

Therapeutic Hypothermia for Myocardial Protection in ST Elevation Myocardial Infarction

Gabriel A. Delgado, Alexander G. Truesdell and J. Dawn Abbott*

Division of Cardiology, Warren Alpert Medical School of Brown University, Providence, Rhode Island, USA

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.

***Corresponding author:** J. Dawn Abbott, MD, Division of Cardiology, Rhode Island Hospital, Assistant Professor of Medicine, Warren Alpert Medical School, Brown University, 814 APC, 593 Eddy St, Providence, RI, USA, Tel: (401) 444-8540; Fax: (401) 444-8158; Email: jabbott@lifespan.org

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 Clin Experiment Cardiol S5:003. doi:10.4172/2155-9880.S5-003

Copyright: © 2011 Delgado GA, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

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

Mechanism	Reference	Type of study
Reduces myocardial metabolic demand and oxygen consumption	Miki et al. 1998 ⁵⁵ , Schwartz et al. 2001 ⁵⁶ , Dae et al. 2003 ⁵⁷ , Maeng et al. 2003 ⁵⁸	Animal model
Preserves myocyte membrane function, intracellular calcium and pH hemostasis	Schwartz et al. 2001 ⁵⁶ , Inoue et al 2003 ²⁸	Animal model
Decreases free radical and cytotoxin generation	Maeng et al. 2006 ⁵⁹	Animal model
Decreases infarct size	Otake et al. 2007 ⁶⁰	Animal model
Prevents microvascular obstruction and no-reflow phenomenon	Hale et al. 2003 ⁶¹ , Gotberg et al. 2008 ⁶²	Animal model
Inhibits mediators of inflammatory response and myocyte apoptosis	Dixon et al. 2005 ⁵⁰	Human
Reduces post-infarct reactive hyperemia	Olivecrona et al. 2007 ²⁹	Animal model
Maintains myocardial cell integrity and mitochondrial function	Ning et al. 1998 ⁶³ , 2007 ⁶⁴	Animal model
Inhibits platelet aggregation	Frelinger et al. 2003 ⁶⁵	Human

Table 1: Cardioprotective mechanisms of therapeutic hypothermia.

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, $p =$ 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 $< 35^{\circ}\text{C}$ 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 $< 35^{\circ}\text{C}$ 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, $p = 0.09$) [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 ($29.8 \pm 12.6\%$ for the hypothermic group versus $48.0 \pm 21.6\%$ 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

Study	Trial design	Patient population	n =	Cooling method	Target temp	Cooling time	Primary Endpoint	Secondary Endpoint	Reperfusion therapy	Results
Dixon et al., 2002 ¹¹	Prospective RCT	STEMI within 6 hrs of onset	42	Endovascular catheter	33°C	4 hours	MACE at 30 days	Infarct size at 30 days *	Primary PCI	Non-significant decrease in MACE and infarct size
COOL MI O'Neill et al., 2003 ¹²	Prospective RCT	STEMI within 6 hrs of onset	357	Endovascular catheter	33°C	n/a	Infarct size and MACE at 30 days *	ST segment resolution, LVEF, CK-MB and myoglobin release	Primary PCI	No difference in MACE or infarct size Non-significant reduction in infarct size with anterior MI ‡
COOL MI II Carozza et al., 2005 ⁴⁵	Prospective RCT	Anterior STEMI within 6 hrs of onset	n/a	Endovascular catheter	33°C	n/a	Infarct size * Safety profile	Infarct size, ST segment resolution, LVEF †	Primary PCI	Trial halted prior to completion due to funding reasons
LOWTEMP Kandzari et al., 2004 ⁴¹	Feasibility cohort	STEMI within 6 hrs of onset	20	Endovascular catheter	32-34°C	4 hours	Infarct size at 30 days *,†	ST-segment resolution	Primary PCI	Feasible, associated with favorable safety, infarct size and ST-segment resolution outcomes
ICE-IT Grines et al., 2004 ¹³	Prospective RCT	Anterior or large inferior STEMI within 6 hrs of onset	228	Endovascular catheter	32-34°C	6 hours	Infarct size at 30 days *	n/a	Primary PCI	No difference in infarct size Non-significant reduction in infarct size with anterior MI ‡
Hovdenes et al., 2007 ⁵³	Prospective observational	Comatose, VF-OHCA eligible for PCI	50	Cold NS infusion and external cooling	32-34°C	24 hours	Survival and neurological outcome at 6 months #	n/a	Primary or facilitated PCI	82% survival at 6 months Larger infarct size in those with unfavorable neurological outcome †,‡
Wolfrum et al., 2008 ⁴⁸	Prospective observational with historical controls	Comatose, VF-OHCA with STEMI	33	Cold NS infusion and external cooling	32-34°C	24 hours	Survival and neurological outcome at 6 months #	n/a	Primary PCI	10% mortality reduction, improved neurological outcome Non-significant reduction in infarct size with anterior MI ‡
Schefold et al., 2009 ⁵⁴	Prospective observational with historical controls	Comatose, OHCA with STEMI	62	Cold NS infusion and external cooling	33°C	24 hours	Survival and neurological outcome at discharge #	Bleeding complications **	Thrombolysis, PCI	Improved neurological outcome Non-significant reduction in infarct size
Gotberg et al., 2010 ⁴⁵	Prospective RCT	STEMI within 6 hrs of onset	20	Cold NS infusion and endovascular catheter	33°C	3 hours	Myocardium at risk and infarct size after 4 days ***	n/a	Primary PCI	38% reduction in infarct size normalized to myocardium at risk

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.

Table 2: Human studies analyzing hypothermia effects in AMI.

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 MACE, and lower mortality.

References

1. Roger VL, Go AS, Lloyd-Jones D, Adams RJ, Berry JD, et al. (2011) Heart disease and stroke statistics-2011 update: a report from the American Heart Association. *Circulation* 123: e18-e209.
2. Kushner FG, Hand M, Smith SC Jr, King SB 3rd, Anderson JL, et al. (2009) 2009 focused update: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update). *J Am Coll Cardiol* 54: 2205-2241.
3. Gueugniaud PY, Mols P, Goldstein P, Pham E, Dubien PY, et al. (1998) A comparison of repeated high doses and repeated standard doses of epinephrine for cardiac arrest outside the hospital. *N Engl J Med* 339: 1595-1601.
4. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, et al. (2002) Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 346: 557-563.
5. Hypothermia after Cardiac Arrest Study Group (2002) Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 346: 549-556.
6. Nolan JP, Morley PT, Vanden Hoek TL, Hickey RW, Kloeck WG (2003) Therapeutic hypothermia after cardiac arrest: an advisory statement by the advanced life support task force of the international liaison committee on resuscitation. *Circulation* 108: 118-121.
7. Hazinski MF, Nolan JP, Billi JE, Botinger BW, Bossaert L, et al. (2010) Executive summary: 2010 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Circulation* 122: S250-S275.
8. Holzer M (2010) Targeted temperature management for comatose survivors of cardiac arrest. *N Engl J Med* 363: 1256-1264.
9. Sagalyn E, Band RA, Gaieski DF, Abella BS (2009) Therapeutic hypothermia after cardiac arrest in clinical practice: review and compilation of recent experiences. *Crit Care Med* 37: S223-S226.
10. Field JM, Hazinski MF, Sayre MR, Chameides K, Schexnayder SM, et al. (2010) Executive summary: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 122: S640-S656.
11. Dixon SR, Whitbourn RJ, Dae MW, Grube E, Sherman W, et al. (2002) Induction of mild systemic hypothermia with endovascular cooling during primary percutaneous coronary intervention for acute myocardial infarction. *J Am Coll Cardiol* 40: 1928-1934.
12. O'Neill WW, on behalf of the COOL-MI Investigators (2003) A prospective, randomized trial of mild hypothermia during PCI treatment of ST elevation MI. Presented at Transcatheter Cardiovascular Therapeutics 2003.
13. Grines CL, on behalf of the ICE-IT Investigators (2004) Intravascular cooling adjunctive to percutaneous coronary intervention for acute myocardial infarction. Presented at Transcatheter Cardiovascular Therapeutics 2004.
14. Yellon DM, Hausenloy DJ (2007) Myocardial reperfusion injury. *N Engl J Med* 357: 1121-1135.
15. Piper HM, Garcia-Dorado D, Ovize M (1998) A fresh look at reperfusion injury. *Cardiovasc Res* 38: 291-300.
16. Lemasters JJ, Bond JM, Chacon E, Harper IS, Kaplan SH, et al. (1996) The pH paradox in ischemia-reperfusion injury to cardiac myocytes. *EXS* 76: 99-114.
17. Negovsky VA (1988) Postresuscitation disease. *Crit Care Med* 16: 942-946.
18. Neumar RW, Nolan JP, Adrie C, Aibiki M, Berg RA, et al. (2008) Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. *Circulation* 118: 2452-2483.
19. Li C, Jackson RM (2002) Reactive species mechanisms of cellular hypoxia-reoxygenation injury. *Am J Physiol Cell Physiol* 282: C227-C241.
20. Hess ML, Manson NH (1984) Molecular oxygen: friend and foe. The role of the oxygen free radical system in the calcium paradox, the oxygen paradox and ischemia/reperfusion injury. *J Mol Cell Cardiol* 16: 969-985.
21. Safar P (1988) Resuscitation from clinical death: pathophysiologic limits and therapeutic potentials. *Crit Care Med* 16: 923-941.
22. Laurent I, Monchi M, Chiche JD, Joly LM, Spaulding C, et al. (2002) Reversible myocardial dysfunction in survivors of out-of-hospital cardiac arrest. *J Am Coll Cardiol* 40: 2110-2116.
23. Keeley EC, Boura J, Grines CL (2003) Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomized trials. *Lancet* 361: 13-20.
24. Polderman KH (2009) Mechanisms of action, physiologic effects, and complications of hypothermia. *Crit Care Med* 37: S186-S202.
25. Howes D, Green R, Gray S, Stenstrom R, Easton D (2006) Evidence for the use of hypothermia after cardiac arrest. *CJEM* 8: 109-115.
26. Meybohm P, Gruenewald M, Albrecht M, Zacharowski KD, Lucius R, et al. (2009) Hypothermia and postconditioning after cardiopulmonary resuscitation reduce cardiac dysfunction by modulating inflammation, apoptosis, and remodeling. *PLoS One* 4: e7588.
27. Bernard SA, Buist M (2003) Induced hypothermia in critical care medicine: a review. *Crit Care Med* 31: 2041-2051.
28. Inoue K, Ando S, Gyuan F, Takaba T (2003) A study of the myocardial protective effect of rapid cooling based on intracellular Ca, intracellular pH, and HSP70. *Ann Thorac Cardiovasc Surg* 9: 301-306.
29. Olivecrona GK, Gotberg M, Harnek J, Van der Pals J, Erlinge D (2007) Mild hypothermia reduces post-ischemic reactive hyperemia. *BMC Cardiovasc Disord* 7: 5.
30. Simkhovich BZ, Hale SL, Kloner RA (2004) Metabolic mechanism by which mild regional hypothermia preserves ischemic tissue. *J Cardiovasc Pharmacol Ther* 9: 83-90.
31. Azmoon S, Demarest C, Pucillo AL, Hjemdahl-Monsen C, Kay R, et al. (2011) Neurologic and cardiac benefits of therapeutic hypothermia. *Cardiol Rev* 19: 108-114.
32. Oddo M, Schaller M, Feihl F, Ribordy V, Liaudet L (2006) From evidence

- to clinical practice: Effective implementation of therapeutic hypothermia to improve patient outcome after cardiac arrest. *Crit Care Med* 34: 1865-1873.
33. Holzer M, Mullner M, Sterz F, Robak O, Kliegel A, et al. (2006) Efficacy and safety of endovascular cooling after cardiac arrest: cohort study and Bayesian approach. *Stroke* 37: 1792-1797.
34. Arrich J (2007) Clinical application of mild therapeutic hypothermia after cardiac arrest. *Crit Care Med* 35: 1041-1047.
35. Antman EM, Tanasijevic MJ, Thompson B, Schactman M, McCabe CH, et al. (1996) Cardiac-Specific Troponin I Levels to Predict the Risk of Mortality in Patients with Acute Coronary Syndromes. *N Engl J Med* 335: 1342-1349.
36. Bolli R, Becker L, Gross G, Mentzer R, Balshaw D, et al. (2004) Myocardial protection at a crossroads: the need for translation into clinical therapy. *Circ Res* 95: 125-134.
37. Schwartz Longacre L, Kloner RA, Arai AE, Baines CP, Bolli R, et al. (2011) New horizons in cardioprotection: recommendations from the 2010 national heart, lung, and blood institute workshop. *Circulation* 124: 1172-1179.
38. Kloner RA, Schwartz Longacre L (2011) State of the science of cardioprotection: challenges and opportunities – proceedings of the 2010 NHLBI workshop on cardioprotection. *J Cardiovasc Pharmacol Ther* 16: 223-232.
39. Hale SL, Kloner RA (2010) Mild hypothermia as a cardioprotective approach for myocardial infarction: laboratory to clinical application. *J Cardiovasc Pharmacol Ther* 16: 131-139.
40. Ly HQ, Denault A, Dupuis J, Vadeboncouer A, Harel F, et al. (2005) A pilot study: the noninvasive surface cooling thermoregulatory study for mild hypothermia induction in acute myocardial infarction (the NICAMI study). *Am Heart J* 150: 933.
41. Kandzari DE, Chu A, Brodie BR, Stuckey TA, Hermiller JB, et al. (2004) Feasibility of endovascular cooling as an adjunct to primary percutaneous coronary intervention (results of the LOWTEMP pilot study). *Am J Cardiol* 93: 636-639.
42. Kanemoto S, Matsubara M, Noma M, Leshnower BG, Parish LM, et al. (2009) Mild hypothermia to limit myocardial ischemia-reperfusion injury: importance of timing. *Ann Thorac Surg* 87: 157-163.
43. Koreny M, Sterz F, Uray T, Schreiber W, Holzer M, et al. (2009) Effect of cooling after human cardiac arrest on myocardial infarct size. *Resuscitation* 80: 56-60.
44. Carrozza PJ, Dixon SR COOL MI II: Cooling as an adjunctive therapy to percutaneous intervention in patients with acute myocardial infarction. *ClinicalTrials.gov*: NCT 00248196.
45. Gotberg M, Olivecrona GK, Koul S, Carlsson M, Engblom H, et al. (2010) A pilot study of rapid cooling by cold saline and endovascular cooling before reperfusion in patients with ST-elevation myocardial infarction. *Circ Cardiovasc Interv* 3: 400-407.
46. Erlinge D, Olivecrona GK CHILL-MI: Efficacy of endovascular catheter cooling combined with cold saline for the treatment of acute myocardial infarction. *ClinicalTrials.gov*: NCT01379261.
47. McMullan P. CHIPAHA: Can hypothermia be incorporated into primary angioplasty for heart attack. *ClinicalTrials.gov*: NCT00763828.
48. Wolfrum S, Pierau C, Radke PW, Schunkert H, Kuroswki V (2008) Mild therapeutic hypothermia in patients after out-of-hospital cardiac arrest due to ST-segment elevation myocardial infarction undergoing immediate percutaneous coronary intervention. *Crit Care Med* 36: 1780-1786.
49. Knafelj R, Radsel P, Ploj T, Noc M (2007) Primary percutaneous coronary intervention and mild induced hypothermia in comatose survivors of ventricular fibrillation with ST-elevation acute myocardial infarction. *Resuscitation* 74: 227-234.
50. Dixon RA, O'Neill WW (2005) Hypothermia for Acute Myocardial Infarction. In: Mayer SA, Sessler DI, editors. *Therapeutic Hypothermia*. Marcel Dekker, New York.
51. Williams R, Marber M (2010) The winding road to cardioprotection. *Heart Metab* 46: 25-33.
52. Merchant RM, Becker LB, Abella BS, Asch DA, Groeneveld PW (2009) Cost-effectiveness of therapeutic hypothermia after cardiac arrest. *Cir Cardiovasc Qual Outcomes* 2: 421-428.
53. Hovdenes J, Laake JH, Aaberge L, Haugaa H, Bugge JF (2007) Therapeutic hypothermia after out-of-hospital cardiac arrest: experiences with patients treated with percutaneous coronary intervention and cardiogenic shock. *Acta Anesthesiol Scand* 51: 137-142.
54. Schefold JC, Storm C, Joerres A, Hasper D (2009) Mild therapeutic hypothermia after cardiac arrest and the risk of bleeding in patients with acute myocardial infarction. *Int J Cardiol* 132: 387-391.
55. Miki T, Liu GS, Cohen MV, Downey JM (1998) Mild hypothermia reduces infarct size in the beating rabbit heart: a practical intervention for acute myocardial infarction? *Basic Res Cardiol* 93: 372-383.
56. Schwartz DS, Bremner RM, Baker CJ, Uppal KM, Barr ML, et al. (2001) Regional topical hypothermia of the beating heart: preservation of function and tissue. *Ann Thorac Surg* 72: 804-809.
57. Dae MW, Gao DW, Ursell PC, Stillson CA, Sessler DI (2003) Safety and efficacy of endovascular cooling and rewarming for induction and reversal of hypothermia in human-sized pigs. *Stroke* 34: 734-738.
58. Maeng M, Kristiansen SB, Mortensen UM, Andersen HR (2003) Myocardial cooling for reperfusion injury protection achieved by organ specific hypothermic autologous perfusion. *Scand Cardiovasc J* 37: 297-303.
59. Maeng M, Mortensen UM, Kristensen J, Kristiansen SB, Andersen HR (2006) Hypothermia during reperfusion does not reduce myocardial infarct size in pigs. *Basic Res Cardiol* 101: 61-68.
60. Otake H, Shite J, Paredes OL, Shinke T, Yoshikawa R, et al. (2007) Catheter-based transcatheter myocardial hypothermia attenuates arrhythmia and myocardial necrosis in pigs with acute myocardial infarction. *J Am Coll Cardiol* 49: 250-260.
61. Hale SL, Dae MW, Kloner RA (2003) Hypothermia during reperfusion limits 'no-reflow' injury in a rabbit model of acute myocardial infarction. *Cardiovasc Res* 59: 715-722.
62. Gotberg M, Olivecrona GK, Engblom H, Ugander M, van der Pals J, et al. (2008) Rapid short-duration hypothermia with cold saline and endovascular cooling before reperfusion reduces microvascular obstruction and myocardial infarct size. *BMC Cardiovasc Disord* 8: 7.
63. Ning XH, Xu CS, Song YC, Xiao Y, Hu YJ, et al. (1998) Hypothermia preserves function and signaling for mitochondrial biogenesis during subsequent ischemia. *Am J Physiol* 274: 786-793.
64. Ning XH, Chi EY, Buroker NE, Chen SH, Xu CS, et al. (2007) Moderate hypothermia maintains myocardial integrity and modifies response of cell survival proteins after reperfusion. *Am J Physiol Heart Circ Physiol* 293: H2119-H2128.
65. Frelinger AL, Furman MI, Barnard MR, Krueger LA, Dae MW, et al. (2003) Combined effects of mild hypothermia and glycoprotein IIb/IIIa antagonists on platelet-platelet and leukocyte-platelet aggregation. *Am J Cardiol* 92: 1099-1101.
66. Gotberg M, van der Pals J, Goterg M, Olivecrona G, Kanski M, et al. (2011) Optimal timing of hypothermia in relation to myocardial reperfusion. *Basic Res Cardiol* 106: 697-708.
67. Ye S, Weng Y, Sun S, Chen W, Wu X (2011) Comparison of the Durations of Mild Therapeutic Hypothermia on Outcome Following Cardiopulmonary Resuscitation in the Rat. *Circulation*.

This article was originally published in a special issue, [Myocardial Infarction and Protection](#) handled by Editor(s). Dr. Dayue Darrel Duan, University of Nevada, USA