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Therapeutic hypothermia for acute myocardial infarction:
a narrative review of evidence from animal and clinical studies

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Running title: Therapeutic hypothermia for AMI

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Abstract

Myocardial infarction (MI) is the leading cause of death from coronary heart disease and requires immediate reperfusion therapy with thrombolysis, primary percutaneous coronary intervention, or coronary artery bypass grafting. However, myocardial reperfusion therapy is often accompanied by cardiac ischemia/reperfusion (I/R) injury, which leads to myocardial injury with detrimental consequences. The causes of I/R injury are unclear, but are multifactorial, including free radicals, reactive oxygen species, calcium overload, mitochondria dysfunction, inflammation, and neutrophil-mediated vascular injury.

Mild hypothermia has been introduced as one of the potential inhibitors of myocardial I/R injury. Although animal studies have demonstrated that mild hypothermia significantly reduces or delays I/R myocardium damage, human trials have not shown clinical benefits in acute MI. In addition, the practice of hypothermia treatment is increasing in various fields such as surgical anesthesia and intensive care units. Adequate sedation for anesthetic procedures and protection from body shivering have become essential during therapeutic hypothermia. Therefore, anesthesiologists should be aware of the effects of therapeutic hypothermia on the metabolism of anesthetic drugs.

In this paper, we review the existing data on the use of therapeutic hypothermia for acute MI in animal models and human clinical trials to better understand the discrepancy between perceived benefits in preclinical animal models and the absence thereof in clinical trials thus far.

Keywords: Anesthesia; Animals; Hypothermia; Humans; Myocardial infarction; Myocardial ischemia; Myocardial reperfusion injury; Rewarming; Shivering.
**Introduction**

Coronary heart disease (CHD) is the leading cause of death worldwide. CHD mortality in the United States in 2017 was over 360,000 [1] and worldwide, 3.8 million men and 3.4 million women die of the disease each year [2,3]. Myocardial infarction (MI), also known as a heart attack, is the major cause of death in CHD and over 100,000 Americans died of MI in 2017 [1].

The myocardium performs structural and biomechanical functions that are essential for health and survival. Myocardial loss caused by injury, disease, or aging accounts for a significant number of clinical disorders and substantial human suffering at an enormous social and economic cost [4]. Infarctions usually result in the formation of fibrotic scars that permanently impair the biomechanical function of the heart because the heart exhibits a minimal capacity for self-repair [5].

MI occurs when the blood supply to the heart is severely reduced or completely blocked. As a result, cardiac muscle cells do not receive sufficient oxygen and may die through forms of necrosis and apoptosis that contribute to the death of cardiomyocytes [6]. This most commonly occurs when a coronary artery becomes occluded and a blood clot forms acutely following the rupture of an atherosclerotic plaque. Major surgery and anesthesia may also induce cardiovascular risk, particularly in patients with cardiovascular disease [7]. For example, cardiac ischemia/reperfusion (I/R) injury is frequently induced or may occur during coronary angioplasty, cardiac valve replacement, coronary artery bypass grafting, and cardiac transplantation [7,8].

Early myocardial reperfusion with the use of thrombolytic therapy or primary percutaneous coronary intervention (PCI) is the most effective strategy to reduce infarct size and improve clinical outcomes [3,8]. However, the process of restoring blood flow to the ischemic myocardium can cause injury, and this phenomenon, termed “myocardial reperfusion injury”, can diminish the beneficial
effects of myocardial reperfusion [2,3,8]. The mechanism of I/R injury is unclear, but several hypotheses have been proposed: formation of free radical or reactive oxygen species (ROS), calcium overload, hyperglycemia, mitochondrial dysfunction, inflammation, neutrophil-mediated vascular damage, microvascular hypoperfusion, and depletion of high energy phosphates [8,9]. Reperfusion has deleterious effects and reperfusion injury can contribute to up to half of the final myocardial infarct size [2,3,8].

The development of effective adjunct therapy is necessary to improve clinical outcomes in acute MI (AMI) and to reduce the risk of heart failure (HF) and sudden death after MI. For these reasons, various approaches and therapies have been tested to reduce the detrimental effects of I/R. However, these have not shown any beneficial cardioprotective effects in the clinical setting [8,10-12].

Mild hypothermia has been introduced as a potential inhibitor of myocardial I/R injury. Although animal studies have demonstrated that mild hypothermia significantly reduces or delays I/R myocardial damage [13-18], human trials have not replicated clinical benefits in AMI [10-12,19,20]. In this article, we review the evidence and issues from animal and clinical studies regarding the effects of hypothermia therapy on AMI.

Pathophysiology of MI and I/R injury

Ischemia: MI results from an imbalance in the myocardial oxygen supply/demand mismatch, typically due to insufficient coronary blood flow. Various causes of coronary stenoses, such as atherosclerosis, vasoconstriction, or mechanical pressure can cause coronary ischemia. Usually, coronary blood flow is maintained through autoregulation, which controls the tone and coronary artery luminal size through mediators of the myocardium or endothelium [21]. However, when the
coronary endothelial function is abnormal due to coronary artery disease, coronary blood flow cannot be sufficiently maintained through this mechanism.

Factors influencing the size of subsequent infarcts include the duration of ischemia, the size of the ischemic territory (area at risk, AAR), collateral blood flow, myocardial metabolic rate, and temperature during ischemia [22,23]. Ischemia duration longer than 40 minutes results in irreversible myocardial damage and loss of cardiac function, and I/R injury may occur after 50 min [2,24]. In the absence of collateral circulation, necrosis occurs in most of the AARs if reperfusion is not performed in a timely manner. Long-term consequences of MI include ventricular remodeling of the remaining myocardium, ventricular failure, arrhythmia, and sudden death [25,26].

**Reperfusion & Reperfusion Injury:** Reperfusion therapy, such as PCI or thrombolysis, is essential for the survival of damaged myocardial tissue by ischemia, especially in the setting of acute ST-segment elevation myocardial infarction (STEMI) [3,22]. Clinically, reperfusion significantly reduces mortality after MI by approximately 75% [23]. However, reperfusion can be a “double-edged sword” due to I/R injury [27-29].

The pathological mechanisms of I/R injury are multifactorial [2,8,23,24]. Infarcted myocardium undergoes necrosis characterized by calcium overload with contracted myofibrils, sarcolemmal rupture with edema, mitochondrial collapse, microvascular obstruction, capillary rupture, hemorrhage, and leukocyte infiltration [2,8]. Necrotic changes during reperfusion are accelerated by multiple pathways, such as calcium overload, oxidative stress by ROS, inflammatory response, and activation of the calpain system [2,8,23]. In addition to necrotic cell death, the regulated process of cell death via apoptosis, autophagy, and necroptosis also occurs through the regulation of the calpain system [24]. Myocardial reperfusion results in four types of cardiac dysfunction: 1) myocardial stunning, 2) no-reflow phenomenon, 3) reperfusion arrhythmias and 4) irreversible fatal reperfusion
injury, which involves severe myocardial damage including increased infarct size and impairment of myocardial contractility [3].

**Inflammation & Remodeling:** After MI, macrophages, monocytes, and neutrophils migrate and trigger intracellular signaling processes, resulting in inflammatory responses [25,30,31]. The degradation of collagen struts by matrix metalloproteinases activation and serine proteases results in infarct expansion. Infarct expansion leads to wall thinning and ventricular dilatation, increasing myocardial wall stress. This early remodeling occurs within 72 hours, and the expansion of the infarct zone leads to changes in loading conditions.

When ventricular load increases and cardiac output decreases, there is a release of norepinephrine, and activation of the renin-angiotensin-aldosterone system, resulting in myocardial hypertrophy. During late remodeling (more than 72 hours), reparative changes occur in the global ventricle including both infarcted and non-infarcted myocardium. The release of transforming growth factor-β (TGF-β) facilitates fibroblast proliferation and angiotensin II production. Macrophage activation stimulates nitric oxide stimulation that increases vascular permeability.

Oxidative stress facilitates post-MI inflammatory responses in both infarcted and non-infarcted myocardium through enhanced ROS production and impaired antioxidant capacity. These changes induce an inflammatory response in the infarct zone and stimulate fibrosis by collagen synthesis. Ventricular dilatation, myocyte hypertrophy, and the formation of collagen scar result in distortion of the shape of the ventricle until the ventricular wall stress is balanced with the tensile strength of fibrous tissue [25,26].

Survival after MI is determined by the effect of ventricular remodeling on contractile function and end-systolic volume, which is based on the infarct size, location, and shape of the left
ventricle [30,32]. Adverse ventricular remodeling, which does not normalize the intracavitary stress of the ventricular wall, results in excessive dilatation of the ventricles and fibrosis and decreased contractile function [8,25,31]. Patients with preserved left ventricular systolic function have a higher survival rate, while adverse ventricular remodeling is associated with significantly higher mortality [30]. Therefore, left ventricular remodeling is considered a surrogate for HF, and maintaining a normal end-systolic volume and ejection fraction during remodeling is an important goal for survival [30,32].

Myocardial Infarction Size Measurement

The size of MI in the clinical trials can be measured by the techniques as below:

**Single-photon emission computed tomography (SPECT):** SPECT imaging with Technetium-99m 2-methoxyisobutylisonitrile (99mTc-sestamibi, also termed as 99mTc MIBI) is the most practical and widely used tool for the clinical evaluation of MI [33]. SPECT imaging is used to visualize areas of reduced blood flow due to physiologic/pharmacologic stress or pathological conditions and to determine the viability of cardiac tissue. There is a close association between SPECT MI size and other parameters including left ventricular function, end-systolic volume, creatine kinase release, and MRI infarct size, as well as patient mortality [33]. There is also a good correlation between the SPECT MI size and the actual amount of pathological fibrosis in the human heart [33]. The major limitation is that radioisotopes are required as contrast agents. In addition, due to the spatial resolution (10 mm) of SPECT images, SPECT misses small infarcts, particularly subendocardial infarcts that do not involve the entire heart wall, and their sizes exceed the spatial resolution of SPECT.
**MRI:** Although SPECT is an established method for infarct quantification, cardiovascular MR techniques play an important role in the assessment of myocardium viability and infarct detection because of their advantages of superior spatial resolution (60-fold greater than SPECT) and tissue characterization, performed under resting conditions, and without exposure of radiation [34]. Contrast-enhanced MRI allows real-time visualization of cardiac motion with superior anatomical and functional definition, and is useful and accurate for the noninvasive determination of infarct size. In addition, contrast-enhanced MRI enables accurate delineation between infarct and viable myocardium, while cardiac MR can visualize both reversible and irreversible injury and determine the presence of residual MI [34]. This allows a comprehensive assessment of the sequels of acute MI that can help guide patient management [34].

Since the contrast agent (gadolinium) is extracellular and interstitial, the volume of distribution of the contrast increases within the infarcted imaging voxel. Since the increased gadolinium concentration in the infarcted tissue shortens the relaxation time, the infarct appears to be hyper-enhanced [34]. MRI shows excellent accuracy in the delineation of scars when compared to scintigraphic techniques (SPECT) [35]. The hyper-enhanced area of the MR images shows a near-perfect correlation with the irreversibly injured regions defined triphenyl tetrazolium chloride (TTC) staining [35].

Recently, MRI techniques have demonstrated high accuracy in measuring microvascular obstruction, necrotic core, total infarct size, and the area at risk in reperfused infarcts which allows direct quantification of myocardial salvage [36,37]. In addition, infarct size by MRI has higher reproducibility than SPECT [38]. In humans, MRI accurately predicts the reversibility of associated myocardial dysfunction [39,40].
Animal models for AMI

The normal core temperature of animals is higher (i.e., pig: 38.5-39°C) than that of humans (36.5-37.5°C). However, experimental animal models can help to evaluate the effect of hypothermia on I/R injuries before conducting clinical trials, and it would be recommended to focus on the degree change in infarct size with changes in core temperature rather than the absolute temperature of hypothermia.

**Techniques:** There are several animal models of MI that include small animals such as rodents, or large animals such as swine and sheep. The pig model is an attractive choice given its similarity to humans in terms of cardiac circulatory anatomy and cardiac contraction relaxation kinetics, and cardiac output [41]. In pigs, the left coronary artery is larger and longer than the right coronary artery, as in humans. There is little collateral blood flow with scant collateral arteries which localize to the mid myocardium and sub-endocardium. These properties of the coronary system allow for predictable infarct size. Pigs have a heart rate of about 105 ± 10.6 beats/min and a mean arterial blood pressure of 102 ± 9.3 mmHg [42,43]. After the occlusion of a coronary artery, the ischemic myocardium ceases aerobic metabolism within a few seconds, resulting in severe systolic dysfunction [44]. An occlusion period of less than 15 min in pigs causes reversible myocardial ischemia, and ischemic myocardial tissues may survive after the restoration of coronary blood flow. A duration of occlusion between 15-30 minutes causes irreversible myocardial damage with histological changes as mentioned above in the infarction area.

**Effect of the duration of occlusion on the infarct size [13,18,45-65]:** In pigs, the percentage of infarct size in the risk area after reperfusion increases with the duration of coronary artery occlusion: % infarct size was 30 ± 15% AAR after 30 min occlusion, 66 ± 12% AAR after 60 min occlusion, and 68% AAR after 90 min occlusion. A duration of occlusion of about 180 minutes results in a complete infarct with an AAR size greater than 80% [23].
Hypothermia Therapy

Effects of hypothermia on infarct reduction: During mild hypothermia, the heart rate decreases while cardiac contractility is preserved, thus reducing myocardial work and oxygen consumption [66,67]. In addition, as the metabolism of the whole body, as well as the heart, is suppressed, the oxygen demand decreases. Reduction of cellular metabolism, preservation of adenosine triphosphate (ATP) concentration, reduction of ROS production, and regulation of apoptosis is associated with energy preservation and reduction in infarct size. The prophylactic effect of hypothermia on I/R injury is also associated with modulation of the mitochondrial permeability transition pore (mPTP), reduction of calcium overload during hypothermia, and regulation of cellular signaling (Akt pathways, heat-shock proteins, extracellular-regulated kinase, etc.), reducing the inflammatory response [67].

Animal studies

Table 1 summarizes the effect of mild hypothermia therapy on infarct size in animal models. Therapeutic mild hypothermia in the setting of AMI, usually left anterior descending (LAD) occlusion, in animal models has effectively reduced myocardial infarct size and microvascular dysfunction, particularly when initiated before reperfusion, but not after reperfusion [13-15, 17, 18]. Duncker et al. [49] found a positive correlation between infarct size and temperature. Other studies have demonstrated a beneficial temperature-related effect of hypothermia on infarct size. However, Maeng et al. [61] found no benefit of hypothermia induced in conjunction during or after reperfusion. In addition, studies that reached the target temperature after perfusion in which cooling was initiated
concurrently with rapid reperfusion failed to show the same level of protection [61]. These previous studies have suggested that the timing of cooling relative to end-ischemia and early reperfusion is critical for optimizing its benefit.

Dae et al. [13] studied the cooling effect on MI in a human-sized pig model. Systemic cooling with an endovascular temperature catheter was started 20 min into a total 60 min coronary occlusion followed by gradual rewarming during reperfusion for about 3 hours. The size of the AAR was comparable in the hypothermic (19 ± 3%) and normothermic (20 ± 7%) animals. However, infarct size significantly decreased in hypothermic animals (9 ± 6% vs 45 ± 8%).

The mechanism by which mild hypothermia exerts its effect is not fully elucidated yet. The protective effect of hypothermia is mediated in part through reduced reperfusion injury [68]. Cardiac hypothermia is known to decrease myocardial oxygen consumption and slow the rate of ATP depletion during ischemia [69]. This may be mediated by decreased release of vasodilatory mediators but may also reflect decreased responsiveness of endothelial and vascular smooth muscle cells. Shao et al. [70] suggested that significant acceleration of myocardial death occurs within the first hour of reperfusion, preceded by a burst of oxidants, and cytochrome c release that occurs within minutes of reperfusion.

It has been difficult to translate this finding into a clinical setting because the methods used to induce hypothermia (e.g., cardiac surface cooling, arteriovenous extracorporeal heat exchangers, and peritoneal cooling) and the cooling rate are different and rapid intervention times are impractical for implementation. In addition, porcine myocardium, the most popular animal model for MI studies, has little collateral blood flow, unlike human myocardium; this may lead to a slower onset of infarction in humans.
**Human clinical trials**

**a. Effect of target temperature:** Several human clinical trials have assessed the effect of hypothermia on the reduction of infarct size and HF in patients with AMI (Table 2). Most human clinical trials have used mild hypothermia of 32-34°C as a target hypothermia temperature for adjuvant PCI therapy [11].

The COOL-MI InCor Trial (Cooling as an Adjunctive Therapy to Percutaneous Intervention in Acute Myocardial Infarction), in which hypothermia was maintained using the endovascular cooling method with a target temperature of 32 ± 1°C showed no difference in AAR (14.1% vs. control 13.8%) and ventricular function (43.3 ± 11.2% vs. control 48.3 ± 10.9%) [71]. However, hypothermia less than 35°C applied to anterior MI patients resulted in a significant decrease in infarct size (9.3% vs. control 18.2%). A small pilot study, Rapid MI-ICE (The Rapid Cooling by Cold Saline and Endovascular Cooling Before Reperfusion in Patients with ST-Elevation Myocardial Infarction), in which hypothermia was maintained with a target temperature of 33°C by forced infusion of 4°C cold saline for 3 hours [72], showed a 38% reduction in infarct size/AAR and no HF development.

A multicenter randomized clinical trial, CHILL-MI Trial (A Randomized Controlled Study of the Use of Central Venous Catheter Core Cooling Combined With Cold Saline as an Adjunct to for the Treatment of Acute Myocardial Infarction) aimed at rapid induction of hypothermia (33°C for 1 hour) but did not achieve an overall reduction in infarct size/AAR [73]. Relatively longer door to balloon time in the study group (about 9 min longer) and failure to achieve goal temperature in some patients may be responsible for the failure to reduce infarct size. However, the trial showed a 33% reduction
in infarct size/AAR on the anterior wall and a lower incidence of HF at 45 days follow-up (3% vs. 14% of control).

Interestingly, the VELOCITY trial (The Evaluation of Ultrafast Hypothermia Before Reperfusion in STEMI Patients) used an automated peritoneal lavage device for mild hypothermia targeting a temperature below 35°C did not yield meaningful results [74]. The VELOCITY trial showed no change in infarct size or microvascular obstruction and an increase in major cardiac adverse events in 30 days. In addition, the door to balloon time was increased by about 15 min, and stent thrombosis occurred only in the hypothermia group. These results indicate that the potential risk of peritoneal cooling methods for therapeutic hypothermia and duration of ischemia may be more important factors for infarct size than prevention of I/R injury by hypothermia.

The COOL AMI EU pilot trial (a multicenter, prospective, randomized controlled trial to assess cooling as adjunctive therapy to percutaneous intervention in patients with acute myocardial infarction) showed a successful ~30% reduction in infarct size/left ventricular mass in anterior STEMI patients (16.7% vs. 23.8% of control) [75]. This trial used a rapid cooling protocol that achieved 33.6°C during reperfusion and lowered the temperature by more than 1.1°C compared to the previous clinical trials with 17 minutes cooling-related delay to reperfusion.

Most randomized clinical trials have not shown positive results with hypothermia as an adjunct therapy to primary coronary intervention in patients with AMI [19,71,73,74]. However, clinical trials have demonstrated the safety and feasibility of adjuvant hypothermia induced by cold saline and endovascular cooling during coronary intervention in patients with AMI; mild hypothermia at the time of reperfusion is effective in reducing infarct size and the incidence of HF [11]. In particular, in the subgroup analysis, patients with body temperature reaching < 35°C before reperfusion and significant anterior wall MI showed a decrease in infarct size, suggesting a benefit of inducing
hypothermia before reperfusion. Moreover, a pooled analysis of clinical trials showed a reduction in ischemia size and HF incidence in patients with large AARs, at least 30%, when the core temperature reached ≤35°C at the time of reperfusion [76,77]. These results suggest that it is essential to reach a core body temperature of < 35°C before reperfusion to reduce the size of MI and that a lower temperature close to 32°C, the lower limit of mild hypothermia, may be more effective.

**b. Consideration for hypothermia in clinical practice:** Although animal studies have demonstrated the cardioprotective effects of hypothermia during reperfusion procedures, clinical trials have shown poor clinical relevance. A systematic review and meta-analysis of hypothermia trials after AMI confirmed that hypothermia is a safe and feasible intervention. However, there are controversies about the reduction of infarct size and major adverse cardiovascular events (MACE). Mottillo et al. [78] suggested that more evidence is needed although mean infarct size decreased according to the subgroup analysis of anterior wall infarction and there was no significant difference in the cardiac outcome. Villablanca et al. [79] reported that hypothermia had limited benefits in reducing infarct size only in anterior wall MI and no significant benefit in reducing MACE and mortality. These results suggest that further studies are needed for different indications and protocols in humans by comparing the methods and results of animal studies.

In animal studies showing the benefits of hypothermia, hypothermia and MI were typically undertaken simultaneously, and hypothermia was maintained throughout the ischemic period. However, it is almost impossible to apply hypothermia in humans from the onset of MI in clinical situations. It is also difficult to apply rapid hypothermia to humans, and a sufficiently low temperature may not be achieved before reperfusion. Moreover, the benefits of hypothermia may be lost in some patients with spontaneous reperfusion of an occluded coronary artery prior to the reperfusion
procedure [67]. Also, the actual temperature of myocardial tissues may differ from the core
temperature or blood temperature measured by a cooling device [80].

As the ischemic myocardium is a part of the loss of blood circulation, the measured temperature
does not reflect the tissue of interest and may be insufficient to protect against I/R injury. Salvage of
reperfused myocardial tissue is correlated with tissue temperature at the border of the ischemic region,
not with core temperature. Therefore, hypothermia precisely confined to the infarct region may be
effective to prevent I/R injury in humans.

Consequently, adequate hypothermia with practically optimal temperature and time duration is
considered to be limited in some areas of emergency care, cardiac surgery, or post-conditioning
strategies, and further research and technology development are required.

c. The temporal window for efficacy: According to the results from small animals, a pooled
analysis showed that the reduction in infarct size decreased exponentially with increasing
hypothermia induction time [66]. In addition, delayed hypothermia, initiated just prior to reperfusion,
may have little effect on reducing ischemic size after reperfusion. The protective effect of
hypothermia was completely lost when cooling was delayed 15 minutes post-reperfusion [70].
Interestingly, hypothermia induced after reperfusion reduced the no-reflow phenomenon without the
benefit of reduced infarct size [61,81]. Therefore, it is clear that hypothermia should be applied prior
to reperfusion and initiated as soon as possible for the reduction of infarct size, no-reflow
phenomenon, and remodeling [14,51,81,82].

d. Optimal target temperature: Therapeutic hypothermia is classified as mild (32–35°C), moderate
(28–32°C), severe (20–28°C), and profound (<20°C) depending on the target body temperature [83].
There is still no optimal target temperature in clinical practice. Experimental results show that the
reduction in infarct size is closely related to the target temperature, which decreases by 10-20% for every 1°C decrease in temperature [11]. Therefore, a lower temperature is associated with a reduction in infarct size. However, in clinical practice, only mild hypothermia is acceptable except under special circumstances such as surgery or cardiac arrest because the life-threatening risks associated with hypothermia are less with mild grade. Mild hypothermia reduces heart rate and cardiac output while maintaining stroke volume and mean arterial pressure. In general, a target temperature of 32–34°C is recommended [11,84].

Safety during hypothermia

Deep hypothermia may be associated with various complications such as hemodynamic deterioration, ventricular arrhythmia, or coagulopathy. However, mild to moderate hypothermia does not appear to cause these complications [19]. The feasibility and safety were successfully confirmed in clinical trials using endovascular cooling to lower core body temperature to below 34-35 °C [19,72,85,86]. There was no hemodynamic instability or bleeding complications during mild to moderate hypothermia with endovascular cooling. Although some patients with anterior MI may develop ventricular arrhythmias during hypothermia with endovascular cooling [19] or intracoronary cooling [87], these arrhythmias can be easily controlled by DC cardioversion, so mild hypothermia seems to be safe in patients with AMI. However, peritoneal cooling appears to be associated with some safety concerns. Peritoneal cooling increases stent thrombosis due to increased platelet activation and respiratory suppression due to effects on diaphragmatic excursion [74]. Yet, the application of mild to moderate hypothermia is well tolerated in patients with MI and does not cause serious complications when it is controlled by adequate treatment and sedation.

Future studies
**Optimal cooling & rewarming pattern:** Although the potential of mild hypothermia for myocardial recovery strategies after MI has been introduced by animal and human studies, there are few studies on optimal rewarming patterns. Unfortunately, while most studies on rewarming after hypothermia have focused on neurological outcomes after cardiac arrest, few studies have focused on the cardiac outcomes after MI, such as infarct size or cardiac function. Rewarming may induce adverse effects, such as “rewarming shock”, characterized by hypotension, tachycardia, and acidosis due to the return of altered cardiovascular functions during hypothermia [88]. For example, increased metabolic rate and cardiac output can cause a mismatch between oxygen demand and supply.

Changes in oxygen delivery can occur due to changes in body temperature associated with changes in oxygen extraction rates, hemoglobin dissociation curve, and blood viscosity. In addition, increased oxygen consumption may occur due to the resumption of the inflammatory process and free radical oxidation. Shivering during rewarming may also contribute to the mismatch. Ventricular dysfunction associated with decreased sensitivity of myofibrils to calcium due to increased troponin C phosphorylation may also occur after rewarming [89].

Animal studies have shown worse results at faster-rewarming rates [88]. Therefore, a slow and targeted rewarming protocol is necessary after applying hypothermia. In the case of mild hypothermia after cardiac arrest, a slow rewarming of 0.25°C/hour to normothermia (37°C) is suggested because of the long duration of hypothermia application (12 to 24 hours) with a cooler temperature than coronary reperfusion (32-33°C) [84]. This slow rewarming takes almost 12 hours or more. However, previous clinical trials of AMIs using both active and passive rewarming protocols showed somewhat rapid rewarming time [71-75,90].

The duration of rewarming took 3-4 hours for the active rewarming protocols and 3-6 hours for the passive or spontaneous rewarming protocol. It seems the shorter duration of hypothermia (1-3 hours),
the higher temperature at reperfusion period (33-35°C), and the absence of risks of neurological
damage unlike cardiac arrest or cerebral ischemia make the immediate rewarming with a shorter
duration possible in hypothermic therapy during reperfusion procedure in patients with AMI.
However, further controlled studies using longer rewarming duration or programmed rewarming
protocol with shivering prophylaxis using sedatives or analgesics, oxygen balance optimization, and
goal-directed hemodynamic optimization are needed to identify the optimal rewarming protocol.

**Effect of adequate sedation & body shivering:** Shivering can occur as a natural reflex from
discomfort, pain, or cold- including therapeutic hypothermia- in most patients [84,91]. Shivering
increases metabolic rate, oxygen consumption, and sympathetic tone, which increase heart rate and
cardiac output. In particular, shivering is more likely to occur during hypothermia induction at
temperatures between 35°C and 37°C and less likely at target temperatures for mild hypothermia
between 32°C to 34°C, thus shivering may delay reaching the target temperature [84]. These effects
may offset the therapeutic effects of hypothermia for I/R injury. Therefore, adequate management of
shivering with sedatives, analgesics, and other interventions is required.

It is known that low skin temperature is responsible for about 20% of shivering, so an application
of counter-warming with a forced-air warmer on the body surface, especially in areas where
cutaneous temperature sensors are concentrated, such as the face and hands, may help inhibit
shivering [84,91]. However, counter-warming alone is not sufficient and simultaneous rapid
pharmacologic suppression of shivering is required during the induction of hypothermia. Because the
target temperature should be reached rapidly, it is recommended to prevent shivering with the most
effective combination of treatments.

According to previous clinical trials [71-74], shivering prophylaxis using various
pharmacological agents that lower the shivering threshold is recommended (Table 3). If shivering
prophylaxis is unsuccessful with routine pharmacological agents, sedation with propofol or
midazolam or analgesic with additional opioids such as fentanyl or hydromorphone can be used, but
cautions required for respiratory depression [84]. In the case of refractory shivering, neuromuscular
blockers can be used with mechanical ventilation after intubation, but sedation and analgesia are
mandatory.

Localized myocardial hypothermia: Recently, a new method for localized myocardial
hypothermia in AMI has been introduced, although it has already been used in various cardiac
surgeries in the surgical field. As mentioned above, disappointing results of mild hypothermia in
human clinical trials are thought to be due to inadequate core temperature for I/R injury prevention,
slow cooling rate, prolonged infarct duration during systemic cooling, the actual difference between
tissue and core temperature, and adverse effects of cooling such as shivering.

A modified technique using selective intracoronary hypothermia can be rapidly achieved target
region hypothermia by infusion of cold saline at 4°C for 10 minutes during reperfusion. This method
can induce hypothermia during coronary angiography by injecting a small amount of saline of only
several hundred milliliters to avoid volume overload and detained control of temperature, infusion
rate, and pressure with sensors of the intracoronary catheter which provide safety [87,92,93].
Although there have been several reports of the feasibility and reproducibility of selective
intracoronary hypothermia, clinical data on its effectiveness in reducing I/R injury, infarct size,
ventricular dysfunction, or MACE compared with prior techniques are unknown, and more evidences
are required.

Therapeutic hypothermia in anesthesia and critical care
For anesthesiologists, hypothermia is associated with complications such as myocardial ischemia, coagulopathy, wound infection, shivering, or long-term recovery from anesthesia [94,95]. However, they are also becoming accustomed to hypothermia and rewarming in the fields of cardiac anesthesia, neurosurgery, or various critical cares [94,95]. For example, it is known that hypothermia during cardiopulmonary bypass (CPB) is primarily suitable for protecting neurological functions, including the prevention of brain damage and vital organs.

Although there is endless debate about the benefits of hypothermia on neurologic function and mortality during CPB, hypothermia may reduce oxygen demand and myocardial damage [96,97]. In addition, as mentioned above, adequate sedation and protection of body shivering required for anesthetic procedures during therapeutic hypothermia have become essential. Therefore, anesthesiologists should be familiar with metabolic changes in anesthetics for the safety of patients as long as hypothermic technique is used [95,97,98].

Hypothermia impairs temperature-sensitive enzymes, leading to changes in distribution volume and decreased drug metabolism [97]. A 3°C decrease in core body temperature results in a 28% increase in propofol concentrations due to decreased intercompartmental clearance, decreased metabolism due to reduced hepatic blood flow, and changes in the cytochrome enzyme (cytochrome P450 2B6) system [97,99,100]. The clearance of midazolam decreases by 11.1% for each 1°C decrease in temperature below 36.5 °C [101]. Fentanyl is metabolized primarily by cytochrome P450 3A4, similar to midazolam, but due to its high distribution and high clearance properties, clearance is dependent on hepatic blood flow [100]. During hypothermia, plasma concentrations of fentanyl increase due to decreased clearance [102]. Remifentanil has a short half-life due to its rapid hydrolysis by nonspecific esterase [100]. The clearance of remifentanil decreases by 6.37% for a 1°C decrease in temperature below 37 °C, and a 30% decrease in infusion rate is recommended for a 5°C decrease in temperature [103].
Hypothermia also affects the duration of action and recovery time of muscle relaxants. A 3°C lower core temperature due to changes in Hofmann degradation or ester hydrolysis increases the duration of atracurium by approximately 60% [99]. In the case of mild hypothermia, vecuronium recovery time is increased about 2.2 times compared to normal body temperature [104]. Similarly, hypothermia may increase the duration of action of rocuronium [105]. Interestingly, after reversal using sugammadex, the recovery time of rocuronium also increased about 1.4-fold compared to normothermia [106]. The long-term effects of these neuromuscular blockers are due to changes in pharmacokinetics, primarily clearance, rather than pharmacodynamics [105]. Also, neuromuscular monitoring may not be possible in hypothermic conditions [107].

Conclusion

Available evidence suggests that therapeutic hypothermia has the potential to reduce myocardial ischemic injury in humans. However, randomized clinical trials have not reproduced the promising results seen in preclinical studies. Compared to many studies regarding the role of therapeutic hypothermia on post-resuscitation brain injury or myocardial protection for surgery, limited studies have focused on improving myocardial reperfusion injury. There are many questions left to be answered, which include: (1) the optimal target temperature for STEMI; (2) the optimal therapeutic hypothermia method; (3) the need for a target temperature to be achieved prior to reperfusion; (4) optimal duration of hypothermia; (5) myocardial protective mechanisms; (6) optimal target patient population; and (7) optimal protocol for rewarming. The emergence of new devices that allow for faster cooling may help to better define some of these questions and lead to positive results in future clinical trials.
Table 1. Summary of previous hypothermia researches.

<table>
<thead>
<tr>
<th>Author</th>
<th>Subject</th>
<th>Period of ischemia</th>
<th>Objectives</th>
<th>Details of Study</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duncker</td>
<td>Pig</td>
<td>45 min of left coronary occlusion</td>
<td>1) the effect of body core temperature in the normothermic range on myocardial infarct size (MIS). 2) the effect of blockade of endogenous adenosine on MIS in relation to body core temperature.</td>
<td>8-phenyltheophylline (5 mg/kg iv), adenosine deaminase (25 U/kg) into the coronary artery</td>
<td>1) Profound effect of core body temperature on the MIS 2) no protective effect of endogenous adenosine against irreversible damage</td>
</tr>
<tr>
<td>Hale</td>
<td>Rabbit</td>
<td>30 min of circumflex occlusion</td>
<td>To test the hypothesis that regional myocardial hypothermia reduces infarct size</td>
<td>Bag with ice and water on the surface of the heart; 20 min before occlusion</td>
<td>Profound reduction in MIS with hypothermia</td>
</tr>
<tr>
<td>Hale</td>
<td>Rabbit</td>
<td>30 min of circumflex occlusion</td>
<td>To test the hypothesis that regional myocardial hypothermia</td>
<td>Bag with ice and water on the surface of the heart; 10 min and 25 min after occlusion</td>
<td>Reduction in MIS with hypothermia during coronary ischemia</td>
</tr>
<tr>
<td>Author</td>
<td>Species</td>
<td>Duration</td>
<td>Methodology</td>
<td>Outcome</td>
<td></td>
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<tr>
<td>Miki (1998)</td>
<td>Rabbit (N=44, 1.8-2.4 kg)</td>
<td>30, 45, or 60 min of left coronary artery occlusion</td>
<td>To test the effect of hypothermia on infarct size with various onset times</td>
<td>Extracorporeal heat exchanger (32°C or 35°C); 5 min before and 10 and 20 min after occlusion</td>
<td>Significant reduction in MIS with hypothermia; reduction effect even during occlusion in early stage but not late-stage</td>
</tr>
<tr>
<td>Dave (1998)</td>
<td>Rabbit (N=20, 2.2-3.2 kg)</td>
<td>30 min of circumflex occlusion</td>
<td>To investigate the effect of pericardial space cooling on MIS</td>
<td>Pericardial fluid exchange with continuous cold Ringer's lactate; 30 min before occlusion</td>
<td>Significant reduction in myocardial temperature and MIS</td>
</tr>
<tr>
<td>Schwartz (2001)</td>
<td>Swine (N=16, 30-40 kg)</td>
<td>40 min of coronary occlusion</td>
<td>To test the effect of regional topical hypothermia on MIS</td>
<td>Bag with iced saline slush on the epicardial surface; during the occlusion</td>
<td>Significant less in myocardial necrosis with regional hypothermia</td>
</tr>
<tr>
<td>Author</td>
<td>Species</td>
<td>Number of Animals</td>
<td>Duration of Occlusion</td>
<td>Method of Cooling</td>
<td>Temperature</td>
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<tr>
<td>Dae (2002) [13]</td>
<td>Swint</td>
<td>(N=22 &amp; 11, 60-80 kg)</td>
<td>60 min of left coronary occlusion</td>
<td>To test endovascular cooling would reduce the temperature in a large heart rapidly and decrease infarct size</td>
<td>Cooling (target temp=34°C) started 20 min after occlusion and continued for 15 min after reperfusion</td>
</tr>
<tr>
<td>Hale (2003) [14]</td>
<td>Rabbit</td>
<td>(N=32, 2.2-3.2 kg)</td>
<td>30 min of circumflex occlusion</td>
<td>To test the effects of myocardial hypothermia, instituted late in the ischemic period</td>
<td>Cooling (target temp=32°C) started 20 min after occlusion and continued for 120 min after reperfusion</td>
</tr>
<tr>
<td>Maeng (2006) [61]</td>
<td>Swine</td>
<td>(N=15, 70-80 kg)</td>
<td>45 min of left coronary occlusion</td>
<td>To evaluate a method for regional myocardial cooling (RMC) during reperfusion reduces the myocardial size</td>
<td>RMC (target temp= 33°C). Started 2 min before reperfusion &amp; sustained 2 hrs and then rewarming (2°C every 5 mins)</td>
</tr>
<tr>
<td>Tissier (2007) [108]</td>
<td>Rabbit</td>
<td>(N=30)</td>
<td>30 min of left coronary occlusion</td>
<td>To evaluate whether total liquid ventilation (TLV) can rapidly cool and protect the infarcting heart</td>
<td>5 different group: 1) 100% Oxygen (38 °C), 2) liquid warm (38 °C), 3) liquid cool (32°C), 4) liquid cool (32 °C) with 2 cm water PEEP, 5) liquid cool (32°C) 5 min before reperfusion</td>
</tr>
<tr>
<td>Study</td>
<td>Species</td>
<td>N</td>
<td>Duration of Occlusion</td>
<td>Hypothermia Protocol</td>
<td>Hypothermia Effect</td>
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</tr>
<tr>
<td>Olivecrona (2007) [68]</td>
<td>Pig</td>
<td>16, 25-30 kg</td>
<td>10 min of left coronary occlusion</td>
<td>Intravascular cooling, hypothermia (34 °C) vs control (37 °C)</td>
<td>Mild hypothermia significantly reduces (by 43%) post-ischemic hyperemia</td>
</tr>
<tr>
<td>Gotberg (2008) [51]</td>
<td>Pig</td>
<td>19, 40-50 kg</td>
<td>40 min of coronary occlusion</td>
<td>Cold saline (4 °C) infusion &amp; endovascular cooling, 3 groups: hypothermia 15 min before and immediately after reperfusion and no hypothermia, hypothermia target temp =33 °C</td>
<td>Rapid hypothermia before reperfusion reduces myocardial infarct size and microvascular obstruction</td>
</tr>
<tr>
<td>Kanemoto (2009) [109]</td>
<td>Rabbit</td>
<td>76, 3-4 kg</td>
<td>30 min of circumflex occlusion</td>
<td>Surface cooling (target temp=2 to 2.5 °C below initial body temp). Normothermia and 5 different cooling start times before reperfusion</td>
<td>Mild hypothermia significantly reduced myocardial infarct size. The temperature at reperfusion correlated strongly with infarct size.</td>
</tr>
<tr>
<td>Hamamoto (2009) [110]</td>
<td>Sheep (N=30, 35-40 kg)</td>
<td>60 min of left coronary occlusion</td>
<td>To determine the effect of mild hypothermia on the regional distribution of myocardial reperfusion injury</td>
<td>Cooling pad &amp; ice bags. 5 different temp groups (39.5 to 35.5 °C)</td>
<td>Temperature reduction improved myocardial salvage and microvascular integrity</td>
</tr>
</tbody>
</table>
Table 2. Summary of previous clinical trials of therapeutic hypothermia during reperfusion therapy.

<table>
<thead>
<tr>
<th>Trial name (year)</th>
<th>Cooling method</th>
<th>Target temperature</th>
<th>Average body temperature during coronary reperfusion</th>
<th>% of hypothermic patients during reperfusion</th>
<th>Hypothermia maintenance time</th>
<th>Heating</th>
<th>door-to-balloon time</th>
<th>infarct size (IS)</th>
<th>left ventricular ejection fraction</th>
<th>Major adverse cardiac events and complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid MI-ICE (2010) [72]</td>
<td>Endovascular hypothermia with cold saline (4°C)</td>
<td>33°C</td>
<td>34.7±0.3°C</td>
<td>100%</td>
<td>3 hours</td>
<td>Active 36-37°C during 3 hours</td>
<td>43±7 min vs. control 40±6 min</td>
<td>38% reduction (29.8±12.6% vs. control 48.0±21.6%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CHILL-MI (2014) [73]</td>
<td>Endovascular hypothermia with cold saline (4°C)</td>
<td>33°C</td>
<td>≤35.4°C (91%) ≤35°C (76%)</td>
<td>1 hour after reperfusion</td>
<td>Spontaneous rewarming</td>
<td>Increased 9 min due to hypothermia 33.3±21.2 min vs. control 42.7±16.6 min</td>
<td>9% reduction (36.6% vs. control 40.6%)</td>
<td>50% vs. control 51%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Study</td>
<td>Methodology</td>
<td>Temperature</td>
<td>Survival</td>
<td>Time</td>
<td>3-5 days:</td>
<td>23-27 days:</td>
<td>Safety problem:</td>
<td>Stent thrombosis:</td>
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<tr>
<td>VELOCITY (2015) [74]</td>
<td>Automated Peritoneal Lavage System with lactated Ringer’s solution</td>
<td>&lt;35°C</td>
<td>88.9%</td>
<td>3 hours</td>
<td>62 min vs. control 47 min</td>
<td>16.1% vs. control</td>
<td>17.2%*</td>
<td>11% vs. control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COOL-MI InCor Trial (2020) [71]</td>
<td>Endovascular hypothermia with cold saline (1-4°C)</td>
<td>32°C±1°C</td>
<td>100%</td>
<td>1-3 hours</td>
<td>Active 1°C/h for 4 hours.</td>
<td>92.1±20.5 min vs. control</td>
<td>43.3±11.2% vs. control</td>
<td>21.7% vs. control</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*%, % of total left ventricular mass;
Table 3. Pharmacological agents for reducing the shivering

<table>
<thead>
<tr>
<th>Agent</th>
<th>Route</th>
<th>Dosage</th>
<th>Mechanism</th>
<th>Cautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buspirone</td>
<td>Oral</td>
<td>30 - 60 mg</td>
<td>Partial 5HT1A agonist, D2 receptor agonist</td>
<td>Sedation, dizziness, nausea</td>
</tr>
<tr>
<td>Meperidine</td>
<td>Intravenous</td>
<td>Loading: 1 mg/kg (or 0.5 mg/kg in case of other opioid use) over 15 to 20 minutes, Maintenance: 25-30 mg/h titrated to effect, Bolus: 25 mg for shivering</td>
<td>Agonist at opioid receptors (μ and κ) and α-2B receptors, Antagonist at NMDA receptor</td>
<td>Sedation, respiratory depression, seizure</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Intravenous</td>
<td>Loading: 2 -4g bolus over 4 hours, Maintenance: 0.5 g/h, Goal serum Mg level: 3-3.5 mg/dL</td>
<td>Antagonist at NMDA receptor, Calcium channel blocking</td>
<td>Hypotension, nausea, vomiting</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>Intravenous</td>
<td>0.2 - 0.7 mcg/kg/hr</td>
<td>α-2 receptor agonist</td>
<td>Hypotension, bradycardia, sedation</td>
</tr>
</tbody>
</table>
References


