Targeted temperature management for survivors of sudden cardiac arrest

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Background

It is estimated that over 300,000 people each year with suffer from Sudden Cardiac Arrest (SCA) in the United States [1]. SCA frequently leads to prolonged hospitalization and is highly fatal with a mortality rate of approximately 90%. The leading cause of morbidity and mortality in SCA is profound neurologic injury, primarily due to lack of cerebral circulation during the arrest period, followed by secondary insults such as cerebral edema, reperfusion injury and hyperthermia [2]. SCA most commonly occurs outside of the hospital where mortality is significantly worse than in patients who suffer SCA inside a hospital [1,3]. SCA is often further stratified by presenting rhythm that can be "shockable" (treated with an electrical defibrillation such as Ventricular Tachycardia (VT) / Ventricular Fibrillation (VF)) versus rhythms not treated with defibrillation such as pulseless electrical activity (PEA) or asystole.

Since the landmark trials of *Treatment of comatose survivors of out of hospital cardiac arrest with induced hypothermia* [4] and *the hypothermia after cardiac arrest study group* [5], TTM has become a standard of care for Out of Hospital Cardiac Arrest (OHCA) survivors who are comatose. Although initial trials only demonstrated a benefit of TTM after VF / VT arrest, the practice has been expanded to nearly all patients due to the improvement in neurologic outcomes and survival [6-8].

In December 2013 Nielsen et al. published the *Targeted Temperature Management 33°C versus 36°C after cardiac arrest* [9] trial which resulted in an increased focus on maintaining normothermia after cardiac arrest and led to the currently preferred term "Targeted Temperature Management" (TTM) over mild therapeutic hypothermia. At this time cooling to a target temperature of 32°C to 34°C is still standard of care in comatose survivors of OHCA, though adoption rates vary between institutions [10].

Treating patients with temperature management

In 2002 The International Liaison Committee on Resuscitation (ILCOR) released an advisory statement stating, "Unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32°C to 34°C for 12 to 24 hours when the initial rhythm was Ventricular Fibrillation (VF) and noting that such cooling may also be beneficial for other rhythms or in-hospital cardiac arrest" [11]. Since then the American Heart Association guidelines has also incorporated recommendations for temperature management for survivors of SCA with non-shockable rhythms [12].

The decision to initiate TTM in comatose survivors of SCA should be made quickly as evidence suggests that mortality increases with each hour of treatment delay [13]. Cold saline can be safely infused rapidly and can be made available in emergency response vehicles [14], however caution should be used when infusing cold saline in patients who have not achieved ROSC or are hemodynamically unstable given the findings of the RINSE trial, in which cold saline infusion prior to ROSC appeared to be associated with a decreased rate of ROSC in patients with VT/VF but overall had no impact on outcomes [15].

Targeted temperature management can be achieved with conventional methods or with modern commercial cooling devices [16]. Conventional methods often include an initial bolus of 4°C saline followed by the placement of ice bags to the neck, groin and axilla or the use of rubber cooling blankets. These methods, while having the benefit of being widely available and quick to initiate, lack the internal feedback of intravascular cooling and are less effective in maintaining the targeted temperature [17,18]. There are commercially available surface cooling devices such as Arctic Sun device (Medivance) and others. These systems have internal feedback to avoid overcooling and seem to be more efficient at reaching targeted temperatures [19].

Intravascular cooling is able to rapidly achieve targeted temperature and may reduce the time out of the targeted range better than surface cooling techniques [19]. These systems use a closed circuit of cooled fluid that circulates past venous blood. The primary complications associated with these devices are similar to other central lines and are related to vessel injury, venous thrombosis and catheter related bloodstream infection [20,21]. In general, however, these catheters appear to be safe when inserted by experienced intensivists.

In 2015 Deye *et al.* published a randomized control trial comparing endovascular and external temperature management [17]. In this study 400 survivors of SCA were randomly assigned to the Coolgard (Zoll) catheter or external cooling using fans, ice packs to the torso, groin and head, and a tent. There was no identifiable difference in neurologic recovery, however the group receiving endovascular TTM more rapidly achieved and maintained the targeted temperature (33° C).

Prognosis

Despite advances in post cardiac arrest care, a resuscitated cardiac arrest survivor still has a very poor prognosis. One of the most challenging aspects in caring for SCA survivors who are treated with TTM is estimating the specific prognosis of the individual patient. Determination of prognosis is typically deferred for 72 hours after a

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hypoxic ischemic event and is often based primarily on physical exam [22]. The implementation of temperature management, however frequently requires the use of sedatives and paralytics to reduce shivering, thus limiting the ability to determine prognosis by physical examination alone [23].

In 2010 Rossetti *et al.* studied 111 patients after cardiac arrest that were treated with TTM and observed that at 72 hours after the arrest patients were more likely to have false negative predictors of poor prognosis such as incomplete brainstem reflexes, myoclonus, and especially absent pain responses [24]. Somatosensory Evoked Potentials and EEG may be useful tools in determining a prognosis in comatose patients, yet these methods have their limitations as well [25]. Patients generally must be free from all sedating and neuromuscular blocking agents prior to attempting prognostication.

It can be difficult to clinically ascertain which patients will benefit from temperature management prior to initiating treatment. Since the adoption of TTM after SCA, attempts have been made to determine early in the patient's course the likelihood of an individual surviving with good neurologic recovery. Reduced time from activation of emergency services to spontaneous circulation is strongly associated with better neurologic outcomes presumably due decreased time without cerebral perfusion [26]. Clinical models have been developed following flow diagrams using patient specific characteristics including time to ROSC to predict outcomes [27]. Unfortunately it is common that the exact time that an individual became pulseless cannot be determined.

A recently published scoring system by Kiehl *et al.* called C-GRApH enables the clinician to stratify the likelihood of poor neurologic outcome based on 5 equally weighted variables which are quantitative and typically known at the time of initial hospital evaluation [28]. In this scoring system the patient receives one point for each of the following: known history of (C)AD at the time or presentation, serum (G)lucose ≥200 mg/dL, (R)hythm of arrest other than VT/VF, (A)ge >45, and (pH) ≤7.0. Higher scores indicate increased likelihood of poor neurologic outcomes. This scoring system focuses on variables that are available at the time of admission to the hospital, such as rapidly available labs, and does not rely on time of the arrest or ROSC.

Economic cost of medical care after SCA

Data on the economic costs of medical care associated with SCA is limited and largely from before the advent of TTM [29-32]. In the era of TTM and early percutaneous coronary intervention in post-SCA patients with favorable resuscitation features [33], economic (and emotional) costs have almost certainly increased. One more recent single-center study conducted in the United Kingdom of 69 patients admitted for OHCA reported an approximate cost per survivor to discharge, which accounts for the total cost of survivors and non-survivors, of £50,000. The cost per survivor with a Cerebral Performance Score of 1-2 (indicating good neurologic outcome) was £65,000 with an estimated cost per quality of life year (QALY) of £16,000, 69% of these costs were related to intensive care [34].

Summary

Sudden cardiac arrest is a common, unfortunate, and highly fatal event which is often associated with poor neurologic recovery. SCA is associated with significant emotional and economic burdens on families. TTM is an effective treatment that improves neurologic outcomes in selected patients. Determining prognosis in SCA can be challenging in the era of TTM, however novel models and diagnostic tools may aid in the early stratification of comatose patients.

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