mean arterial blood pressure.⁵ Note that the EKG may show a Osborne wave at 33°C and lower.⁹ Prior to clinical studies, a major cardiovascular concern with TH was arrhythmia as it is known that there is an increased risk of ventricular fibrillation with accidental hypothermia below 28°C.⁹ This was not found in either randomized controlled trial.^{3,5}

Respiratory:

Therapeutic hypothermia has few direct effects on the respiratory system, but since it decreases metabolic rate by 25-30%, minute ventilation must be decreased to maintain PCO₂ in a normal range. Also, the solubility of gases changes in hypothermic blood and controversy remains as to whether it is better to use corrected or uncorrected values in clinical decision making.⁹

Renal/ Electrolytes:

During hypothermia, there can be significant diuresis due to decreased solute reabsorption in the ascending limb of the loop of Henle. Care must be taken to monitor strict ins and outs, and replace fluid lost during diuresis. The induction of hypothermia causes potassium shift into cells which then is released back in to circulation during rewarming. There is concern that repletion of potassium during the hypothermic phase can precipitate hyperkalemia during rewarming. Hypothermia is also known to decrease phosphorous levels.⁹ Therefore electrolytes must be followed closely and repleted as necessary.

Gastrointestinal:

With hypothermia there is also decreased gut motility which has led to concerns about delayed enteral feeding.⁹ However, to the best of this author's knowledge this has not been reported in the literature. Increased glucose has also been noted. This is likely due to decreased secretion of insulin from the pancreas during hypothermia.⁹ Patient glucose must be monitored closely and use of exogenous insulin should be used if necessary for tight glucose control.

Hematologic:

In previous studies of prolonged hypothermia at cooler temperatures, decreased number and function of white blood cells were noted.⁹ However a statistically significant difference between hypothermic patients and controls was not found at the temperature and duration used in these more recent studies.⁵ There are also concerns regarding increased infection rate due to attenuation of the immune response with TH and while not statistically significant, a trend towards increased rates of sepsis and pneumonia were noted in the HACA study.³ This was not noted in the study by Bernard, which used a smaller number of subjects.⁵ Prolonged hypothermia also leads to decrease in number and function of platelets which has led to concerns of prolonged clotting time and coagulopathy, though this was not noted in either study which, again, used hypothermia at higher temperatures and for shorter duration than prior studies.^{3,5} In fact, in a more recent study patients on aspirin, clopidogrel and abciximab with percutaneous intervention and intra-aortic balloon placement experienced no significant bleeding with therapeutic hypothermia.¹⁰

Metabolic:

ICU patients who have suffered cardiac arrest are on multiple medications and the use of therapeutic hypothermia raises concerns regarding changes in drug metabolism and toxicity. A recent review paper found that for each 1°C below 37°C systemic clearance of cytochrome P450 metabolized drugs decreased between 7% and 22%. Such medications include various antibiotics, neuromuscular blockers and steroids. It was also noted that hypothermia decreases the potency and efficacy of certain drugs.¹¹ Though much is not known regarding the effects of hypothermia on drug metabolism, the intensivist must be cognizant of these concerns and recognize that decreased dosages of medications may be necessary. Use of a peripheral nerve stimulator should be considered to guide dosage of neuromuscular blockers.

Note that prior to the randomized controlled trials in 2002, many of the proposed side effects and contraindications were theoretical or noted in animal studies or human studies for other indications which used much lower temperatures and longer durations of hypothermia. Though the above side effects are discussed in the literature, it remains to be seen which are clinically significant and to what degree. A survey of German ICU physicians evaluated whether they thought these main side effects had therapeutic consequences and found that physicians felt that these side effects were therapeutically relevant in only a minority of instances (see Table 2)¹²

Table 2- Side effects of mild therapeutic hypothermia after cardiac arrest

Side effect	[No. of ICUs/MTH-users]	(%)	Therapeutic consequences (%)
Infection	60/93	64.5	21.5
Hypotension	58/93	62.4	22.6
Bleeding	45/93	48.4	10.8
Electrolyte disarrangements	8/93	8.6	62.5
Arrhythmias	6/93	6.5	33.3
Changes in glucose levels	2/93	2.1	50.0

Results of a nationwide survey on the use of mild therapeutic hypothermia (MTH) after cardiac arrest. Side effects and therapeutic relevance are listed as reported by the MTH-users.

Cooling Methods:

Methods of cooling can be divided into non- invasive, or surface cooling, and invasive categories.

Non-invasive

Ice packs used in the study by Bernard et al were effective and cost-efficient, resulting in a temperature decrease of 0.9°C/hr, reaching the target temperature of 33°C in 2 hours.⁵ A cooled air mattress has been shown to be less effective. In the study the HACA group it did not achieve target temperature in 93 of 137 cases, in which ice packs were used in addition.³ Cooling caps or helmets have been used with success in infants, but have been less successful in adults taking 180 minutes to reach 34°C.^{3,13} This is likely due to decreased ratio of head to body surface area in adults. Adhesive hydrogel coated pads, marketed under the name Arctic Sun, circulate temperature controlled water and cover a greater surface area as compared to cooling blankets.¹³ In a recent study, they were shown to have an average cooling rate of 1.2°C/hr with an average time to target temperature of 137min. Pads were peeled back every 8 hours to examine skin and no adverse effects were noted.¹⁴ Cold water and air blankets have also been compared and shown to cause relatively slow induction of hypothermia. Whole body ice-water immersion is very effective, but highly impractical in the ICU setting.⁹

Invasive

While many forms of invasive cooling exist, only two are used in common practice. Infusion of intravenous 4°C normal saline and lactated ringers solutions have been used to induce hypothermia in both weight based and non-weight based bolus protocols. Temperature decreased rapidly an average of 1.2-1.6°C with these chilled intravenous boluses.^{15,16,17} Issues regarding the importance of rapid induction of hypothermia will be discussed later in this paper. While induction with cold infusions is highly effective, maintenance of hypothermia goals with infusions alone has been unsuccessful.¹⁸ Chilled intravenous fluids are often used in conjunction with another method to maintain hypothermia. The other commonly used invasive cooling method is an endovascular cooling catheter, such as CoolGard 3000 (Alsuis Corporation, CA). This catheter is inserted into the SVC or IVC via a central vein and uses a closed-system of ice-cold fluid that circulates to cool the surrounding blood and is regulated by an external pump and monitor.¹³ Though it is frequently used especially in Europe, it has a slow time to achieve temperature goal at 3 hours and 39 minutes with an average rate of 0.8°C/hour.¹⁹ It also carries all risks that go with placing an indwelling femoral line.

There may also be some delay in initiating TH as it is an invasive procedure and might not be started as quickly as a surface method. The best method to achieve target temperature for TH should be inexpensive, achieve the target temperature quickly, be easy to initiate, and have few associated complications. This author believes that these goal may be most easily achieved by a combination of cold intravenous fluids for induction of TH in combination with a surface cooling method.

Utilization of Therapeutic Hypothermia

Since the international recommendations for therapeutic hypothermia for out of hospital cardiac arrest were made by ILCOR in 2002, implementation has been slow but progressive. Reasons for this delayed implementation have recently been evaluated in the literature. In 2007 a survey of German ICUs that treat patients after cardiac arrest it was found that only 23.5% of ICUs use TH. University hospitals, larger ICUs, internal medicine trained physicians, and availability of 24 hour PCI were positively related to the use of TH (see figure 2). The survey also revealed that use of TH in ICUs was increasing, from only 7.5% of the TH users implementing the therapy prior to 2003, to 51% starting in 2005. Reasons for not using TH included inexperience or lack of enough information, feeling that it was too difficult to perform, and a belief that the method was not yet evidence based. The study concluded that TH was underused in Germany, but did note that use was increasing and more than 1650 patients have already received the therapy.¹²

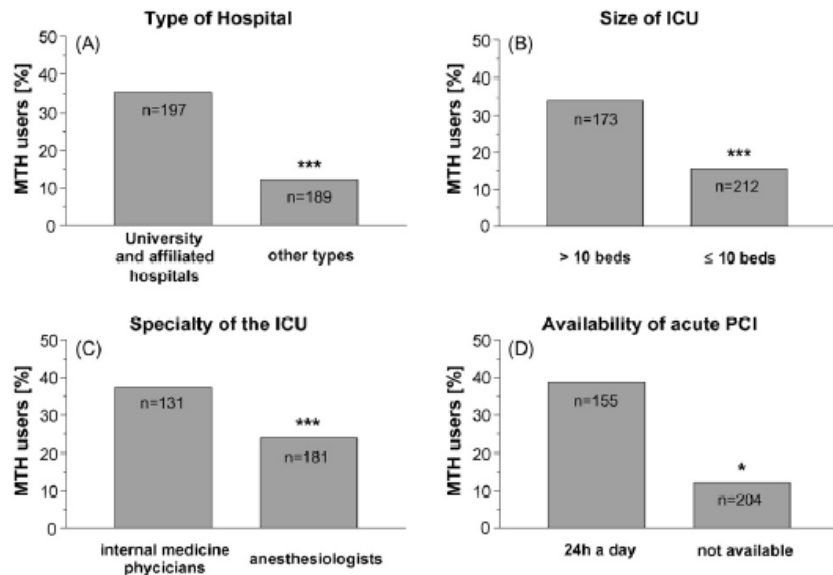


Figure 2- Hospital characteristics affecting the use of mild therapeutic hypothermia (MTH) after cardiac arrest. *P<0.05; *P<0.001**

A study of Finnish ICUs evaluated all 1555 adult patients treated in ICUs after cardiac arrest during 2004 and 2005. It noted good use of TH with 19 of the 20 ICUs utilizing the therapy. Of the 1555 patients who suffered cardiac arrest, 407 received TH. Twenty of these patients suffered in-hospital cardiac arrest. Unfortunately, initial rhythm was not recorded in the database for analysis. Evaluation of in-hospital mortality demonstrated an increase in survival associated with younger age, with 11 of 12 patients younger than 45 surviving to discharge (see Figure 4). Evaluation of outcomes at 6 months showed that 55.3% of patients who received TH were alive at 6 months. Much like the German study, increase in use was noted with time, with 4% of SCA patients receiving TH in 2002 and 28% receiving TH in 2005 (see Figure 3).²⁰

Figure 3 - In-hospital mortality in different age groups (A). Patients who received hypothermia treatment (n=407), (B) patients who received standard treatment (n=1148)

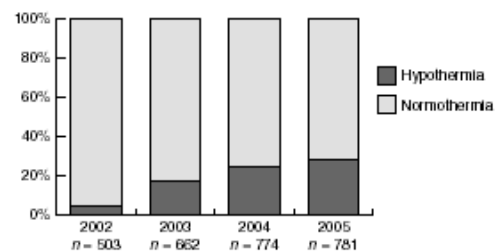
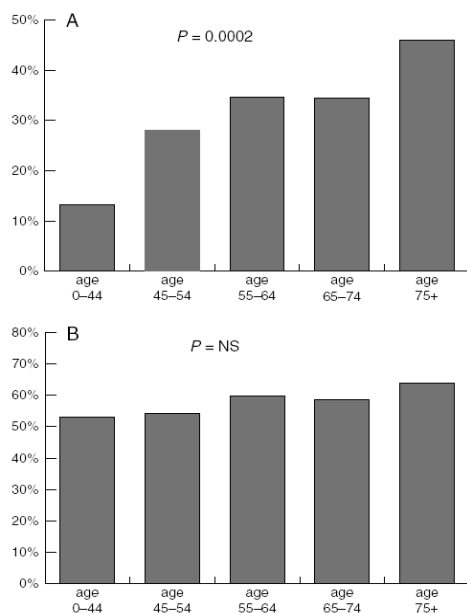


Figure 4 - Proportion of patients treated with mild hypothermia of all post resuscitation patients admitted to ICU's in Finland in 2002-05

Compared to in Europe, TH is used far less in the United States. A 2006 survey of American physicians in the fields of critical care, cardiology, and emergency medicine found that 74% had never used TH, as opposed to 64% of non-US physicians. It is likely that the percentage of total US physicians who have used TH is much lower, as 79% of respondents in this study were at university or teaching hospitals. The study found that among US physicians critical care physicians were most likely to have used TH, followed by cardiologists and emergency physicians.²¹ This appears to be logical as emergency departments should be more likely to initiate they therapy if it will be continued in the ICU. The most common reasons for not using TH in the survey were “not enough data,” “too technically difficult,” “have not considered it,” and “not part of ACLS.” Interestingly, in the same survey 34% of US physicians felt “it would be unethical to conduct a study in which one group of patients was randomized to normothermia.”²¹

Subsequent Clinical Studies of TH

Clinical Application of Mild Therapeutic Hypothermia After Cardiac Arrest

Current clinical studies have sought to confirm results of the initial randomized controlled trials and answer further questions. The largest study to date was conducted by the European Resuscitation Council and collected data on both in and out-of-hospital cardiac arrest patients at 19 sites throughout Europe over 2 years. A total of 462 of 587 patients who met inclusion criteria received TH. Sixty two percent had an initial rhythm of VF/VT. Forty-three patients were treated with TH after in-hospital arrest. In SCA from all rhythms combined, unfavorable outcome was noted in 55% of the TH group compared to 68% in the normothermia group ($p=0.02$). Forty-three percent in the TH group vs. 68% in the normothermic group died during hospital stay ($p<0.001$). For patients who had PEA/asystole mortality was lower for patients who received TH, 65% vs. 81% of normothermic patients ($p=0.023$). This is the first time survival benefit has been shown in this group. There was no significant difference in neurological outcome after PEA/asystolic arrest between those who were treated with TH and those who were not (Table 3). Neurologic outcomes and mortality rates were not separated out in the analysis for patients with VF.²²

Table 3- Outcome and temperature profiles of patients with pulseless electrical activity / electromechanical dissociation or asystole as first rhythm (n=197)

	Hypothermia (n = 124)	Normothermia (n = 73)	p Value
Outcome			
Unfavorable outcome, n (%)	89 (81)	59 (81)	.977
Died during hospital stay, n (%)	79 (65)	59 (81)	.023

The study also evaluated cooling methods and found that 75% of patients were treated with an endovascular cooling device and 25% were treated with surface methods and cold fluids. Note that this study was supported by a corporation that manufactures an endovascular cooling device and this was the only method of cooling used for the first 7 months of the study.²³ Average cooling rate of all patients was 1.1°C/hr. It took an average of 150 minutes to initiate endovascular cooling versus 75 minutes for surface cooling or cold fluids. It was also noted that high-enrolling sites used endovascular cooling less often and had shorter interval to initiation of cooling.²²

Adverse events were also analyzed. There was a 3% rate of hemorrhage and a 6% rate of arrhythmia. Arrhythmia rate was higher in those patients with endovascular cooling devices (7.2% vs 0.9%, $p=0.01$). There was no significant difference in bleeding complications for those in which an endovascular cooling device was used.²²

Several smaller studies of implementation and outcomes for TH have been published recently. A study at one Swedish hospital demonstrated a favorable neurological outcome in 58% of patients who had an initial rhythm of VF and received TH as opposed to a 34% of historical controls who did not receive TH.²⁴ Another small study demonstrated a survival to discharge rate of 56 % in patients who had a VF arrest, as compared to 36% in historical controls.²⁵ To the best of this author's knowledge there is no meta-analysis of TH trials to date.

Cardiovascular Concerns:

Cardiac catheterization was not specifically addressed in initial studies and patients with cardiogenic shock were excluded from those trials.^{3,5} The recent literature has begun to evaluate the use of TH for patients with SCA in whom cardiac intervention is necessary. In a study by Hovdenes et al. Fifty patients with out of hospital VF arrest were treated with TH and received cardiac catheterization and intra-aortic balloon pump placement (IABP) if needed. Ninety eight percent of patients had a catheterization and 72% of patients had PCI. Twenty three patients received an IABP. Evidence for myocardial infarction by enzymes was noted in 80% of patients. TH was routinely begun in the ICU after cardiac intervention, however the authors note that cooling with cold infusions and ice packs was often begun in the ambulance. The study demonstrated an 82% 6 month survival rate. Survival rate was not statistically significant between patients who required IABP and those who did not, indicating that TH is not contraindicated in those with cardiogenic shock. This study demonstrates that patients benefit from the combination of TH and cardiac catheterization whether or not they are in cardiogenic shock.¹⁰

TH can be successfully initiated prior to cardiac intervention without an increase in complications. A recent study evaluated patients who received TH in the emergency department, prior to cardiac catheterization and IABP placement. Ninety percent of patients had VF as their initial rhythm. Seventy seven percent of patients underwent cardiac catheterization and 15% had IABP placement. This study showed a 56% survival to hospital discharge with favorable neurological outcome. The study found no statistically significant difference in complication rate, specifically pneumonia, sepsis, and arrhythmia when compared to historical controls who did not receive TH or cardiac catheterization.²⁴

Future Directions: Time to onset of TH

Animal models have been used to demonstrate improved benefit with early induction and intra-arrest induction of hypothermia. A study in dogs compared induction of hypothermia at time of ROSC versus 15 minutes after ROSC. It found that this delay negated the beneficial effect of hypothermia.²⁶ In a murine model those with intra-arrest induction of hypothermia had a better 72 hour survival rate than those in which hypothermia was induced after ROSC.²⁷ This was then evaluated in the larger dog model. Dogs received mild hypothermia with cold saline to 34°C after 10 or 20 minutes of VF before advanced life support was started at 20 minutes. Seven of 9 dogs survived in the 10 minute group as opposed to 2 in the delayed hypothermia group. (Figure 5) This suggests a benefit to intra-arrest cooling, and that a delay in hypothermia reduces its efficacy.²⁸ In another study pigs were subjected to 15 minutes of VF and then either received a cold saline aortic flush with no CPR for 20 minutes or 20 minutes of CPR before being placed on cardiopulmonary bypass. Improved neurologic performance and survival rates were seen in the aortic flush / no CPR group, with 5 of 6 pigs surviving to 9 days and only 4 of 7 pigs surviving to 9 days in the CPR group (p=0.03).²⁹ (Figure 6)

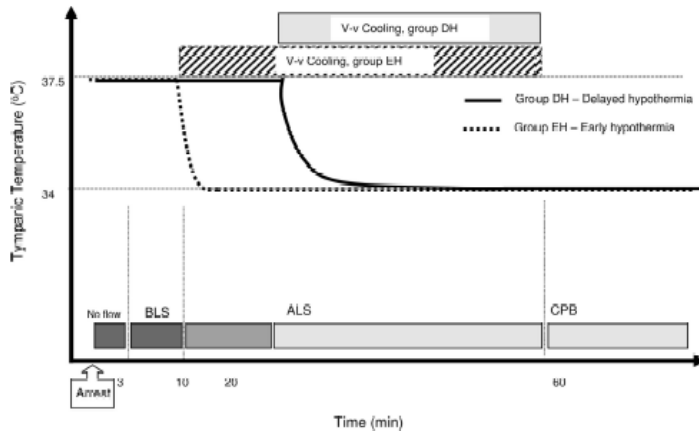
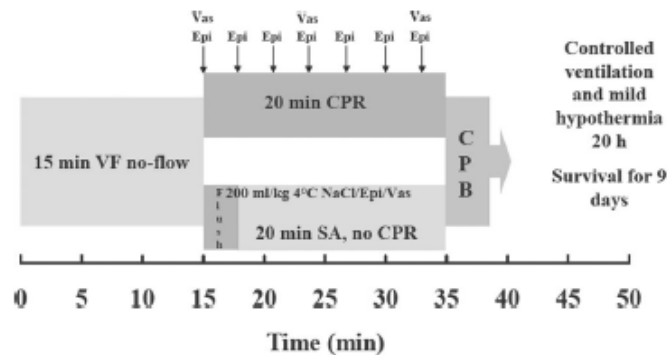


Figure 5 - Study protocol. Three minutes of normovolemic VF was followed by 7 minutes of BLS and 50 minutes of ALS. V-v indicates venovenous

Figure 6 - Experimental protocol. VF, ventricular fibrillation; Vas, vasopressin 0.4 IU/kg; Epi, epinephrine 0.04 mg/kg; CPR, cardiopulmonary resuscitation; CPB, cardiopulmonary bypass



No human studies to date have demonstrated an improved outcome with earlier induction of hypothermia. This may be because it is not being initiated early enough to demonstrate benefit as a significant amount of time passes between the start of the arrest and arrival at the hospital where still more time may pass before TH is started. The most rapid and practical way to induce hypothermia is likely with cold intravenous fluids. An infusion of lactated ringers solution at 30ml/kg over 30 minutes in the emergency department in comatose survivors of out-of hospital SCA showed an average decrease in body temperature of 1.6°C without inducing pulmonary edema in any patient.¹⁵ In another pilot study of out-of-hospital SCA survivors, 2L of 4°C normal saline was infused over 20-30 minutes with an average decrease in temperature of 1.7°C in patients who received neuromuscular blockers and 1.1°C in those who did not. The pre-infusion mean ejection fraction was 34.5% and post-infusion echocardiogram showed no signs of fluid overload.¹⁶ Post-infusion ejection fraction 39.6% and the difference between pre and post-infusion ejection fractions was not statistically significant. This same group then evaluated the feasibility of using this therapy in the field. In a pilot study they showed that 2L of 4°C normal saline and neuromuscular blockage could be successfully administered after ROSC by paramedics. The average decrease in temperature was 1.24°C. There was a trend toward improved survival to discharge in patients with an initial rhythm of VF who received cooling in the field. However, not all hospitals performed TH once patients arrived at their facilities. Perhaps if they had, the difference

in survival rate would have been statistically significant. As in the prior study, the fluid bolus was not associated with pulmonary edema.¹⁷ Further study is needed to evaluate whether early induction of TH in the field with continued TH in-hospital provides added neurologic and mortality benefit.

Conclusion

Over the past five years, therapeutic hypothermia has emerged as a revolutionary tool in the treatment of comatose cardiac arrest survivors. It has already been used in thousands of patients and its use continues to increase. The HACA group estimated in their original article that over 375,000 Europeans suffer cardiac arrest every year, 30,000 of whom would meet their original inclusion criteria, and 1200 to 7500 of whom would have improved neurologic outcome with TH. Physicians who utilize TH provide their patients treatment which has consistently proven to offer improved neurologic outcome and mortality benefit. It has now been five years since TH was internationally recommended as standard of care by ILCOR.⁶ However, while it is currently being used at some academic medical centers and community hospitals, use of TH is increasing only slowly. In the meantime most Americans who suffer a cardiac arrest continue to be denied this proven beneficial therapy. Current research continues to better define methods, side effects and expanded uses for TH. While original studies showed benefit in only out-of hospital VF arrest, further studies suggest possible benefit in other rhythms and with in-hospital arrest. Ideal time of induction of TH is an intriguing area of research which may show improved benefit with earlier induction in further years. This is an exciting and growing area in critical care as it offers better neurologic outcomes than ever before for those who have suffered a cardiac arrest.

*Please see Appendix A for a sample TH protocol, used at University of Washington Hospital

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