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Mild Induced Therapeutic Hypothermia for Survivors of Cardiac Arrest

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1. Introduction

Despite advances in emergency response and critical care, good neurologic outcome after cardiac arrest is difficult to achieve, and interventions during the resuscitation phase and treatment within the first hours after the event are crucial. Although recommended by organizations such as the American Heart Association (AHA) and the International Liaison Committee on Resuscitation (ILCOR), implementation of induced mild therapeutic hypothermia for survivors of cardiac arrest in the United States has been slow, at least in part, because of the perception that this therapy is technically difficult, especially at the community level. In this chapter, we review the pathophysiology, cooling techniques, clinical evidence and uses (including costs), and effectiveness of induced mild therapeutic hypothermia in adult patients after cardiopulmonary resuscitation, using any cooling method applied within six hours of arrest. Neurologic outcome, survival and adverse events are the main outcome parameters outlined here. In addition, we also include a discussion of the applicability of mild therapeutic hypthermia for both academic health centers and community hospitals, as well as areas of uncertainty, guidelines, and recommendations.

2. Epidemiology of cardiac arrest

The incidence of out-of-hospital sudden cardiac arrest in industrialized countries is about 62 cases per 100,000 a year making sudden cardiac arrest a major cause of death in the United States amounting to more than 300,000 occurrences of cardiac arrests outside of hospital each year (Adler et al, 2011). Resuscitation is attempted on roughly 100,000 of these arrest patients but results in only 40,000 patients who survive upon arrival to the hospital (Holzer, 2010).
Despite advances in emergency medical services the mortality and morbidity associated with out-of hospital cardiac arrest is high. In 2006, the National Registry of Cardiopulmonary Resuscitation (CPR) published statistics on 19,819 adults and 524 children with return of spontaneous circulation after cardiac arrest. The mortality rates were 67% among adults and 55% among children (Jacobshagen et al, 2010). Currently, less than half of cardiac arrest patients survive to discharge and less than a third of those discharged have a good neurologic outcome as defined by the Cerebral Performance Category (CPS) Scale (Adler et al, 2011). The cost of caring for patients with poor neurologic function within the first six months alone can range anywhere from $10,000 to $300,000, with an increasing morbidity generally associated with increasing cost (Merchant et al, 2009).

3. Pathophysiology of induced mild therapeutic hypothermia

The brain receives approximately 15% of the human resting cardiac output despite comprising 1-2% of our total body weight, illustrating the high metabolic demands associated with the brain. During cardiac arrest the blood supply is interrupted leading to global cerebral ischemia.

Ischemic events are especially detrimental to the brain and are a major cause of morbidity in cardiac arrest survivors. Areas such as the hippocampus, neocortex, cerebellum, corpus striatium, and thalamus are the most vulnerable to global ischemia. Necrosis and apoptosis have both been reported in cardiac arrest victims and it still is unclear the extent to which each of these processes contribute to neuronal cell death. The brain is damaged through an ischemic cascade of events occurring on a time scale of minutes-to-days after cardiac arrest and is summarized below.

A lack of oxygen hinders the neurons ability to produce ATP. Consequently, cells switch to anaerobic metabolism which consumes glucose and produces lactic acid. As glucose concentrations are exhausted, ion transporters using ATP fail to function. Cells become depolarized allowing ions, including calcium, to flow into the cell. Due to the lack of ATPase activities, cells cannot pump calcium out of the intracellular space, and as intracellular calcium levels rise they trigger the release of excitatory neurotransmitters. Glutamate, one of the excitatory neurotransmitters, acts on AMPA and NMDA receptors to allow more calcium into cells and thereby increases the intracellular calcium leading to production of neurotoxic chemicals such as free radicals, reactive oxygen species and calcium-dependent enzyme (Sinclair & Andrews, 2010). This process is referred to as excitotoxicity. Calcium-dependent enzymes such as calpain, endonucleases, and phospholipases break down cells making them more permeable to harmful chemicals and leads to damage of the mitochondrial membrane, ultimately causing release of pro-apoptotic factors that stimulate the caspase cascade and inducing cell suicide. Cells that die due to necrosis cause a release of glutamate and other neurotoxic compounds that act on surrounding cells and perpetuate excitotoxicty.

Hypothermia exerts its effect on the ischemic cascade mentioned above to improve neurologic outcome after cardiac arrest. The following discussion will elaborate on mild therapeutic hypothermia and how it mitigates the pathologic processes involving: 1) blood-brain barrier permeability and edema, 2) inflammation, 3) metabolism, 4) excitotoxicity, 5) intracellular calcium-dependent signaling 6) cerebral vascular effects, and 7) neuronal cell death.

3.1 Blood-brain barrier permeability and edema

The blood-brain barrier displays increased permeability after ischemia and allows the entrance of water, electrolytes, and potentially toxic substances into the brain parenchyma. Hypothermia has been shown to decrease the extravasation of certain protein markers such as horseradish peroxidase from the serum into the brain. Studies have also demonstrated that treatment with hypothermia in focal ischemia results in a decrease in brain water content as measured by MRI, and leads to a reduction in the diffusion of water into the brain and a consequent reduction in vasogenic edema by alleviating blood-brain barrier injury (Sinclair & Andrews, 2010). Vasogenic edema is a result of damage to the blood-brain barrier and the passage of large osmotically-active proteins like albumin into the brain.

The attenuation of matrix metalloproteases is another effect of hypothermia that reduces the permeability of the blood-brain barrier. Matrix metalloproteases are important for the extravasation of several substances into the brain including immunologic and other inflammatory cells. Reducing movement of these cells into the brain decreases deleterious edema associated with inflammatory immune responses to ischemia and neuronal cell injury.

3.2 Inflammation and immune response

Hypothermia mitigates the inflammation response by reducing the leukocyte extravasation as well as the endogenous inflammatory response of the brain to ischemia. Astrocytes and microglia respond to tissue damage in the brain by proliferating and secreting large quantities of pro-inflammatory cytokines such as tumor necrosis factor-α and interleukin-1 which recruit cells of the immune system. Hypothermia reduces the activation of astrocytes and microglia thereby reducing the pro-inflammatory signaling and the ensuing immune response (Sinclair & Andrews, 2010).

The inflammatory response in the brain also results in the release of reactive oxygen species by astrocytes and microglia. Hypothermia, therefore, also reduces the levels of potentially damaging free radicals such as superoxide, nitric oxide, and hydroxyl radicals within the brain by decreasing their secretion from microglia and astrocytes. Hypothermia also increases the levels of superoxide dismutase, the enzyme that clears superoxide from the body, and decreases nitric oxide synthase, the enzyme responsible for production of nitric oxide. This reduction in reactive oxygen species production and increase in reactive oxygen species scavenger enzymes results in decreased neuronal damage.

3.3 Metabolism

Hypothermia has been proven to decrease glucose utilization. Studies implementing 2-deoxyglucose, a glucose analog that can be taken up by glucose transporters but not digested, has shown that hypothermia decreases utilization of glucose when compared to normothermia. Global ischemia affects the brain more than the liver due to the small stores of glycogen found in the brain compared to large stores found in the liver. Therefore, any reduction in glucose utilization will attenuate the damaging effects of poor cerebral perfusion. Hypothermia reduces the metabolic demands of the cell, preserving cellular ATP concentration more effectively when compared to normothermia. Reducing core temperature 1°C decreases metabolic rate by approximately 6%-8% (Adler et al, 2011).

The cell's ability to maintain electrochemical gradients depends heavily upon ATP concentrations. Loss of transmembrane electrochemical gradients directly precedes failure of synaptic transmission and axonal conduction. Hypothermia's ability to reduce metabolic demands, preserve ATP, and potentiate electrochemical gradients translates to better neurologic outcomes after recovery from cardiac arrest.

3.4 Excitotoxicity

The metabolic depletion of ATP associated with ischemia in cardiac arrest results in an inappropriate release of excitatory neurotransmitters such as glutamate. A reduction in the blood flow to the brain allows levels of glutamate to build up in the extracellular space around neurons. This rise in glutamate leads to activation of glutamatergic receptors AMPA (alpha-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate) and NMDA (*N*-methyl d-

aspartate). Glutamate acts through AMPA and NMDA to produce an influx of calcium from the extracellular fluid to the intracellular fluid. This inflow of calcium can injure the cell by initiating several cascades within the cell including, free radical generation, mitochondrial injury, and ultimately apoptosis (Nolan et al, 2008). Hypothermia inhibits the release of glutamine and dopamine while also inducing neurotrophic factors that further reduce glutamine release.

3.5 Intracellular calcium-dependent signaling

Global ischemia leads to an increase in intracellular calcium, thereby affecting normal signaling protein kinases in the cell. Proteins such as calmodulin-dependent kinase II (CaMKII) and protein kinase C (PKC) are rescued by hypothermia (Sinclair & Andrews, 2010). These proteins, as well as other signaling factors, are temperature-sensitive. Controlling signaling factors and proteins such as CaMKII and PKC through hypothermia influences neuronal injury and normal cell signaling.

3.6 Cerebral vascular and cellular effects

Hypothermia affects secretion of vasoactive substances such as endothelin, thromboxane A2, and prostaglandin I2 in the brain. Endothelin and thromboxane A2 have vasoconstrictive effects while prostaglandin I2 is a vasodilator. Thromboxane A2, endothelin, and prostaglandin I2 mediate vascular homeostasis in the brain; during ischemic and traumatic events homeostatic balance is shifted towards vasoconstriction, hypoperfusion, and thrombus formation. Hypothermia has been shown in animal models and small clinical studies to alter the response to injury by attenuating the vasconstrictive response. However, regulation of cerebral perfusion is complex and dependent on several factors including the presence or absence of cerebral autoregulation, ventilator settings, serum blood gas levels, systemic blood pressure, osmotic therapy, etc (Sinclair & Andrews, 2010).

Necrosis and apoptosis are the result of prolonged tissue ischemia and can be influenced by hypothermia. Several gene families associated with apoptosis are temperature-sensitive. Brain cells can sense irreversible injury and begin the process of self-destruction. Hypothermia leads to a delayed response of the cell to injury and this slowed response is mediated by a delay in genetic regulation (Sinclair & Andrews, 2010). Ultimately, hypothermia slows secondary injury and apoptosis through delaying the cells initial reaction to damage. Apoptosis occurs over the time frame of hours-to-days making hypothermia a major factor in mitigating apoptosis during the post-resuscitation phase.

4. Cooling methods

Several different cooling techniques are available for use in therapeutic hypothermia; however, all of the various techniques fall into two general categories: surface cooling and core cooling. Surface cooling can be carried out in two ways; the first utilizes pre-cooled pads while the second makes use of heat-exchanging mattresses or pads. Surface cooling was used in the two hallmark clinical trials carried out in 2003 in Europe and Australia that first demonstrated the beneficial effects of hypothermia on witnessed cardiac arrest survivors (Bernard et al, 2003; Holzer & Sterz, 2003).

Core cooling can be achieved with the use of intravascular cooling catheters filled with cold saline or by intravenous injection of cold fluids. Devices for core cooling and surface cooling have been specifically designed for use in therapeutic hypothermia but the ultimate goal,

whether using either surface or core cooling methods, is to rapidly cool the patient and maintain a stable temperature between 32-34°C for at least 24 hours.
Various measurements and devices may be used to monitor relevant core body temperature including esophageal probes, endotracheal tube cuff monitors, and non-invasive continuous cerebral temperature monitoring (Zeiner et al, 2010; Haugk et al, 2010). During the initial phase of head and neck cooling, jugular bulb temperature (Tjb), (which may reflect brain temperature) appears to be lower than esophageal temperature (Wandaller et al, 2009).

4.1 Surface cooling

4.1.1 Ice packs

Ice packs are an inexpensive and easy technique to initiate cooling. However, they can be messy and less effective at cooling and maintaining target temperature. Ice packs can be placed all over the body, but are more effectively placed in anatomic areas that have large heat-exchange capability due to their blood flow. These areas include the head, neck, axillae, and groin. The average temperature drop attained by using ice packs is between 0.03-0.98°C per hour (Adler et al., 2011).

4.1.2 Blankets or surface heat-exchange devices

Conventional surface cooling blankets are not ideal because of poor surface contact with the patient's skin. Generally, water-circulating cooling devices and ice packs used in combination can be effective at rapidly cooling patients. Many clinical studies have used this combination as their cooling technique. The patient is sandwiched between two blankets or cooling devices and ice packs are then applied. Once target temperature is achieved, the ice packs are removed and the blanket or cooling devices are used alone to maintain the target temperature. Newer cooling devices, specific for use in therapeutic hypothermia, use an adhesive gel to facilitate heat exchange that make them more effective at obtaining and maintaining target temperature.
Weihs and coworkers (2011) used adult, human-sized pigs to study the importance of surface area for the cooling efficacy of mild therapeutic hypothermia. Each of five adult, human-sized pigs (88-105 kg) was randomly cooled in three phases with pads that covered different areas of the body surface corresponding to humans (100% or 30% [thorax and abdomen] or 7% [neck]). The cooling pads were effective and safe for rapid induction of mild hypothermia in these porcine simulators. depending on the percentage of body surface area covered. Extrapolating to humans, covering only the neck, chest, and abdomen may achieve satisfactory cooling rates.
Convective-immersion surface cooling using a continuous shower of 2 degrees C water (ThermoSuit System) has also been found to be a rapid, effective method of inducing therapeutic hypothermia (Howes et al, 2010) and demonstrated improvement in survival and neurologic outcome in swine compared to normothermia (Weihls et al, 2008).

4.1.3 Cooling helmet

Helmet cooling devices are also available and have been used in some clinical trials. These helmets contain a solution of glycerol that facilitates heat exchange. Although this method is effective in cooling the brain it is much slower at reducing overall body temperature when compared to other methods.

4.2 Core cooling

4.2.1 Catheter-based technologies

Catheter-based technologies are usually placed in the femoral vein and provide heat exchange between the cooled saline that passes through a large coil in the catheter and the blood. The coiling provides a mechanism to increase surface area, thereby increasing the heat exchange between blood passing over the catheter. Internal cooling and rewarming is much faster and superior to other techniques in tightly regulating target temperature; it is possible to cool patients by 1.46°C - 1.59°C per hour (Jacobshagen et al, 2010). A potential advantage of using catheter-based cooling combined with anxiolytics is that it may avoid the need to use paralytics to decrease the shiver seen in surface cooling techniques.

4.2.2 Cold fluid infusion

Several studies have made use of intravenous cold fluid infusion for the induction of hypothermia. The rates of infusion differ between studies but the overall outcome is rapid cooling of the patient. Cold fluid infusion is a means of inducing hypothermia and cannot be used in the long-term maintenance of hypothermia. Usually, cold fluid infusions are used in conjunction with surface cooling methods to regulate and maintain patient body temperature. Most studies have used either normal saline or lactated Ringer solution as their cooling fluids. Evidence from reports using cold fluid infusion have not been associated with increased venous pressure, left atrial filling pressures, pulmonary pressures, pulmonary edema, cardiac arrhythmia, or other major complications.

Categories of Cooling	Techniques of Cooling	Advantages	Disadvantages
Surface Cooling	Ice packs	Inexpensive can be implemented very quickly.	Slow rate of cooling and provides poor regulation of target temperature.
	Cooling blankets and surface heat-exchange devices	Fair regulation of target temperature once it is obtained.	Slow rate of cooling unless used in conjunction with other techniques.
	Cooling helmet	Fair regulation of target temperature once it is obtained.	Slowest rate of cooling among techniques unless used in conjunction with other cooling methods.
Core Cooling	Catheter-based technologies	Rapid rate of cooling, tight target temperature regulation, minimize shiver and possible avoidance of paralytic usage.	Increased chance of thrombus formation
	Infusion of cold fluids	Rapid rate of cooling	Poor regulation of target temperature

Table 1. Cooling Technique Summary

5. Clinical evidence and uses

5.1 Clinical studies

The abovementioned landmark clinical trials from Europe and Australia, respectively, in 2003 established the benefits of hypothermia and have served as the basis for subsequent therapeutic hypothermia guidelines and clinical trials. Most clinical trials evaluate the

benefits of hypothermia by scoring patients on the CPC Scale, a tool that rates a patient's neurologic status, or by measuring survival rates.

The European trial enrolled 275 patients whose cardiac arrest was caused by ventricular fibrillation or pulseless ventricular tachycardia. Patients were randomly assigned to either hypothermic (n = 137) or normothermic (n = 138) groups. Hypothermic subjects were cooled to between 32-34°C for 24 hours with a cold air mattress. The primary endpoint of this study was to establish a favorable neurologic outcome in patients six months after cardiac arrest. The authors found that 55% of surviving hypothermic patients had a favorable neurologic outcome, as defined by a score of 1 or 2 on the CPC Scale, compared to 39% of surviving normothermic patients. A secondary endpoint was to evaluate complications within the first seven days after cardiac arrest, and mortality rate at six months. The European study demonstrated that neurologic outcome, as well as patient survival at six months (55% vs. 41%), both significantly improved in the hypothermic group as compared to the normothermic group (Holzer, 2002).

In the Australian trial, 77 comatose cardiac arrest survivors with ventricular fibrillation or pulseless ventricular tachycardia as the initial rhythm were similarly assigned to normothermic (n = 34) or hypothermic (n = 43) groups based on randomization. The hypothermic group was cooled to 33°C with ice packs for 12 hours and showed a 49% survival with favorable neurologic outcome (i.e., discharged home or to a rehabilitation facility, with no or moderate disability), while the normothermic group had a 26% survival with favorable neurologic outcome at hospital discharge (Bernard et al, 2002).

In 2009, Arrich and colleagues performed a Cochrane systematic review and meta-analysis to assess the effectiveness of therapeutic hypothermia in patients after cardiac arrest. Neurologic outcome, survival and adverse events were the main outcome parameters. The authors included all randomized controlled trials assessing the effectiveness of the therapeutic hypothermia in patients after cardiac arrest without language restrictions. Studies were restricted to adult populations cooled with any cooling method applied within six hours of cardiac arrest. Four trials and one abstract reporting on 481 patients were included in the systematic review. Quality of the included studies was good in three out of five included studies. For the three comparable studies on conventional cooling methods all authors provided individual patient data. With conventional cooling methods patients in the hypothermia group were more likely to reach a best cerebral performance category score of 1 or 2 (CPC, 5-point scale; 1 -- good cerebral performance, to 5 -- brain death) during hospital stay (individual patient data; RR, 1.55; 95% CI 1.22 to 1.96) and were more likely to survive to hospital discharge (individual patient data; RR, 1.35; 95% CI 1.10 to 1.65) compared to standard post-resuscitation care. Across all studies, there was no significant difference in reported adverse events between hypothermia and control. The authors concluded that conventional cooling methods to induce mild therapeutic hypothermia seem to improve survival and neurologic outcome after cardiac arrest, and their review supports the current best medical practice as recommended by the International Resuscitation Guidelines.

Testori and colleagues (2011) retrospectively studied 347 cardiac arrest survivors aged $\geq$ 18 years suffering a witnessed out-of-hospital cardiac arrest with asystole or pulseless electric activity as the first documented rhythm, for whom hypothermia was induced in 135 patients. They found that subjects who were treated with mild therapeutic

hypothermia at a temperature of 32-34°C for 24 hours were more likely to have good neurologic outcomes in comparison to patients who were not treated with hypothermia, with an odds ratio of 1.84 (95% confidence interval: 1.08-3.13). In addition, the rate of mortality was significantly lower in the hypothermia group (odds ratio: 0.56; 95% confidence interval: 0.34-0.93).

While shortening the delay from spontaneous circulation to hypothermic target temperature has been theorized as a way of improving survival and neurologic outcome, randomized controlled trials and clinical registries have not shown evidence of whether the time to target temperature correlates with neurologic outcome. A recent study has reported that in comatose cardiac arrest patients treated with therapeutic hypothermia after return of spontaneous circulation, a faster decline in body temperature to the 34°C target appears to predict an unfavorable neurologic outcome (Haugk, 2011). Among 588 survivors of cardiac arrest managed with therapeutic hypothermia, the median time from restoration of spontaneous circulation to reaching a temperature of less than 34°C was 209 minutes (interquartile range [IQR]: 130-302) in patients with favorable neurologic outcomes compared to 158 minutes (IQR: 101-230) ($p < 0.01$) in patients with unfavorable neurologic outcomes. The adjusted odds ratio for a favorable neurologic outcome with a longer time to target temperature was 1.86 (95% CI 1.03 to 3.38, $p = 0.04$). Whether faster cooling is detrimental or patients with more severe neurologic damage show a faster cooling rate has to be further evaluated.

Animal and human studies have suggested that hypothermia impairs renal function. Zeiner et al (2004) reported that 24 hours of mild therapeutic hypothermia was associated with a delayed improvement in renal function that was not reflected in serum creatinine values, and this transient impaired renal function appeared to be completely reversible within 4 weeks. In trying to determine the relationship between acute kidney injury on survivors of cardiac arrest treated with therapeutic hypothermia we found that the incidence of acute kidney injury in patients with a CPS 1 or 2 score was 13.6% compared to 86.4% in patients with a CPS score > 2 ($p < 0.001$) (J. Prior, personal communication). Stage 3 acute kidney injury correlated with poor neurologic outcome ($p = 0.04$) but there was no correlation between Stages 1 and 2 and neurologic recovery. A longer duration of cardiac arrest was predictive of the subsequent development of acute kidney injury ($p = 0.01$). In summary, the presence of acute kidney injury in survivors of cardiac arrest treated with therapeutic hypothermia appears to be associated with poorer neurologic function determined at the time of hospital discharge. Acute kidney injury in this population may serve as a marker for the severity of anoxic injury incurred during arrest.

5.2 Indications and contraindications

5.2.1 Indications

The AHA has recommended that therapeutic hypothermia is indicated in adult patients with out-of-hospital cardiac arrests and who have an initial rhthym of ventricular fibrillation or nonperfusing ventricular tachycardia, that are comatose or have a Glasgow coma score < 8, that are hemodynamically stable, and lack a verbal response. Although these are the criteria for which hypothermia is recommended, there are other patients that may benefit from therapeutic hypothermia such as post-resuscitation patients having initial rhthyms other than ventricular fibrillation or nonperfusing ventricular tachycardia, as well as in-hospital cardiac arrest patients.

Survivors of witnessed out-of-hospital cardiac arrest of suspected cardiac origin
Persons with a Glasgow Coma Scale ≤ 8
Persons with ventricular fibrillation or non-perfusing ventricular tachycardia (those with other rhythyms such as asystole or electomechanical dissociatrion *may* also benefit although firm data is lacking)
Persons who are hemodynamically stable (those in cardiac shock *may* also benefit although firm data is lacking)
Consider for survivors of in-hospital cardiac arrest (although firm data is lacking)

* Adapted from Holzer 2010.

Table 2. Summary of indications for induced therapeutic hypothermia in comatose survivors of cardiac arrest.

5.2.2 Contraindications

Exclusion criteria for the use of therapeutic hypothermia are based upon increased risks to the patient. Studies have reported increased but non-significant increases in risk for the following patients: having major surgery within the previous 14 days; having systemic infections or sepsis, in a coma which is non-cardiac in origin, having active known bleeding or inherited bleeding disorder, being pregnant or terminally ill, those with a do-no-resuscitate (DNR) order, or having a tympanic temperature < 30°C upon admission (Oommen & Menon, 2011).

6. Outcomes

Various methods have been used to try and determine the likelihood of neurologic recovery after cardiac arrest, but no single test is effective in accurately predicting neurologic outcome post-resuscitation. Clinical trials have established that combining examinations, laboratory tests and accounting for co-morbidities is often more accurate in determining neurologic outcome. Precise predictors of neurologic recovery are lacking and seriously limit the way clinicians assess patient prognosis, develop appropriate plans of care, and counsel family members. Therefore, more clinical studies are required to determine a uniform protocol for predicting neurologic outcome.

6.1 Modalities predicting neurological outcome

6.1.1 Neurologic examination

A neurologic examination is a fairly reliable predictor of neurological outcome after cardiac arrest. The presence of neurologic function during or immediately after return of spontaneous circulation (ROSC) roughly predicts a good neurologic outcome. Conversely, patients with a Glasgow Coma motor score of ≤ 2 or absent pupillary or corneal reflex at 72 hours can be predicted to have a poor neurologic outcome. The CPC Scale has also been classically used to predict patient outcome. Patients with a CPC scale score of 1 and 2 are likely to have good

outcomes, while patients scoring 3, 4 or 5 have a significantly higher chance of having a poor neurologic outcome or death (Nolan et al, 2008). It is worth noting that the neurologic exam and CPC score can be influenced by the physiologic circumstances of the patient such as hypotension, shock, and severe metabolic dysfunction. Interventions such as paralytics, sedatives, and hypothermia also influence the findings of a neurologic examination and must be taken into account. Cranial nerve findings and motor response to pain are the best physical features estimating neurologic status and recovery.

1	Good cerebral performance: conscious, alert, able to work, might have mild neurologic or psychologic deficit.
2	Moderate cerebral disability: conscious, sufficient cerebral function for independent activities of daily life. Able to work in sheltered environment.
3	Severe cerebral disability: conscious, dependent on others for daily support because of impaired brain function. Ranges from ambulatory state to severe dementia or paralysis.
4	Coma or vegetative state: any degree of coma without the presence of all brain death criteria. Unawareness, even if appears awake (vegetative state) without interaction with environment; may have spontaneous eye opening and sleep/awake cycles. Cerebral unresponsiveness.
5	Brain death: apnea, areflexia, EEG silence, etc.

Note: If patient is anesthetized, paralyzed, or intubated, use "as is" clinical condition to calculate scores.

Table 3. Cerebral Performance Categories Scale (CPC Scale)

6.1.2 Neurophysiologic tests

Electroencephalography (EEG) has been used to characterize the degree of brain damage after cardiac arrest. Various EEG patterns have been associated with poor neurologic outcome such as generalized suppression, burst-suppression patterns with generalized epileptiform activity, and generalized periodic complexes on a flat background. Nevertheless, EEG alone is likely to be insufficient to prognosticate neurologic recovery. The EEG requires a physician with experience in its interpretation and knowledge of the influence of drugs and metabolic disorders on its results.

Madl & Holzer (2004) reviewed the literature on the pathophysiology of brain injury caused by cardiac arrest and the beneficial effect of therapeutic hypothermia on neurologic outcome. They summarized that electrophysiologic techniques and molecular markers of brain injury allow the accurate assessment and prognostication of long-term outcome in cardiac arrest survivors. In particular, somatosensory evoked potentials (SSEPs) appear to have the highest prognostic reliability; a systematic review of 18 studies analyzed the predictive ability of SSEPs performed early after onset of coma and found that absence of cortical SSEPs identify patients not returning from anoxic coma, with a specificity of 100%. Somatosensory-evoked potentials test the patency of the neuronal pathways, and are less affected by common drugs and metabolic disorders, making them a more reliable predictor of neurologic outcome than other modalities (Nolan et al, 2008). However, use of SSEPs in post-resuscitation patients requires advanced neurologic training which is usually restricted to specialized centers.

6.1.3 Neuroimaging

Neuroimaging is often performed to define structural brain injury related to cardiac arrest (either as a cause or consequence), including hemorrhage and cerebral vascular occlusion.

Most clinical studies evaluating neurologic outcome after use of therapeutic hypothermia do not make use of neuroimaging. The most common type of neuroimaging employed has been cranial computed tomography (CT), predominately because of the technical difficulties in performing magnetic resonance imaging (MRI) and positron emission tomography (PET) scans in the setting of arrest. Limited studies have shown that diffusion-weighted imaging (DWI), fluid attenuated inversion recovery (FLAIR), abnormalities in PET, and magnetic resonance spectroscopy can help predict poor neurologic outcome (Nolan et al, 2008).

6.1.4 Biochemical markers

Biochemical markers derived from the cerebrospinal fluid (CSF) and peripheral circulation, such as creatine phosphokinase (CPK) and neuron-specific enolase (NSE) respectively, have been used to predict neurologic outcome after cardiac arrest. The ease of obtaining blood compared to CSF has favored blood-based biochemical markers. Neuron-specific enolase is easily measured in the blood after injury to the brain and is, therefore, a good marker for neurologic outcome. Studies have shown that values of NSE > 33μg/L are predictor of poor neurologic outcome.

A calcium-binding protein from astroglia and Schwann cells, S100β, may also be a marker of neurologic outcome. An S100 β concentration > 1.2 μg/L, drawn between 24 and 48 hours after ROSC, is indicative of poor neurologic recovery (Nolan et al, 2008). Biomarker threshold values established in clinical trials vary based on the time blood and CSF are drawn after ROSC and the method for measuring the biomarker. Therefore, standardization must be applied in future clinical trials so that true threshold values can be elucidated and used to predict patient outcome.

6.1.5 Co-morbidities

We previously reported that the risk of poor neurologic outcome among patients treated with mild therapeutic hypothermia was related to the number of risk factors present (Table 4) (Vanston et al, 2010). A first rhythm of non-ventricular tachycardia/ventricular fibrillation after cardiac arrest, acute kidney injury within the first 72 hours of intensive care, and any treated cardiac arrhythmia were factors significantly associated with poor neurologic outcome and death (Table 4).

	No. patients			
	Good CPS (*n* = 17)	Poor CPS (*n* = 24)	Risk of poor CPS (%)	No. risk factors[d] (95% CI)
None	6	1	17	(0.3-52.6)
One	9	2	18	(2.3-51.8)
Any two	2	15	88[b]	(63.6-98.5)
All three	0	6	100[c]	(54.1-100)

[a] CPS. Pittsburgh Cerebral Performance Scale; C.I. = confidence intervals
[b] Significantly greater than the risk of poor neurologic outcome amongs patients with no predictive factors ($p = 0.004$).
[c] Significantly greater than the risk of poor neurologic outcome amongs patients with no predictive factors ($p = 0.002$).
[d] Include first rhythym other than ventricular fibrillation/ ventricular tachycardia, any arrhythmia, and acute kidney injury.

Table 4. Risk of poor neurologic outcome among patient treated with mild therapeutic hypothermia, according to number of risk factors present.[a]

6.2 Adverse effects

Adverse effects of mild induced therapeutic hypothermia are either directly related to the cooling device or due to hypothermia itself. In 41 clinical trials using therapeutic hypothermia the overall rate of adverse events related to a cooling device was 1% (Holzer, 2010). These adverse effects included three cases of bleeding, eight cases of infection, ten cases of deep venous thrombosis, and eight cases of pulmonary edema. The cases of deep venous thrombosis were seen in patients that were cooled with a catheter-based device, while the cases of pulmonary edema occurred in patients that were cooled with cold intravenous fluid.

Hypothermia causes a decrease in insulin secretion, as well as insulin resistance in many patients. This state of hyperglycemia requires administration of insulin to maintain glucose levels within an acceptable range. More importantly, during the re-warming phase patients can regain appropriate sensitivity to insulin rapidly, making them susceptible to hypoglycemia if insulin administration is not reduced accordingly. Glycemic lability is one of several reasons why re-warming rates after hypothermia are typically slow and controlled.

Some of the adverse effects most commonly associated with therapeutic hypothermia include pneumonia, shivering hyperglycemia, cardiac arrhythmias, seizures, and electrolyte disorders. Less frequently seen complications are sepsis, coagulopathy, and metabolic disturbances. Many of these effects can be easily managed by proper patient monitoring. In a study compiling data from major clinical trials on adverse effects unrelated to the cooling devices, such events occurred in 74% of patients who were treated with hypothermia (223 events in 300 patients) and in 71% of 285 patients given standard, normothermic treatment (Holzer, 2010). The incidences of cardiac arrhythmia, hemodynamic instability, bleeding, pneumonia, sepsis, renal failure, seizures, and pancreatitis were not significantly different between the two groups.

7. Slow implementation

Although its use is becoming more widespread, therapeutic hypothermia is still not appropriately initiated for a majority of eligible patients. Concerns with the ease of use, efficacy, and cost have limited use in the community setting. The current level of implementation of therapeutic hypothermia is difficult to measure, although hypothermia registries are attempting to bridge the gap. The AHA, along with some local communities, is advocating for the care of all patients with cardiac arrest at centers specializing in post-arrest care in order to provide the best possible outcomes. Such centers would have the capability to perform therapeutic hypothermia, perform percutaneous coronary intervention, and utilize standardized protocols for the treatment of cardiac arrest survivors, as well as pay close attention to related aspects of overall management including hemodynamic stability, ventilator support (with timely normalization of FiO_2 and pCO_2), thromboembolic prophylaxis, and glycemic control.

8. Ongoing and potential future research

8.1 Neurologic prognosis

In patients managed with therapeutic hypothermia clinical research is ongoing regarding clinical modeling and the use of aspects of the neurologic exam and acute and chronic

medical co-morbidities in predicting neurologic recovery. We have previously found that several simple and reproducible clinical markers (i.e., first rhythm at cardiac arrest; the presence of acute kidney injury in the ICU; any treated cardiac arrhythmia after admission; and Glasgow Coma Score < 8 determined 12 hours after re-warming) can help predict neurologic prognosis during and after treatment, in patients managed with therapeutic hypothermia for cardiac arrest (Vanston, 2010). Additional investigation is neded to examine the potential role of other exam techniques, and electrophysiologic and neurobiochemical tests in reliably predicting neurologic outcomes, and to determine the correlation between laboratory values or exam scores and time after return of spontaneous circulation.

8.2 Non-shockable rhythms/ other cardiac

Small randomized trials and registries have begun to collect data on the use of therapeutic hypothermia in cardiac arrests with non-shockable rhythms and in-hospital cardiac arrests. Recently, in a retrospective cohort study treatment with mild therapeutic hypothermia at a temperature of 32-34°C for 24 hours was associated with improved neurologic outcome and a reduced risk of death following out-of-hospital cardiac arrest in 135 with non-shockable rhythms (Testori et al, 2011). To date, the level of evidence is inadequate to firmly recommend therapeutic hypothermia for these patients; nevertheless, many of these patients are treated with therapeutic hypothermia in the community if their arrest is thought to be of cardiac origin or if the initial rhythm after arrest is unknown. Further research is needed to determine the potential role of therapeutic hypothermia for these subsets of patients. The ILCOR currectly advocates the use of therapeutic hypothermia following perinatal asphyxia-related cardiac arrest in term newborns.

At least one study (a retrospective analysis of the Hypothermia after Cardiac Arrest (HACA) trial) suggested that cooling after successful resuscitation for ventricular fibrillation cardiac arrest did not influence infarct size (Koreny et, 2009). The authors contended that cautious interpretation of the subgroup analysis may indicate a favorable trend for early cooling, and thus additional research is indicated.

8.3 Non-cardiac applications

Clinical trials are still revealing further application of therapeutic hypothermia. It is likely that recommendations and the use of therapeutic hypothermia will expand to encompass several other pathologies such as traumatic brain and spinal cord injury and acute ischemic stroke. Currently, therapeutic hypothermia is not approved by an advisory panel for any other use besides comatose patients after return of spontaneous circulation due to ventricular fibrillation or pulseless ventricular tachycardia (Adler et al, 2011).

8.4 Aspects of treatment

Current and potential future areas of clinical research on treatment aspects of therapeutic hypothermia include, among others:

- Optimal target temperature, duration, onset, cooling rates, and re-warming rates
- Use of external, internal, or mixed modality cooling techniques
- Pharmacologic uses and standardized drug protocols i.e. (analgesics, sedatives, paralytics, etc.)

9. Areas of uncertainty

Some persistent unexposed topics that relate to the pathophysiology of therapeutic hypothermia include the precise mechanism(s) of greatest importance for good neurologic recovery, the mechanism(s) through which hypothermia exerts the most influence, the effects of co-morbidities in reducing the efficacy of therapeutic hypothermia, and the time course of cellular cascades and the ability to attenuate these processes (Holzer, 2010).

10. Guidelines

Sedation, analgesia, and paralysis should be initiated prior to hypothermia to prevent shivering which can increase oxygen consumption, promote labored breathing, increase heart rate, delay hypothermic induction, and increase patient discomfort.

The ILCOR and the AHA recommend that core body temperature of unconscious adult patients with spontaneous circulation after an out-of- hospital ventricular fibrillation cardiac arrest should be lowered to 32-34°C. The cooling process should be started in the pre-hospital setting or as soon as possible and continued for 12-24 hours. Core temperature should be continuously monitored via the esophagus, rectum, trachea or bladder. General management of hypothermia patients includes concurrent measurement of mean arterial pressure, central venous pressure, urine output, arterial blood gases, central venous oxygen saturation, serum lactate, blood glucose, electrolytes, and complete blood count, and continuous ECG monitoring and stabilization.

After hypothermia, patients should be re-warmed at a rate of 0.5°C per hour with avoidance of hyperthermia. Potassium administraction should be stopped to avoid hyperkalemia during the re-warming phase. After re-warming to 36°C, sedation and paralytic agents should be discontinued and the patient should be weened off ventilator support (Jacobshagen et al, 2010). Neurologic recovery can take several hours after discontinuation of hypothermia. Therefore, it is important to wait until the patient is completely re-warmed and stabile before evaluating patients with prognositic neurologic exams like the Glasgow Coma Scale.

11. Conclusions

Mild therapeutic hypothermia is indicated for use in witnessed out-of-hospital cardiac arrest patients with a return of spontaneous circulation, for persons with an initial rhythm of ventricular fibrillation or non-perfusing ventricular tachycardia, for persons who are comatose or have a Glasgow coma score < 8, those who are hemodynamically stable, and those who lack a verbal response. Clinical evidence has shown that mild hypothermia decreases mortality and increases the proportion of patients with a favorable neurologic outcome (score of 1 or 2 on the CPC Scale) with mininimal risk of adverse effects. Therapeutic hypothermia is a relatively inexpensive treatment modality with an incremental cost-effectiveness ratio of $47,168 (Merchant et al, 2009) and can be implemented in a variety of settings from rural community-based hospitals to specialized cardiac and neurologic centers. The indications for mild therapeutic hypothermia will broaden in the future as more clinical trials are conducted. It is important to understand the pathophysiologic processes involved in the post-cardiac arrest syndrome, as well as the concominant changes in human physiology during induced mild therapeutic hypothermia.

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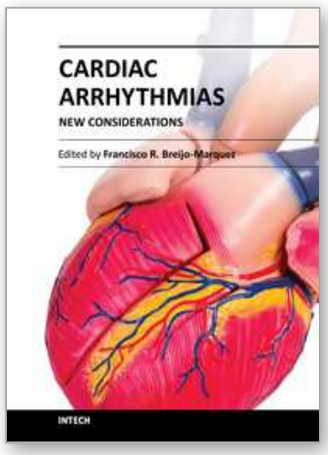

Cardiac Arrhythmias - New Considerations

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The most intimate mechanisms of cardiac arrhythmias are still quite unknown to scientists. Genetic studies on ionic alterations, the electrocardiographic features of cardiac rhythm and an arsenal of diagnostic tests have done more in the last five years than in all the history of cardiology. Similarly, therapy to prevent or cure such diseases is growing rapidly day by day. In this book the reader will be able to see with brighter light some of these intimate mechanisms of production, as well as cutting-edge therapies to date. Genetic studies, electrophysiological and electrocardiographyc features, ion channel alterations, heart diseases still unknown , and even the relationship between the psychic sphere and the heart have been exposed in this book. It deserves to be read!

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