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Review

Prehospital Use of Therapeutic Hypothermia After Resuscitation from Cardiac Arrest

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The use of therapeutic hypothermia (TH) in the care of patients after resuscitation from sudden cardiac arrest (SCA) has been shown to improve both survival and neurologic outcomes in randomized, controlled trials and a growing number of cohort studies with historical controls. The robust nature of the data supporting postarrest TH is reflected in the wide variety of clinical investigations that have confirmed outcome benefits of similar magnitude. A number of important questions remain surrounding the implementation of postarrest TH, including the timing of cooling induction and how rapidly providers need to initiate cooling therapy. Several investigations have suggested that earlier cooling may maximize the benefit from TH and that, conversely, increasing delays to TH induction may lead to worse patient outcomes. Prehospital initiation of TH has been proposed as a means to address time barriers inherent in out-of-hospital SCA. In this paradigm, emergency medical service (EMS) personnel are able to start cooling therapies immediately after resuscitation, which can then be continued during transport. Newer technologies may provide other opportunities for rapid cooling in the field; however, the risks and benefits of prehospital cooling remain poorly understood. This review will describe the growing literature and future directions pertaining to prehospital induction of TH after SCA.

Introduction

The use of therapeutic hypothermia (TH) in the care of patients after resuscitation from sudden cardiac arrest (SCA) has been shown to improve both survival and neurologic outcomes in randomized, controlled trials (Hachimi-Idrissi *et al.*, 2001; Bernard *et al.*, 2002; The Hypothermia after Cardiac Arrest Study Group, 2002) and a growing number of cohort studies with historical controls (Arrich *et al.*, 2007; Nielsen *et al.*, 2009; Sagalyn *et al.*, 2009). The robust nature of the data supporting postarrest TH is reflected in the wide variety of clinical investigations that have confirmed outcome benefits of similar magnitude (Sagalyn *et al.*, 2009). In addition, the growing body of literature evaluating postarrest TH has demonstrated that adverse effects from cooling are modest, further supporting broad utilization.

A number of important questions remain surrounding the implementation of postarrest TH, including the timing of cooling induction. Upon presentation of a patient after successful resuscitation, how rapidly do providers need to initiate cooling therapy? Current evidence suggests that reaching a goal temperature of 32°C–34°C by ~4–8 hours after resuscitation confers a significant survival benefit (Bernard *et al.*, 2002; The Hypothermia after Cardiac Arrest Study Group, 2002); in practical terms, this usually requires cooling initiation within several hours of return of spontaneous circulation (ROSC). However, several laboratory investigations (Kuboyama *et al.*, 1993; Abella *et al.*, 2004) and now one randomized clinical study (Castrén *et al.*, 2010) have suggested that earlier cooling may maximize the benefit from TH and that, conversely, increasing delays to TH induction may lead to worse patient outcomes. Given the complexity of TH induction from a logistical perspective, delays in induction and reaching goal temperature are common in clinical practice (Nielsen *et al.*, 2009; Sagalyn *et al.*, 2009).

For out-of-hospital victims of SCA who are resuscitated in the prehospital environment, time delays to postarrest care are poorly characterized. In our experience, delays are inherent in the process of transport to the hospital (often 15–30 minutes with the inclusion of ambulance on-loading and off-loading times), initial emergency department evaluation (often an additional 10–20 minutes), and mobilization for TH care (in well-trained environments, this can take up to a further 30 minutes). Thus, even in reasonably functional systems of care, over an hour may elapse from initial resuscitation to the initiation of TH. It is quite likely that this time interval can be much longer in common practice.

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Prehospital initiation of TH has been proposed as a means to address the time barriers inherent in out-of-hospital SCA. In this paradigm, emergency medical service (EMS) personnel are able to start cooling therapies immediately after resuscitation, which can then be continued during the time intervals described earlier. Practical realities of ambulance treatment space and EMS training might limit therapeutic options, but TH induction can be initiated with the intravenous infusion of chilled saline, for example, which can be easily accomplished by EMS providers (Abella *et al.*, 2004; Kliegel *et al.*, 2007; Castrén *et al.*, 2010). Newer technologies may provide other opportunities for rapid cooling in the field (Castrén *et al.*, 2010). However, the risks and benefits of prehospital cooling remain poorly understood. The remainder of this review will describe the growing literature and future directions pertaining to prehospital induction of TH after SCA.

Current TH Recommendations

The International Liaison Committee on Resuscitation has recommended a bundled treatment strategy for comatose survivors of cardiac arrest, including TH, careful hemodynamic support, and percutaneous coronary intervention (PCI) for appropriate patients (Peberdy *et al.*, 2010). Specifically, with regard to TH, it is recommended that adult out-of-hospital comatose survivors of ventricular fibrillation (VF) cardiac arrest should be cooled to 32°C–34°C for 12–24 hours. Adult patients resuscitated from in-hospital cardiac arrest and out-of-hospital adult patients resuscitated after asystole or pulseless electrical activity should be considered for cooling as well, although the strength of this recommendation is weaker (Peberdy *et al.*, 2010).

Timing of TH Induction

Although existing data support the use of TH and help guide patient selection, the optimal timing of cooling remains uncertain. Several laboratory studies have demonstrated that the protective effects of TH decline with delays in induction; these reports suggest that the timing of induced hypothermia may have a significant impact on outcome (Kuboyama *et al.*, 1993; Abella *et al.*, 2004; Nozari *et al.*, 2006; Zhao *et al.*, 2008; Wolff *et al.*, 2009). Kuboyama *et al.* (1993) noted that rapid induction of cerebral hypothermia immediately after ROSC improves neurological function and outcome. Wolff *et al.* (2009), in an examination of the association of time intervals between cardiac arrest and induction of TH, also observed that earlier institution of TH improved the neurological outcome. Further, while data currently support the initiation of TH promptly after ROSC, several investigations employing animal cardiac arrest models suggest that initiation of TH *before* ROSC may further improve outcomes (Kuboyama *et al.*, 1993; Zhao *et al.*, 2008; Abella *et al.*, 2004). Zhao *et al.* (2008) determined that mice receiving intra-arrest cooling had more favorable hemodynamic and neurological outcomes compared with normothermic controls with earlier reperfusion time. Additionally, earlier induction of TH during active resuscitation care may promote improved outcomes; Nozari *et al.* (2006) used a canine model of cardiac arrest to demonstrate a correlation between the time of induction of hypothermia during advanced life support resuscitation and neurological outcomes. Dogs that received hypothermia treatment within 10 minutes of onset of VF had significantly better neurological outcomes than those that received it after 20 minutes of VF (Nozari *et al.*, 2006).

In addition to laboratory findings, several investigations have focused on the applicability of intra-arrest TH in the clinical realm. Bruel *et al.* (2008) successfully employed intra-arrest cooling in the prehospital setting while examining the feasibility of induction in this setting. Thirty-three patients were included in the study; patients were cooled using 2 L of chilled (4°C) saline over 30 minutes. The average time to reach 34°C after ROSC was 16 minutes (Bruel *et al.*, 2008). Castren *et al.* (2010) also demonstrated successful intra-arrest cooling in the prehospital environment using a novel intranasal cooling device. At arrival to the hospital, the average temperature of the cooled patient cohort was 34.2°C (Castrén *et al.*, 2010). These studies demonstrated that inducing hypothermia during intra-arrest care in the prehospital environment is feasible, although it remains unclear what impact this may have as a distraction to cardiopulmonary resuscitation (CPR) and other resuscitation maneuvers. Prehospital hypothermia investigations have not reported on CPR performance or other secondary effects on resuscitation care from cooling implementation, and the two studies referenced here had prehospital physicians available to respond along with either an ACLS unit or two paramedics, representing additional resources that are not common in most EMS systems.

Cost-Effectiveness of TH

Cost considerations of TH have been recently evaluated in terms of quality-adjusted life years. Merchant *et al.* (2009) examined the cost-effectiveness of TH using a model that factored in the cost of equipment used for cooling, training costs and costs associated with the additional nursing care required for patients undergoing TH. Therapeutic hypothermia was demonstrated to have an incremental cost-effectiveness ratio of <$100,000 per quality-adjusted life year, a cost comparable to placing public access defibrillators on U.S. commercial aircraft (Merchant *et al.*, 2009).

With regard to institution of TH in the prehospital environment, the largest investments are the cost of equipment, storage, and training. Should large-volume chilled intravenous fluids be the choice for inducing TH in the field, the additional costs for equipment and storage would be relatively modest. Medical saline is generally readily available within all EMS systems and could be stored in inexpensive cooling chests, for example. Newer technologies would have cost barriers that would then require comparison to the incremental clinical benefit over chilled saline infusion. Additionally, altering current resuscitation protocols might be associated with increased personnel costs, especially during initial development. No published data on prehospital TH costs and labor investment exist to guide providers at the present time.

Prehospital TH After Cardiac Arrest: Evaluation of the Evidence

Although at least 11 studies have demonstrated the ability to induce TH in the prehospital setting (Table 1), it remains unknown whether this earlier temperature management equates to a clinically significant improvement in outcomes. The majority of the prehospital studies included <50 patients without concurrent control groups, making it difficult to as-

Table 1. Prehospital Therapeutic Hypothermia: Summary of Clinical Investigations

Year	*Study*	*Type of study*	*TH induction method*	*Patient cohort size*
2002	Callaway *et al.* (2002)	Cohort with control	Ice packs	b
2004	Virkkunen *et al.* (2004)	Cohort	Cold saline	a
2007	Kim *et al.* (2007)	RCT	Cold saline	c
2008	Kämäräinen *et al.* (2008)	Cohort	Cold saline	a
2008	Storm *et al.* (2008)	Cohort with control	Cooling cap	b
2008	Bruel *et al.* (2008)	Cohort	Cold saline	b
2008	Uray *et al.* (2008)	Cohort	Cooling pads	b
2009	Hammer *et al.* (2009)	Cohort with control	Cold saline	b
2009	Kämäräinen *et al.* (2009)	RCT	Cold saline	b
2010	Bernard *et al.* (2010)	RCT	Cold saline	c
2010	Castrén *et al.* (2010)	RCT	Transnasal cooling	c

Selected clinical studies specifically pertaining to prehospital induction of TH are listed in this table. Types of studies included cohort studies (consecutive enrollment) with or without a comparison control group, and randomized, controlled trials, with parallel enrollment of controls during the investigative period.

Study cohort size was categorized as follows: [a] <20 subjects; [b] >20 but <50 subjects; [c] >50 subjects.

RCT, randomized, controlled trial; TH, therapeutic hypothermia.

certain clinical significance (Callaway *et al.*, 2002; Virkkunen *et al.*, 2004; Kim *et al.*, 2007; Kämäräinen *et al.*, 2008, 2009; Storm *et al.*, 2008; Uray *et al.*, 2008; Hammer *et al.*, 2009; Bernard *et al.*, 2010). For example, Uray and Malzer (2008) and Virkkunen *et al.* (2004) demonstrated the feasibility of prehospital cooling without demonstrable adverse effects, but outcome comparisons with controls were not attempted. Kämäräinen *et al.* (2009) randomized subjects to both a prehospital cooling patient cohort ($n=19$) and a control group ($n=18$), but they found no significant primary or secondary outcome differences in their small investigation.

The most recent and largest randomized, controlled trial of prehospital TH (Bernard *et al.*, 2010) included 234 patients with an initial rhythm of VF; paramedics were able to achieve cooling via rapid infusion of large-volume, ice-cold saline. However, the authors were unable to demonstrate any improvement in survival to hospital discharge among prehospital-cooled patients when compared with patients receiving TH initiated subsequently in the hospital (47.5% vs. 52.6%; $p=0.43$). It should be noted that in this investigation, subjects were received by hospital systems with extensive experience in hypothermia induction, and patients in both prehospital TH and control groups had equivalent temperatures at 60 minutes after ED arrival (34.7°C±1.1°C vs. 34.7°C±0.9°C; $p=0.70$). In contrast, an earlier randomized, controlled trial by Kim *et al.* (2007) found a trend toward improved survival in VF patients who received prehospital cooling: 19/29 (66%) survived to discharge in the prehospital cooling group versus 10/22 (45%) in the group that did not receive prehospital TH. Although this earlier trial did not describe temperatures in the two groups during subsequent hospital care, a large temperature difference was noted between the prehospital-cooled cohort and the control cohort at ED arrival (34.7°C±1.2°C vs. 35.7 C±1.2°C; $p<0.0001$).

Logistical Concerns

A majority of prehospital EMS systems function under conditions of limited resources and staffing; TH induction protocols have the potential to increase individual EMS provider work load and could potentially interrupt other postarrest treatment modalities such as airway management, the establishment of adequate intravenous access, and prompt transport. Should the induction of TH take priority over these other interventions in the field? Considering that many EMS teams may only have 1–2 providers providing direct care to the resuscitated patient, these considerations are not purely academic. With this concern in mind, some providers have opined that basic resuscitation care and postarrest transport should be prioritized over induction of TH.

A survey of EMS physicians identified numerous technical, medical, and other barriers to the initiation of prehospital TH (Suffoletto *et al.*, 2008). Reported barriers included lack of appropriate refrigeration and temperature-monitoring equipment, concern regarding competing priorities for training and patient care, lack of credentialing for the use of paralytic agents that may be required for optimal TH induction, and lack of space in EMS vehicles for cooling equipment. Providers also raised the consideration that short transport times to receiving facilities may render prehospital induction of TH unnecessary in a number of EMS environments.

Physicians who oversee prehospital care systems must address these barriers and take into account other factors during TH protocol design, including patient selection criteria, methods of TH induction, temperature monitoring, scope of practice for paramedics relating to paralytics and sedation, how potential adverse effects such as overcooling (or temperature "overshoots") will be managed, and how medical command will be involved during the TH process. These concerns highlight the complexity of developing and initiating an effective algorithm for induction of prehospital TH. Some of these barriers may not be as concerning in actual practice as they may first appear; for example, overcooling could potentially be of little risk in systems with reasonably short transport times, often documented in developed cardiac-receiving systems to be <10 minutes (Nallamothu *et al.*, 2006). In addition, many EMS systems have a tiered response system wherein firefighter/EMS technician-certified first responders arrive at the scene, followed by paramedic and/or command units arriving after the initial response. Systems using tiered response systems may find these resources ideal for institution of TH in cardiac-arrest survivors while sparing training for the majority of providers (Braun *et al.*, 1990).

Potential for TH Adverse Events in the Prehospital Setting

The published trials of postarrest TH have shown that the risks for adverse events are modest and likely of small clinical consequence. However, the potential still exists for arrhythmias, infection, bleeding, seizures, and other complications (Nolan *et al.*, 2003; Nielsen *et al.*, 2009). Shivering is another potential adverse effect of hypothermia induction that increases oxygen consumption and generates heat, making establishment of a hypothermic state more difficult (Nolan *et al.*, 2003). The potential for such complications highlights the importance of adequate education of prehospital providers and the need for appropriate medical oversight. To ensure that such adverse effects can be effectively managed in the prehospital setting, guidelines for prevention and treatment of common adverse effects would need to be carefully outlined within prehospital protocols.

The risk of complications such as arrhythmias and coagulopathy further increases if the patient is cooled below 32°C (Nolan *et al.*, 2003). Through a retrospective chart review of TH induction at three hospitals, Merchant *et al.* (2006) documented that unintentional overcooling is common during postarrest TH care, specifically when simple cooling methods are utilized without thermostatic control mechanisms (e.g., cold intravenous fluids/ice bag cooling). Overcooling is indeed possible during the induction phase of TH; therefore, it would be important for prehospital personnel to have access to effective methods for careful temperature monitoring. One of the potential solutions to this issue is the use of tympanic thermometer devices, which are generally inexpensive, are readily available, and can be easily and rapidly utilized by prehospital providers. Temperature monitoring can also be performed using various models of prehospital monitors and defibrillators. It is important for EMS protocols to explicitly describe temperature monitoring for patient management during and after TH induction in the field.

Prehospital Induction Methods

The prehospital randomized, controlled trial by Kim *et al.* (2007) showed that the delivery of large-volume chilled intravenous saline in the prehospital setting was feasible, safe, and potentially effective. However, use of prehospital chilled saline infusion may have certain practical limitations. For instance, in a recent study by Bernard *et al.* (2010), the authors found that 52% of subjects did not receive the goal of 2 L intravenous chilled saline because of close hospital proximity with a transport time of <20 minutes. Highlighting this issue, time to transport from the field to the hospital setting was shown to be ~ 7 minutes in one study of prehospital cardiac-arrest care (Spaite *et al.*, 2008). Virkkunen *et al.* demonstrated that it took ~ 25 minutes to infuse ~ 2 L of chilled saline (Virkkunen *et al.*, 2004). It is therefore possible that EMS systems with relatively short transport times may not benefit from prehospital TH initiatives as much as systems that routinely note longer transport times to receiving facilities, especially if chilled saline is chosen as the induction method. Compounding the challenge of using intravenous coolant, a recent study demonstrated that chilled saline warmed during transit through intravenous tubing and generally was not at initial temperature when infused; insulated tubing has been proposed as a possible solution (Mader, 2009). Taken together, these data suggest that a more rapid induction method could be useful in the prehospital setting.

Although most studies have used intravenous chilled fluids to induce TH in the field, there may be other options for more rapid cooling that are currently under evaluation in both clinical and laboratory settings. These include varied methods such as the use of free-standing cooling pads, saline/ice "slurries," chilled perfluorocarbons (PFCs), and transnasal evaporative cooling. For example, Uray *et al.*, (2008) safely utilized a specialized prehospital cooling pad system that was prechilled and stored in an insulated box with a cooling battery. They were able to achieve target temperature within an average of 50 minutes with only mild dermal erythema, which resolved soon after removal of the pads, without significant injury. Microparticulate ice slurry has been shown in animal studies to be an option for rapid provision of organ hypothermia (Laven *et al.*, 2007); although its use for TH induction in human subjects has not been studied, an investigative team has evaluated the induction of hypothermia with ice slurry in swine (Vanden Hoek *et al.*, 2004). The authors found that, compared with chilled saline, the ice slurry mix cooled more rapidly with equal volume. Another novel technique under laboratory evaluation is liquid ventilation with PFCs, which are inert and biologically safe liquids that have been studied as transfusion options given their oxygen-carrying properties. Liquid ventilation with chilled PFCs has the potential to rapidly cool the pulmonary vascular bed, and one animal study by Staffey *et al.* (2008) found that using liquid ventilation with PFCs quickly achieved hypothermia, without adverse effects. An additional swine study also demonstrated an increased rate of ROSC when using PFC liquid ventilation versus chilled saline infusion during experimental cardiac arrest and CPR (Riter *et al.*, 2009).

Another promising new technology has been evaluated for prehospital TH—the use of transnasal cooling, which exploits rapid evaporation of a volatile liquid sprayed in the posterior nasal cavity. A randomized, controlled trial performed in a number of European centers (Castrén *et al.*, 2010) examined the use of transnasal cooling during SCA, using an experimental portable delivery device. Investigators concluded that transnasal cooling was safe and effective during arrest, with a rapid onset of TH in the prehospital setting. Although they did not demonstrate a statistically significant difference in survival to hospital discharge, there was a trend to increased survival in the transnasal cooling group compared with the control group (43.8% vs. 31.0%; $p=0.26$). Further, in a subset analysis of those who had CPR initiated within 10 minutes of collapse, the authors found a statistically significant difference in those who survived in the cooled group versus the control group (56.5% vs. 29.4%; $p=0.04$) and those who were neurologically intact (43.5% vs. 17.6%; $p=0.03$).

Regionalization of TH Care

TH care delivery can be a complex process not only for prehospital providers but also for in-hospital systems; therefore, regionalization of cardiac arrest care to specialized centers has become an important recent consideration (Mechem *et al.*, 2010). Regionalization of care ensures that patients are transported to hospitals with the resources, staffing, and expertise to efficiently deliver postarrest care. A study evaluating TH utilization among physicians in 2006 found that a majority of hospitals that receive cardiac-arrest victims did not routinely provide care specific to the postarrest patient (Merchant *et al.*, 2006); familiarity with TH application remains a problem at many hospitals today. Regionalization of critical care has been well suited for the care of trauma and stroke patients, and it has been shown that transporting patients to hospitals with a recognized proficiency in specialized areas of care can indeed improve outcomes (Bobrow and Kern, 2009). Building on this approach, a number of prehospital emergency care systems including the New York Fire Department have developed algorithms for prehospital TH, which include transporting post–cardiac-arrest patients to only designated facilities that have the recognized capability of continuing TH and postarrest care (Fire Department New York). This is especially important, as the delivery of a cooled patient to a hospital that does not support the continuation of the therapy presents a serious and difficult problem that must be considered by EMS agencies. If a patient is cooled only to be immediately rewarmed in a receiving hospital, in a disease state that is already sensitive to increased oxygen demand and metabolic rate, this may increase harm and risk of post-resuscitation injury. It also presents an awkward problem for EMS personnel as they interact with emergency department colleagues and hospital staff at a receiving facility.

Carr *et al.* (2009) examined the relationship between cardiac arrest mortality and hospital variables to determine which of those variables influenced survival. They found that cardiac arrest mortality was lower in larger, urban, teaching hospitals, suggesting that these hospitals might serve as candidates for postarrest receiving centers.

Other factors relevant to the care of postarrest patients suggest that regionalization to larger centers may be important. Many resuscitated patients require urgent or emergent PCI, and it has been demonstrated that this intervention is underutilized in the postarrest population (Merchant *et al.*, 2008). In addition, neurologic monitoring for seizures, which may occur in as many as 25% of postarrest patients, is limited at many facilities. Processes such as PCI consideration and neurologic monitoring may be considered as part of a "bundle-of-care" approach to the postarrest patient.

Postarrest bundles of care that include both TH and PCI have been effectively implemented with apparent safety. Sunde *et al.* (2007) examined the utilization of a standardized postresuscitation protocol that included both TH and PCI. Patients were cooled prior to and during the PCI procedure without incident. After implementation of this care bundle, the authors noted an increase in survival to hospital discharge with good neurological recovery and 1-year survival in patients who suffered out-of-hospital cardiac arrest of cardiac etiology. Additionally, Batista *et al.* (2010) examined the feasibility and safety of combined PCI and TH following cardiac arrest and determined that PCI can be performed in patients receiving TH without increased cardiovascular or neurological risk. Importantly, in these studies, it did not appear that prior induction of TH delayed the time to cardiac catheterization.

Conclusions

Although the evidence supporting the powerful role of TH in the care of postarrest patients continues to grow, the need for prehospital initiation of TH remains unclear. Initial studies have suggested that prehospital TH induction is feasible and safe, and the earlier application of cooling therapy is grounded in a number of laboratory studies. However, clinical investigations have to yet demonstrate a significant difference in clinical outcomes with the application of prehospital TH using conventional cooling methods such as intravenous chilled saline. Further clinical investigations of prehospital TH are clearly needed, including the development and evaluation of newer technologies that can be applied in the prehospital setting to more rapidly induce TH and potentially yield improvements in clinical outcomes.

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