Therapeutic Hypothermia for Myocardial Protection in ST Elevation Myocardial Infarction

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Abstract

Following the return of spontaneous circulation after cardiac arrest, the use of therapeutic hypothermia (TH) has been demonstrated to improve neurologic outcomes and mortality. The potential cardiac benefits and the role of induced hypothermia as a cardioprotective strategy are less clear. Numerous laboratory and clinical studies implicate both inciting myocardial ischemia and subsequent reperfusion damage in myocardial injury. Based on its established benefit in limiting cerebral ischemia and its widespread availability, TH is an attractive therapy for limiting myocardial ischemia and reperfusion injury in myocardial infarction. Several studies have suggested a positive effect of TH in the prevention of myocardial ischemic injury but to date no clinical trial has conclusively shown mortality benefit with the use of TH in the setting of ST elevation myocardial infarction (STEMI). Subgroup analyses however indicate that TH has the potential to limit infarct size and improve outcomes in certain patient subsets. These findings, alongside the established benefits for cerebral ischemic injury, support performing further large scale randomized controlled trials of the use of TH in STEMI.

Keywords: Therapeutic hypothermia; Myocardial protection; Myocardial infarction; Ischemia-reperfusion injury

Introduction

Nearly 1 million people in the United States suffer from myocardial infarction each year (MI) and coronary heart disease accounts for approximately 15% of the total annual mortality. Despite significant advances in the treatment of heart disease over the past several decades, patients experiencing myocardial infarction (MI) continue to suffer cardiac arrest and develop cardiogenic shock. Those who survive their acute event remain at risk for sudden cardiac death and congestive heart failure [1]. The long term consequences of myocardial infarction are related to the degree of irreversible myocardial injury and thus the primary goal in acute MI is to limit infarct size. In patients with ST elevation myocardial infarction (STEMI) early and successful myocardial reperfusion using thrombolytic therapy or primary percutaneous coronary intervention (PCI) is critical for salvaging ischemic myocardium, reducing infarct size, achieving mechanical and electrical stabilization, and improving subsequent clinical outcomes [2]. While primary reperfusion therapies have consistently been shown to limit infarct size when performed in a timely manner there are still inherent limitations to this technique, to include time delays and reperfusion injury. Therefore, innovative adjunctive cardioprotective strategies to limit ischemia and reperfusion injury in the form of myocardial no-reflow, myocardial stunning, and myonecrosis have become increasingly critical.

The goal of neuroprotection in the treatment of cardiac arrest survivors shares many similarities with cardioprotection. Historically, the acute treatment of cardiac arrest survivors was supportive, with reported in-hospital mortality rates of up to 70% [3]. In 2002, two landmark studies by Bernard et al. and the Hypothermia After Cardiac Arrest study group demonstrated that mild induced therapeutic hypothermia (TH) improved neurologic outcomes and reduced overall mortality in comatose survivors of out-of-hospital cardiac arrest (OHCA) [4,5]. These studies led to recommendations for the use of TH by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation and the inclusion of TH in the current European and American resuscitation guidelines [6,7]. Multiple studies worldwide since 2002 have replicated and validated the neuroprotective effects of TH following OHCA [7-9]. Induced hypothermia is now a recognized therapy for cardiac arrest and carries a class I recommendation for persistently comatose adults after the return of spontaneous circulation following ventricular fibrillation or pulseless ventricular tachycardia arrest [10].

To date there has been limited research regarding the effect of induced hypothermia on the myocardium and its potential cardioprotective benefits, particularly in the setting of STEMI. However, studies are emerging that suggest that TH may have an important role to play in the prevention of myocardial injury and preservation of myocardial function in patients with MI with or without cardiac arrest [11-13].

Ischemia-Reperfusion Injury

Injury to the myocardium during cardiac arrest and MI occurs by two major mechanisms: initial hypoperfusion leading to myocardial ischemia and delayed reperfusion injury that follows restoration of perfusion pressure or successful coronary revascularization. While mechanical and pharmacologic reperfusion therapies are the cornerstones of treatment for myocardial salvage, resumption of blood flow to oxygen-deprived tissue may itself paradoxically induce injury and can account for up to 50% of myocardial injury following AMI [14]. Thus, coupled with a primary reperfusion strategy, adjunctive treatments aimed at preventing or minimizing reperfusion injury present important new targets for therapeutic intervention.

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Received October 31, 2011; Accepted December 17, 2011; Published December 21, 2011

Citation: Delgado GA, Truesdell AG, Abbott JD (2011) Therapeutic Hypothermia for Myocardial Protection in ST Elevation Myocardial Infarction. J Clinic Experiment Cardiol 5:003. doi:10.4172/2155-9880.S5-003

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Reperfusion injury involves a well-accepted cascade of interdependent processes that includes formation and release of reactive oxygen species, increased cytokine activity, impaired calcium transport, neutrophil-mediated myocardial and endothelial injury, lipid peroxidation of cell membranes, vascular plugging and reduced microvascular flow, intracellular acidosis, and apoptosis [14-20]. While long-term adverse outcomes from OHCA are primarily attributable to anoxic brain injury, early morbidity and mortality predominantly stems from myocardial ischemia-reperfusion mediated injury that results in hemodynamic instability, multi-organ system failure, and a mortality rate of nearly 10% despite successful revascularization [21-23].

Mechanisms of Cardioprotection

Pathophysiologic similarities between the mechanisms of harm in both cerebral and myocardial ischemia-reperfusion injury as well as the well-established neuroprotective benefits of hypothermia suggest a potential cardioprotective role as well. Reductions in the metabolic rate and perfusion requirements of the brain occur at temperatures below the 32 to 34°C range tested in most contemporary studies, indicating that TH primarily targets cerebral ischemia-reperfusion injury via mechanisms far more complex than reduced metabolic rate and oxygen consumption alone [24,25]. Induced hypothermia is believed to confer protection against ischemia-reperfusion injury in myocardial tissue via similarly multifaceted mechanisms.

Evidence from pre-clinical and human studies indicates that the cardioprotective properties of mild hypothermia mirror those of neuroprotection following cerebral ischemia. The positive immune modulation and attenuation of inflammatory cell infiltration, apoptosis, and pro-inflammatory cytokine expression that occur in the brain are also observed in the resuscitated hypothermic heart [26]. Mild induced TH targets tissue injury at multiple molecular, cellular, and tissue levels. In early ischemia, hypothermia inhibits both abnormal cellular free radical production and impaired calcium and pH management, while in the delayed post-reperfusion period hypothermia modulates downstream necrotic, apoptotic, and inflammatory pathways that ultimately result in delayed cell death. Induction of hypothermia has also been shown to suppress neutrophil migration as well as the production of free radicals and excitatory amino acids and to reduce detrimental intracellular calcium overload via down-regulation of Na+/Ca2+ exchange [24,25,27]. Furthermore, cooling decreases production of heat shock proteins and minimizes cell death via apoptosis, inhibits platelet aggregation, and attenuates microvascular obstruction and no-reflow [8,14,28-30] Via these and other pathways (Table 1), mild induced hypothermia mitigates the cytotoxic chain-reaction induced by the return of spontaneous circulation that otherwise accentuates the initial hypoxic damage caused by cardiac arrest [16,31].

Clinical Evidence

The studies by Bernard et al. and the Hypothermia After Cardiac Arrest study group firmly established the neuroprotective properties of mild induced hypothermia for survivors of OHCA whose initial rhythm was ventricular tachycardia (VT) or ventricular fibrillation (VF) [4,5]. Subsequent studies have demonstrated similar, albeit less impressive, mortality benefits to patients beyond the VT/VF OHCA population [32-34]. The cardioprotective advantages and morbidity and mortality benefits in the STEMI population are less well-established.

Prognosis for patients presenting with myocardial infarction is directly related to the extent of myocardial necrosis [35]. Although timely reperfusion addresses the initial ischemic insult, additional therapies targeting reperfusion injury are necessary to limit subsequent myocardial damage. Unfortunately, while numerous experimental interventions aimed at limiting myocardial infarct size have been proposed and scientifically evaluated, few have been successfully incorporated into clinical practice [36]. Therapeutic modalities which have failed to demonstrate clinical benefit include oxygen free radical scavengers, nitric oxide donors, calcium modulators, inhibitors of neutrophil adhesion, and the vasodilator nicorandil [37]. In addition to TH, other potentially promising therapies for myocardial salvage adjunctive to early reperfusion that are still under investigation include adenosine, atrial natriuretic peptide, the mitochondrial permeability inhibitor cyclosporine, hyperoxemic reperfusion, and ischemic post-conditioning [38].

In animal models, application of TH following MI and cardiac arrest has demonstrated clear cardioprotective benefit by limiting myocardial infarct size, reducing the no-reflow phenomenon, decreasing post-ischemic reactive hyperemia, and improving healing after infarction [29,39]. Over the past decade, several safety and feasibility studies, such as the Noninvasive Cooling for Acute Myocardial Infarction (NICAMI) trial, the Lowering Adverse Outcomes with Temperature Regulation Feasibility (LOWTEMP) trial, and an endovascular cooling trial conducted by Dixon et al. demonstrated successful applicability of TH to STEMI patients [11,40,41].

Experimental and clinical studies have shown that the benefit of TH is also time-sensitive and enhanced by prompt initiation upon the onset of ischemia and before reperfusion [39,42]. A post-hoc subgroup analysis (n = 111) of the Hypothermia After Cardiac Arrest trial by Koreny et al. identified a statistically significant (p = 0.007) reduction in infarct size as estimated by ECG ST scores and plasma levels of CK and CK-MB for those patients who achieved target temperature early (≤8hrs) versus late (>8h) despite no evidence of overall clinical benefit in the original study [43].

Dixon et al. performed the first multi-center randomized controlled...
trial (RCT) investigating TH and infarct size in patients who underwent primary PCI for STEMI. Forty-two patients presenting within 6 hours of symptom onset were randomized to endovascular cooling (target core temperature 33°C) prior to PCI versus routine PCI. The study showed a positive but non-statistically significant reduction in the primary endpoint of major adverse cardiac events (MACE), defined as death, nonfatal reinfarction, and target vessel revascularization at 30 days (0% in hypothermic patients compared to 10% of controls, \( p = \text{nonsignificant} \)). A favorable trend towards reduction of the secondary endpoint of median left ventricular infarct size at 30 days post MI as measured by SPECT imaging was also observed in the TH arm (2% in the cooled group versus 8% in the control group) but also failed to reach statistical significance (\( p = 0.80 \)) [11].

The Cooling as an Adjunctive Therapy to Percutaneous Intervention in Patients With Acute Myocardial Infarction (COOL-MI) trial was another RCT investigating TH as an adjunctive therapy to PCI in STEMI patients. The trial included 392 patients presenting within 6 hours of symptom onset randomized to primary PCI with or without preceding endovascular cooling. There was no difference between the 2 groups in the primary endpoints of mean left ventricular infarct size measured at 30 days by SPECT imaging (13.8% in the control arm versus 14.1% in the hypothermia arm, \( p = 0.83 \)) or MACE (6.2% in the hypothermia group versus 3.9% in the control group, \( p = 0.45 \)). However, most patients in the hypothermia group did not reach the goal temperature of < 35°C prior to PCI and average door-to-balloon times were 18 minutes longer (110 versus 92 minutes) in the cooled patients compared to controls. Subsequent post-hoc analysis of the subgroup of patients with anterior MI who did reach target temperature prior to PCI (n = 16) demonstrated a significant reduction in infarct size by SPECT imaging (9.3% versus 18.2%, \( p = 0.05 \)) and a trend towards decreased rates of the secondary endpoints of ST segment resolution, CK-MB levels, and left ventricular ejection fraction [12].

To further investigate the subpopulation of patients with anterior MI that demonstrated potential benefit from adjunctive TH prior to PCI, the Cooling as an Adjunctive Therapy to Percutaneous Intervention in Patients with Acute Myocardial Infarction (COOL-MI II) trial was initiated as an extension of the COOL-MI trial. The trial enrolled 225 patients with anterior wall MI with primary endpoints of infarct size as measured by SPECT imaging and biomarker release but was terminated prematurely due to loss of funding without publication of results [44].

The Intravascular Cooling Adjunctive to Percutaneous Coronary Intervention for Acute Myocardial Infarction (ICE-IT) trial randomized 228 patients presenting with an acute MI within 6 hours of symptom onset to endovascular cooling concomitant with PCI versus routine PCI. The primary endpoint of infarct size at 30 days as measured by SPECT imaging was similar between the 2 groups (10% for the hypothermia group versus 13% for the control group, \( p = 0.14 \)). Like the COOL-MI trial, ICE-IT was also an overall negative trial. But while TH did not demonstrate any significant decrease in infarct size overall, a trend towards benefit was again observed on post-hoc analysis of the subgroup with anterior infarction who were sufficiently cooled to a temperature of < 35°C at the time of revascularization (infarct size of 12.9% of the left ventricle in the TH population compared to 22.7% in the control group, \( p = 0.099 \)) [13].

To date, none of the major studies of TH in STEMI have shown a statistically significant reduction in infarct size, MACE, or all-cause mortality in hypothermic groups compared to controls. However, in the case of COOL-MI and ICE-IT it is possible that the overall negative results may be attributable to an insufficient cooling rate resulting in little to no shortening of the normothermic ischemic period. These studies may also have been underpowered to unmask the incremental benefit of cooling outside of the higher risk anterior MI population.

A more recent pilot study by Gotberg et al. of endovascular cooling before reperfusion in patients with STEMI again confirmed the safety and feasibility of TH as an adjunct to primary PCI. Though small (n = 20), this pilot study also demonstrated a statistically significant reduction in the secondary endpoints of MACE, biomarker release, and infarct size as measured by cardiac MRI at 4±2 days after initiation of TH (29.8±12.6% for the hypothermic group versus 48.0±21.6% for normothermic subjects, \( p = 0.041 \)) [45].

Further studies currently in progress continue to examine the feasibility, safety, and effects of cooling conscious patients who have had an acute MI without cardiac arrest. The Efficacy of Endovascular Catheter Cooling Combined With Cold Saline for the Treatment of Acute Myocardial Infarction (CHILL-MI) is an endovascular cooling study with a prespecified primary endpoint of MI size as assessed by cardiac MR at 4±2 days and secondary endpoints of MACE, ST segment resolution, and plasma level of Troponin T [46]. The Can Hypothermia be Incorporated Into Primary Angioplasty for Heart Attack (CHIPAHA) is a surface cooling feasibility study with secondary endpoints of MACE and MI size at 30 days as measured by SPECT imaging [47]. It is hoped that the results of both CHILL-MI and CHIPAHA will further the evidence base for or against the efficacy of TH in the awake alert STEMI population.

Beyond the safety, feasibility, and efficacy questions related to the employment of TH coincident with primary PCI in STEMI patients there is also concern for its potential negative effects on door-to-balloon time. While door-to-balloon times were prolonged in the COOL-MI trial, several other subsequent studies have demonstrated that initiation of TH concurrent with PCI does not delay emergency revascularization if hypothermia protocols are well established and that it can be performed safely as an adjunct to primary PCI [14,45,48,49].

Despite hypothermia’s demonstrated benefits on neurologic outcomes and overall mortality as well as its suggested cardioprotective potential, it also possesses potentially harmful effects that could translate into adverse outcomes if not recognized and promptly addressed. Even at the cooling range of 33 to 35°C initiation and maintenance of hypothermia is associated with peripheral vasoconstriction and elevated systemic vascular resistance, immunosuppression, inhibition of the coagulation cascade and bleeding, hypokalemia, mild metabolic acidosis, enhanced diuresis, and bradycardia [24,31,50]. The rewarming process reverses many of these physiologic effects and in turn leads to peripheral vasodilatation and potentially hypotension as well as significant hyperkalemia. Despite these laboratory and clinical phenomena TH has not demonstrated any significant increases in the incidence of sustained lowering of cardiac output or frequency of vasopressor or inotrope use, infection and sepsis, clinically significant bleeding, or any other major causes of mortality [4,5].

Numerous interventions besides induced mild hypothermia have also been investigated in experimental studies for their potential to reduce ischemia-reperfusion injury. Despite demonstrated promise in the laboratory, follow-on large multicenter studies have been unable to confirm therapeutic efficacy [37,38,51]. It may be difficult to demonstrate the benefits of new therapies such as TH beyond the current management strategy of timely reperfusion and potent antiplatelet and antithrombotic agents – particularly due to the
relatively small infarct size and low mortality of STEMI patients in current contemporary clinical trials. Even if a therapy such as TH does reproducibly reduce infarct size this still may not translate into reduced mortality. In the case of hypothermia a ceiling effect of achievable cardioprotection with present techniques may be approached and thus only large future clinical trials may demonstrate any further clinically relevant cardioprotection and mortality reduction.

The aggregate of available data demonstrates that TH is a safe, feasible, cost-effective, neuroprotective, and potentially cardioprotective intervention in STEMI patients undergoing PCI [52]. However it has not been shown conclusively in prospective RCTs to reduce infarct size or reduce mortality (Table 2). It is possible that such an effect does not exist or that no study to date has adequately addressed this issue conclusively. The preferred duration of hypothermia is also unknown, although recent animal studies suggest that continuation of hypothermia beyond the acute reperfusion injury phase that follows coronary reperfusion may not provide any additional benefit [66,67]. In addition to biomarker evaluation, the degree of myocardial

Table 2: Human studies analyzing hypothermia effects in AMI.

<table>
<thead>
<tr>
<th>Study</th>
<th>Trial design</th>
<th>Patient population</th>
<th>n</th>
<th>Cooling method</th>
<th>Target temp</th>
<th>Cooling time</th>
<th>Primary Endpoint</th>
<th>Secondary Endpoint</th>
<th>Reperfusion therapy</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dixon et al., 2002</td>
<td>Prospective RCT</td>
<td>STEMI within 6 hrs of onset</td>
<td>42</td>
<td>Endovascular catheter</td>
<td>33°C</td>
<td>4 hours</td>
<td>MACE at 30 days *</td>
<td>Infarct size at 30 days *</td>
<td>Primary PCI</td>
<td>Non-significant decrease in MACE and infarct size</td>
</tr>
<tr>
<td>COOL MI O'Neill et al., 2003</td>
<td>Prospective RCT</td>
<td>STEMI within 6 hrs of onset</td>
<td>357</td>
<td>Endovascular catheter</td>
<td>33°C</td>
<td>n/a</td>
<td>Infarct size and MACE at 30 days *</td>
<td>ST segment resolution, LVEF, CK-MB and myoglobin release</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COOL MI II Carrozza et al., 2005</td>
<td>Prospective RCT</td>
<td>Anterior STEMI within 6 hrs of onset</td>
<td>n/a</td>
<td>Endovascular catheter</td>
<td>33°C</td>
<td>n/a</td>
<td>Infarct size * Safety profile</td>
<td>Infarct size, ST segment resolution, LVEF †</td>
<td>Primary PCI</td>
<td>Trial halted prior to completion due to funding reasons</td>
</tr>
<tr>
<td>LOWTEMP Kandzari et al., 2004</td>
<td>Feasibility cohort</td>
<td>STEMI within 6 hrs of onset</td>
<td>20</td>
<td>Endovascular catheter</td>
<td>32-34°C</td>
<td>4 hours</td>
<td>Infarct size at 30 days *, †</td>
<td>ST-segment resolution</td>
<td>Primary PCI</td>
<td>Feasible, associated with favorable safety, infarct size and ST-segment resolution outcomes</td>
</tr>
<tr>
<td>ICE-IT Grines et al., 2004</td>
<td>Prospective RCT</td>
<td>Anterior or large inferior STEMI within 6 hrs of onset</td>
<td>228</td>
<td>Endovascular catheter</td>
<td>32-34°C</td>
<td>6 hours</td>
<td>Infarct size at 30 days *</td>
<td>n/a</td>
<td>Primary PCI</td>
<td>No difference in infarct size Non-significant reduction in infarct size with anterior MI ‡</td>
</tr>
<tr>
<td>Hovdenes et al., 2007</td>
<td>Prospective observational</td>
<td>Comatose, VF-OHCA eligible for PCI</td>
<td>50</td>
<td>Cold NS infusion and external cooling</td>
<td>32-34°C</td>
<td>24 hours</td>
<td>Survival and neurological outcome at 6 months #</td>
<td>n/a</td>
<td>Primary or facilitated PCI</td>
<td>82% survival at 6 months Larger infarct size in those with unfavorable neurological outcome †,‡</td>
</tr>
<tr>
<td>Wolfrum et al., 2008</td>
<td>Prospective observational with historical controls</td>
<td>Comatose, VF-OHCA with STEMI</td>
<td>33</td>
<td>Cold NS infusion and external cooling</td>
<td>32-34°C</td>
<td>24 hours</td>
<td>Survival and neurological outcome at 6 months #</td>
<td>n/a</td>
<td>Primary PCI</td>
<td>10% mortality reduction, improved neurological outcome Non-significant reduction in infarct size with anterior MI ‡</td>
</tr>
<tr>
<td>Schefold et al., 2009</td>
<td>Prospective observational with historical controls</td>
<td>Comatose, OHCA with STEMI</td>
<td>62</td>
<td>Cold NS infusion and external cooling</td>
<td>33°C</td>
<td>24 hours</td>
<td>Survival and neurological outcome at discharge #</td>
<td>Bleeding complications **</td>
<td>Thrombolyis, PCI</td>
<td>Improved neurological outcome Non-significant reduction in infarct size Non-significant reduction in infarct size</td>
</tr>
<tr>
<td>Gotberg et al., 2010</td>
<td>Prospective RCT</td>
<td>STEMI within 6 hrs of onset</td>
<td>20</td>
<td>Cold NS infusion and endovascular catheter</td>
<td>33°C</td>
<td>3 hours</td>
<td>Myocardium at risk and infarct size after 4 days ***</td>
<td>n/a</td>
<td>Primary PCI</td>
<td>38% reduction in infarct size normalized to myocardium at risk</td>
</tr>
</tbody>
</table>

RCT: randomized controlled trial, STEMI: ST elevation myocardial infarction, MI: myocardial infarction, MACE: major adverse cardiac events, VF: ventricular fibrillation, OHCA: out-of-hospital cardiac arrest, PCI: percutaneous coronary intervention, LVEF: left ventricular ejection fraction, CK-MB: creatinine kinase MB isofraction, n/a: not available or not applicable, NS: normal saline, *: infarct size measured by Tc-99 sestamibi SPECT imaging, †: infarct size measured by degree of CK-MB elevation, ‡: post-hoc or sub-group analysis, #: neurological outcome assessed by Pittsburgh Cerebral Performance Category, **: defined as any clinically overt blood loss, ***: assessed by cardiac magnetic resonance imaging.
preservation achieved with TH may also be better estimated using T2-weighted and late gadolinium enhancement magnetic resonance imaging, which is not only more accurate than SPECT, but also permits normalization of infarct size relative to myocardium at risk [44].

While randomization of patients with STEMI complicated by comatose OHCA is difficult in light of the general acceptance of TH as standard of care in eligible patients, opportunities for research exist in the population of conscious patients with acute MI. An optimal study would enroll a prespecified subset of patients with the greatest demonstrated benefit from prior trials, namely those with an acute anterior MI presenting within 6 hours of symptom onset and treated with rapid endovascular cooling to a temperature of < 35°C prior to the initiation of PCI. It would also examine the time, depth, and duration of cooling and focus on hard clinical endpoints in addition to infarct size. A well-coordinated, adequately-powered, randomized control trial of this type might clarify the utility of TH in the conscious STEMI patient.

Conclusions

Presently, early revascularization with thrombolytic therapy or primary PCI is the mainstay of treatment for STEMI, but outcomes may be further improved by preventing the deleterious effects of reperfusion injury. Whether TH can attenuate complications of ischemia-reperfusion damage and serve as a useful adjunct to PCI in STEMI is an area of great interest and intense investigation. Although TH has proven to be a safe and feasible intervention with clear neuroprotective and mortality benefits, unambiguous clinical confirmation of its cardioprotective properties is lacking. Subgroup analysis of clinical trials suggests that TH may reduce infarct size with appropriate timing and efficacy of cooling in patients with anterior wall infarction. Larger trials are needed to determine whether induced hypothermia in conscious patients presenting with STEMI with or without cardiac arrest is definitively associated with limited infarct size, improvements in left ventricular systolic function, fewer MACCE, and lower mortality.

References


