Corresponding author:
Kichang Lee, Ph.D.
Cardiovascular Research Center,
Massachusetts General Hospital, 185
Cambridge Street, 3-224, Boston, MA 02114,
USA
Tel: +1-617-643-7861
Email: kichang.lee@mgh.harvard.edu
ORCID: https://orcid.org/0000-0002-4058-3832

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

Ki Tae Jung[1,2,3], Aneesh Bapat[1,2,4], Young-Kug Kim[5], William J. Hucker[1,2,4], Kichang Lee[1,2,4]

[1]Cardiovascular Research Center, Massachusetts General Hospital, [2]Harvard Medical School, Boston, MA, USA, [3]Department of Anesthesiology and Pain Medicine, College of Medicine and Medical School, Chosun University, Gwangju, Korea, [4]Cardiac Arrhythmia Service, Massachusetts General Hospital, Boston, MA, USA, [5]Department of Anesthesiology and Pain Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

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 (AMI). 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 has 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 AMI 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 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 (MIS) [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, 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 min 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 dysfunc-

tion: 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 h, 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 h), 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].

MI 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-methoxy isobutyl isonitrile (^{99m}Tc-sestamibi, also termed as ^{99m}Tc 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 magnetic resonance imaging (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 condition, 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 AMI 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 (e.g., SPECT) [35]. The hyper-enhanced area of the MR images shows a near-perfect correlation with the irreversibly injured regions defined by triphenyl tetrazolium chloride staining [35].

Recently, MRI techniques have demonstrated high accuracy in measuring microvascular obstruction, necrotic core, total infarct size, and the AAR 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 of changes 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 that 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 [44]. A duration of occlusion between 15 and 30 min causes irreversible myocardial damage with histological changes as mentioned above in the infarction area [44].

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: percentage of 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 min 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, 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 MIS 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.

Table 1. Summary of Previous Hypothermia Research

Author & Year	Subject	Period of ischemia	Objectives	Details of study	Results
Duncker, 1996 [49]	Pig (n = 26, 31–49 kg)	45 min of left coronary occlusion	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	8-phenyltheophylline (5 mg/kg iv), adenosine deaminase (25 U/kg) into the coronary artery	1) Profound effect of core body temperature on the MIS; 2) No protective effect of endogenous adenosine against irreversible damage
Hale, 1997 [15]	Rabbit (n = 29, 1.8–3.0 kg)	30 min of circumflex occlusion	To test the hypothesis that regional myocardial hypothermia reduces infarct size	Bag with ice and water on the surface of the heart; 20 min before occlusion	Profound reduction in MIS with hypothermia
Hale, 1997 [16]	Rabbit (n = 39, 2.2–3.2 kg)	30 min of circumflex occlusion	To test the hypothesis that regional myocardial hypothermia after coronary occlusion reduces infarct size	Bag with ice and water on the surface of the heart; 10 min and 25 min after occlusion	Reduction in MIS with hypothermia during coronary occlusion in early stage but not late-stage
Miki, 1998 [17]	Rabbit (n = 44, 1.8–2.4 kg)	30, 45, or 60 min of left coronary artery occlusion	To test the effect of hypothermia on infarct size with various onset times	Extracorporeal heat exchanger (32°C or 35°C); 5 min before and 10 and 20 min after occlusion	Significant reduction in MIS with hypothermia; reduction effect even during occlusion in early stage
Dave, 1998 [7]	Rabbit (n = 20, 2.2–3.2 kg)	30 min of circumflex occlusion	To investigate the effect of pericardial space cooling on MIS	Pericardial fluid exchange with continuous cold Ringer's lactate; 30 min before occlusion	Significant reduction in myocardial temperature and MIS
Schwartz, 2001 [18]	Swine (n = 16, 30–40 kg)	40 min of coronary occlusion	To test the effect of regional topical hypothermia on MIS	Bag with iced saline slush on the epicardial surface; during the occlusion	Significant reduction in myocardial necrosis with regional hypothermia
Dae, 2002 [13]	Swine (n = 33, 60–80 kg)	60 min of left coronary occlusion	To test the hypothesis that endovascular cooling would reduce the temperature in a large heart rapidly and decrease infarct size	Cooling (target temperature = 34°C) started 20 min after occlusion and continued for 15 min after reperfusion	Significant reduction in MIS with hypothermia
Hale, 2003 [14]	Rabbit (n = 32, 2.2–3.2 kg)	30 min of circumflex occlusion	To test the effects of myocardial hypothermia, instituted late in the ischemic period	Cooling (target temperature = 32°C) started 20 min after occlusion and continued for 120 min after reperfusion	Hypothermia protected against impaired reflow and reduced infarct size
Maeng, 2006 [61]	Swine (n = 15, 70–80 kg)	45 min of left coronary occlusion	To evaluate a method for regional myocardial cooling (RMC) during reperfusion that reduces the myocardial size	RMC (target temperature = 33°C). Started 2 min before reperfusion and sustained 2 h and then rewarming (2°C every 5 min)	RMC did not reduce MIS
Tissier, 2007 [108]	Rabbit (n = 30)	30 min of left coronary occlusion	To evaluate whether total liquid ventilation (TLV) can rapidly cool and protect the infarcting heart	Five different groups: 1) 100% oxygen (38°C); 2) liquid warm (38°C); 3) liquid cool (32°C); 4) liquid cool (32°C) with 2 cmH$_2$O positive end expiratory pressure; 5) liquid cool (32°C) 5 min before reperfusion	Hypothermia protected against impaired reflow and reduced infarct size
Olivecrona, 2007 [68]	Swine (n = 16, 25–30 kg)	10 min of left coronary occlusion	To test whether hypothermia can attenuate the post-ischemic reactive hyperemia	Intravascular cooling, hypothermia (34°C) vs. control (37°C)	Mild hypothermia significantly reduces (by 43%) post-ischemic hyperemia
Gotberg, 2008 [51]	Swine (n = 19, 40–50 kg)	40 min of coronary occlusion	To test the hypothesis that hypothermia had to be induced before reperfusion to reduce myocardial injury	Cold saline (4°C) infusion and endovascular cooling, three groups: hypothermia 15 min before and immediately after reperfusion and no hypothermia, hypothermia target temperature = 33°C	Rapid hypothermia before reperfusion reduces MIS and microvascular obstruction
Kanemoto, 2009 [109]	Rabbit (n = 76, 3–4 kg)	30 min of circumflex occlusion	To understand the temporal effect of mild hypothermia to achieve a salutary effect on myocardial salvage	Surface cooling (target temperature = 2 to 2.5°C below initial body temp). Normothermia and five different cooling start times before reperfusion	1) Mild hypothermia significantly reduced MIS; 2) The temperature at reperfusion correlated strongly with infarct size
Hamamoto, 2009 [110]	Sheep (n = 30, 35–40 kg)	60 min of left coronary occlusion	To determine the effect of mild hypothermia on the regional distribution of myocardial reperfusion injury	Cooling pad and ice bags. Five different temperature groups (39.5 to 35.5°C)	Temperature reduction improved myocardial salvage and microvascular integrity

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 h. 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

Effect of target temperature

Several human clinical trials were conducted to evaluate 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 AMI), 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 MI), in which hypother-

Table 2. Summary of Previous Clinical Trials of Therapeutic Hypothermia during Reperfusion Therapy

Trial name (year)	Cooling method	Target temperature	Average body temperature during coronary reperfusion	Percentage of hypothermic patients during reperfusion	Hypothermia maintenance time	Heating	Door-to-balloon time	Infarct size	Left ventricular ejection fraction	Major adverse cardiac events and complications
Rapid MI-ICE (2010) [72]	Endovascular hypothermia with cold saline (4°C)	33°C	34.7 ± 0.3°C	100%	3 h	Active 36–37°C during 3 h	43 ± 7 min vs. control 40 ± 6 min	38% reduction (29.8 ± 12.6% vs. control 48.0 ± 21.6%)	-	4% vs. control 0%
CHILL-MI (2014) [73]	Endovascular hypothermia with cold saline (4°C)	33°C	-	≤ 35.4°C (91%) ≤ 35°C (76%)	1 h after reperfusion	Spontaneous rewarming	Increased 9 min due to hypothermia 33.3 ± 21.2 min vs. control 42.7 ± 16.6 min	9% reduction (36.6% vs. control 40.6%)	50% vs. control 51%	-
VELOCITY (2015) [74]	Automated peritoneal lavage system with lactated Ringer's solution	< 35°C	34.7°C	88.9%	3 h		62 min vs. control 47 min	3–5 d: 16.1% vs. control 17.2%* 23–27 d: 11.8% vs. control 12.5%*	3–5 d: 43.3% vs. control 46.3% 23–27 d: 50.6% vs. control 48.4%	Safety problem: 21.4% vs. control 0% Stent thrombosis: 11% vs. control 0%
COOL-MI InCor Trial (2020) [71]	Endovascular hypothermia with cold saline (1–4°C)	32°C ± 1°C	33.1 ± 0.9°C	100%	1–3 h	Active 1°C/h for 4 h.	92.1 ± 20.5 min vs. control 97 ± 24.4 min	No differences (14.1% vs. control 13.8%)	43.3 ± 11.2% vs. control 48.3 ± 10.9%	21.7% vs. control 20%

* % of total left ventricular mass

mia was maintained with a target temperature of 33°C by forced infusion of 4°C cold saline for 3 h [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 for the treatment of AMI) aimed at rapid induction of hypothermia (33°C for 1 h) 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-day follow-up (3% vs. 14% of control).

Interestingly, the VELOCITY trial (the evaluation of ultrafast hypothermia before reperfusion in STEMI patients) that 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 AMI) showed a successful reduction in infarct size/left ventricular mass up to 30% 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 min 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.

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-condition-

ing strategies, and further research and technology development are required.

The temporal window for efficacy

According to the results from the studies on 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 min 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].

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 endo-

vascular 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/h to normothermia (37°C) is suggested because of the long duration of hypothermia application (12 to 24 h) with a cooler temperature than coronary reperfusion (32–33°C) [84]. This slow rewarming takes almost 12 h 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 h for the active rewarming

protocols and 3–6 h for the passive or spontaneous rewarming protocol. It seems the shorter duration of hypothermia (1–3 h), 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 and 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 caution is 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 rapidly achieve target region hypothermia by infusion of cold saline at 4°C for 10 min during reperfusion. This method can induce hypothermia during coronary angiography by injecting a small amount of saline of only several hundred milliliters to avoid

Table 3. Pharmacological Agents for Reducing the Shivering

Agent	Route	Dosage	Mechanisms	Cautions
Buspirone	Oral	30–60 mg	Partial 5HT$_{1A}$ agonist	Sedation, dizziness, nausea
			D2 receptor agonist	
Meperidine	Intravenous	Loading: 1 mg/kg (or 0.5 mg/kg in case of other opioid use) over 15 to 20 min	Agonist at opioid receptors (μ and κ) and α-2β receptors	Sedation, respiratory depression, seizure
		Maintenance: 25–30 mg/h titrated to effect	Antagonist at N-methyl-D-aspartate receptor	
		Bolus: 25 mg for shivering		
Magnesium	Intravenous	Loading: 2–4 g bolus over 4 h	Antagonist at N-methyl-D-aspartate receptor	Hypotension, nausea, vomiting
		Maintenance: 0.5 g/h	Calcium channel block	
		Goal serum magnesium level: 3–3.5 mg/dl		
Dexmedetomidine	Intravenous	0.2–0.7 μg/kg/h	α-2 receptor agonist	Hypotension, bradycardia, sedation

volume overload and detained control of temperature, infusion rate, and pressure with sensors of the intracoronary catheter that provide safety [87,92,93]. Although there have been several reports of the feasibility and reproducibility of selective intracoronary hypothermia [87,92,93], clinical data on its effectiveness in reducing I/R injury, infarct size, ventricular dysfunction, or MACE compared with prior techniques are unknown, and more evidence is 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.

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Author Contributions

Ki Tae Jung (Visualization; Writing – original draft; Writing – re-

view & editing)
Aneesh Bapat (Writing – review & editing)
Young-Kug Kim (Writing – review & editing)
William J. Hucker (Writing – review & editing)
Kichang Lee (Conceptualization; Data curation; Project administration; Resources; Supervision; Writing – original draft; Writing – review & editing)

ORCID

Ki Tae Jung, https://orcid.org/0000-0002-2486-9961
Aneesh Bapat, https://orcid.org/0000-0002-1996-522X
Young-Kug Kim, https://orcid.org/0000-0002-1982-3053
William J. Hucker, https://orcid.org/0000-0002-4703-0579
Kichang Lee, https://orcid.org/0000-0002-4058-3832

References

1. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics-2020 update: a report from the American Heart Association. Circulation 2020; 141: e139-596.

2. Hausenloy DJ, Yellon DM. Myocardial ischemia-reperfusion injury: a neglected therapeutic target. J Clin Invest 2013; 123: 92-100.

3. Yellon DM, Hausenloy DJ. Myocardial reperfusion injury. N Engl J Med 2007; 357: 1121-35.

4. Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, et al. Heart disease and stroke statistics--2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2009; 119: e21-181.

5. Talman V, Ruskoaho H. Cardiac fibrosis in myocardial infarction-from repair and remodeling to regeneration. Cell Tissue Res 2016; 365: 563-81.

6. Krijnen PA, Nijmeijer R, Meijer CJ, Visser CA, Hack CE, Niessen HW. Apoptosis in myocardial ischaemia and infarction. J Clin Pathol 2002; 55: 801-11.

7. Dave RH, Hale SL, Kloner RA. Hypothermic, closed circuit pericardioperfusion: a potential cardioprotective technique in acute regional ischemia. J Am Coll Cardiol 1998; 31: 1667-71.

8. Frank A, Bonney M, Bonney S, Weitzel L, Koeppen M, Eckle T. Myocardial ischemia reperfusion injury: from basic science to clinical bedside. Semin Cardiothorac Vasc Anesth 2012; 16: 123-32.

9. Yang CF. Clinical manifestations and basic mechanisms of myocardial ischemia/reperfusion injury. Ci Ji Yi Xue Za Zhi 2018; 30: 209-15.

10. Chavez LO, Leon M, Einav S, Varon J. Editor's choice- inside the cold heart: a review of therapeutic hypothermia cardioprotection. Eur Heart J Acute Cardiovasc Care 2017; 6: 130-41.

11. Kang IS, Fumiaki I, Pyun WB. Therapeutic hypothermia for cardioprotection in acute myocardial infarction. Yonsei Med J 2016; 57: 291-7.

12. Sobczyk A, Świątkowski A, Francuz P, Kowalczyk J, Kalarus Z, Średniawa B. Therapeutic hypothermia and postreperfusion myocardial injury in myocardial infarction. Pol Merkur Lekarski 2020; 48: 365-9.

13. Dae MW, Gao DW, Sessler DI, Chair K, Stillson CA. Effect of endovascular cooling on myocardial temperature, infarct size, and cardiac output in human-sized pigs. Am J Physiol Heart Circ Physiol 2002; 282: H1584-91.

14. Hale SL, Dae MW, Kloner RA. Hypothermia during reperfusion limits 'no-reflow' injury in a rabbit model of acute myocardial infarction. Cardiovasc Res 2003; 59: 715-22.

15. Hale SL, Dave RH, Kloner RA. Regional hypothermia reduces myocardial necrosis even when instituted after the onset of ischemia. Basic Res Cardiol 1997; 92: 351-7.

16. Hale SL, Kloner RA. Myocardial temperature in acute myocardial infarction: protection with mild regional hypothermia. Am J Physiol 1997; 273: H220-7.

17. Miki T, Liu GS, Cohen MV, Downey JM. Mild hypothermia reduces infarct size in the beating rabbit heart: a practical intervention for acute myocardial infarction? Basic Res Cardiol 1998; 93: 372-83.

18. Schwartz DS, Bremner RM, Baker CJ, Uppal KM, Barr ML, Cohen RG, et al. Regional topical hypothermia of the beating heart: preservation of function and tissue. Ann Thorac Surg 2001; 72: 804-9.

19. Dixon SR, Whitbourn RJ, Dae MW, Grube E, Sherman W, Schaer GL, et al. Induction of mild systemic hypothermia with endovascular cooling during primary percutaneous coronary intervention for acute myocardial infarction. J Am Coll Cardiol 2002; 40: 1928-34.

20. Ly HQ, Denault A, Dupuis J, Vadeboncoeur A, Harel F, Arsenault A, et al. A pilot study: the noninvasive surface cooling thermoregulatory system for mild hypothermia induction in acute myocardial infarction (the NICAMI study). Am Heart J 2005; 150: 933.

21. Detry JM. The pathophysiology of myocardial ischaemia. Eur Heart J 1996; 17 Suppl G: 48-52.

22. Heusch G, Gersh BJ. The pathophysiology of acute myocardial infarction and strategies of protection beyond reperfusion: a continual challenge. Eur Heart J 2017; 38: 774-84.

23. Ibáñez B, Heusch G, Ovize M, Van de Werf F. Evolving therapies for myocardial ischemia/reperfusion injury. J Am Coll Cardiol 2015; 65: 1454-71.

24. Neri M, Riezzo I, Pascale N, Pomara C, Turillazzi E. Ischemia/reperfusion injury following acute myocardial infarction: a critical issue for clinicians and forensic pathologists. Mediators Inflamm 2017; 2017: 7018393.

25. Sutton MG, Sharpe N. Left ventricular remodeling after myocardial infarction: pathophysiology and therapy. Circulation 2000; 101: 2981-8.

26. Burchfield JS, Xie M, Hill JA. Pathological ventricular remodeling: mechanisms: part 1 of 2. Circulation 2013; 128: 388-400.

27. Kapur NK, Karas RH. A new shield from the double-edged sword of reperfusion in STEMI. Eur Heart J 2015; 36: 3058-60.

28. Braunwald E, Kloner RA. Myocardial reperfusion: a double-edged sword? J Clin Invest 1985; 76: 1713-9.

29. Liu J, Wang H, Li J. Inflammation and inflammatory cells in myocardial infarction and reperfusion injury: a double-edged sword. Clin Med Insights Cardiol 2016; 10: 79-84.

30. French BA, Kramer CM. Mechanisms of post-infarct left ventricular remodeling. Drug Discov Today Dis Mech 2007; 4: 185-96.

31. Sun Y. Myocardial repair/remodelling following infarction: roles of local factors. Cardiovasc Res 2009; 81: 482-90.

32. White HD, Norris RM, Brown MA, Brandt PW, Whitlock RM, Wild CJ. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. Circulation 1987; 76: 44-51.

33. Gibbons RJ, Valeti US, Araoz PA, Jaffe AS. The quantification of infarct size. J Am Coll Cardiol 2004; 44: 1533-42.

34. Lockie T, Nagel E, Redwood S, Plein S. Use of cardiovascular magnetic resonance imaging in acute coronary syndromes. Circulation 2009; 119: 1671-81.

35. Shan K, Constantine G, Sivananthan M, Flamm SD. Role of cardiac magnetic resonance imaging in the assessment of myocardial viability. Circulation 2004; 109: 1328-34.

36. Aletras AH, Tilak GS, Natanzon A, Hsu LY, Gonzalez FM, Hoyt RF Jr, et al. Retrospective determination of the area at risk for reperfused acute myocardial infarction with T2-weighted cardiac magnetic resonance imaging: histopathological and displacement encoding with stimulated echoes (DENSE) functional validations. Circulation 2006; 113: 1865-70.

37. Friedrich MG, Abdel-Aty H, Taylor A, Schulz-Menger J, Messroghli D, Dietz R. The salvaged area at risk in reperfused acute myocardial infarction as visualized by cardiovascular magnetic resonance. J Am Coll Cardiol 2008; 51: 1581-7.

38. Mahrholdt H, Wagner A, Holly TA, Elliott MD, Bonow RO, Kim RJ, et al. Reproducibility of chronic infarct size measurement by contrast-enhanced magnetic resonance imaging. Circulation 2002; 106: 2322-7.

39. Gerber BL, Garot J, Bluemke DA, Wu KC, Lima JA. Accuracy of contrast-enhanced magnetic resonance imaging in predicting improvement of regional myocardial function in patients after acute myocardial infarction. Circulation 2002; 106: 1083-9.

40. Kim RJ, Wu E, Rafael A, Chen EL, Parker MA, Simonetti O, et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. N Engl J Med 2000; 343: 1445-53.

41. Shin HS, Shin HH, Shudo Y. Current status and limitations of myocardial infarction large animal models in cardiovascular translational research. Front Bioeng Biotechnol 2021; 9: 673683.

42. Bollen PJ, Hansen AK, Alstrup AK. The laboratory swine. Boca Raton, CRC Press. 2010.

43. Lelovas PP, Kostomitsopoulos NG, Xanthos TT. A comparative anatomic and physiologic overview of the porcine heart. J Am Assoc Lab Anim Sci 2014; 53: 432-8.

44. Lindsey ML, Bolli R, Canty JM Jr, Du XJ, Frangogiannis NG, Frantz S, et al. Guidelines for experimental models of myocardial ischemia and infarction. Am J Physiol Heart Circ Physiol 2018; 314: H812-38.

45. Amsterdam EA, Pan HL, Rendig SV, Symons JD, Fletcher MP, Longhurst JC. Limitation of myocardial infarct size in pigs with a dual lipoxygenase-cyclooxygenase blocking agent by inhibition of neutrophil activity without reduction of neutrophil migration. J Am Coll Cardiol 1993; 22: 1738-44.

46. Banz Y, Hess OM, Robson SC, Mettler D, Meier P, Haeberli A, et al. Locally targeted cytoprotection with dextran sulfate attenuates experimental porcine myocardial ischaemia/reperfusion injury. Eur Heart J 2005; 26: 2334-43.

47. Baumert JH, Hein M, Gerets C, Baltus T, Hecker KE, Rossaint R. The effect of xenon anesthesia on the size of experimental myocardial infarction. Anesth Analg 2007; 105: 1200-6.

48. Chareonthaitawee P, O'Connor MK, Gibbons RJ, Ritman EL, Christian TF. The effect of collateral flow and myocardial viability on the distribution of technetium-99m sestamibi in a closed-chest model of coronary occlusion and reperfusion. Eur J Nucl Med 2000; 27: 508-16.

49. Duncker DJ, Klassen CL, Ishibashi Y, Herrlinger SH, Pavek TJ, Bache RJ. Effect of temperature on myocardial infarction in swine. Am J Physiol 1996; 270: H1189-99.

50. Fujiwara H, Matsuda M, Fujiwara Y, Ishida M, Kawamura A, Takemura G, et al. Infarct size and the protection of ischemic myocardium in pig, dog and human. Jpn Circ J 1989; 53: 1092-7.

51. Götberg M, Olivecrona GK, Engblom H, Ugander M, van der Pals J, Heiberg E, et al. Rapid short-duration hypothermia with

cold saline and endovascular cooling before reperfusion reduces microvascular obstruction and myocardial infarct size. BMC Cardiovasc Disord 2008; 8: 7.

52. Hatori N, Segawa D, Hinokiyama K, Kimura T, Iizuka Y, Ochi M, et al. Effects of ischemic preconditioning and synchronized coronary venous retroperfusion in an off-pump coronary artery bypass grafting model. Artif Organs 2001; 25: 47-52.

53. Hinokiyama K, Hatori N, Ochi M, Maehara T, Tanaka S. Myocardial protective effect of lidocaine during experimental off-pump coronary artery bypass grafting. Ann Thorac Cardiovasc Surg 2003; 9: 36-42.

54. Kharbanda RK, Mortensen UM, White PA, Kristiansen SB, Schmidt MR, Hoschtitzky JA, et al. Transient limb ischemia induces remote ischemic preconditioning in vivo. Circulation 2002; 106: 2881-3.

55. Kobayashi S, Tadokoro H, Rydén L, Sjöquist PO, Haendchen RV, Corday E. Local beta-adrenergic blockade does not reduce infarct size after coronary occlusion and reperfusion: a study of coronary venous retroinfusion of metoprolol. Cardiovasc Drugs Ther 1993; 7: 159-67.

56. Kristo G, Yoshimura Y, Niu J, Keith BJ, Mentzer RM Jr, Bünger R, et al. The intermediary metabolite pyruvate attenuates stunning and reduces infarct size in in vivo porcine myocardium. Am J Physiol Heart Circ Physiol 2004; 286: H517-24.

57. Krombach GA, Kinzel S, Mahnken AH, Günther RW, Buecker A. Minimally invasive close-chest method for creating reperfused or occlusive myocardial infarction in swine. Invest Radiol 2005; 40: 14-8.

58. Kupatt C, Hinkel R, Vachenauer R, Horstkotte J, Raake P, Sandner T, et al. VEGF165 transfection decreases postischemic NF-kappa B-dependent myocardial reperfusion injury in vivo: role of eNOS phosphorylation. FASEB J 2003; 17: 705-7.

59. Kupatt C, Wichels R, Deiss M, Molnar A, Lebherz C, Raake P, et al. Retroinfusion of NFkappaB decoy oligonucleotide extends cardioprotection achieved by CD18 inhibition in a preclinical study of myocardial ischemia and retroinfusion in pigs. Gene Ther 2002; 9: 518-26.

60. Liu X, Huang Y, Pokreisz P, Vermeersch P, Marsboom G, Swinnen M, et al. Nitric oxide inhalation improves microvascular flow and decreases infarction size after myocardial ischemia and reperfusion. J Am Coll Cardiol 2007; 50: 808-17.

61. Maeng M, Mortensen UM, Kristensen J, Kristiansen SB, Andersen HR. Hypothermia during reperfusion does not reduce myocardial infarct size in pigs. Basic Res Cardiol 2006; 101: 61-8.

62. Näslund U, Häggmark S, Johansson G, Marklund SL, Reiz S. Limitation of myocardial infarct size by superoxide dismutase as an adjunct to reperfusion after different durations of coronary occlusion in the pig. Circ Res 1990; 66: 1294-301.

63. Schwartz LM, Lagranha CJ. Ischemic postconditioning during reperfusion activates Akt and ERK without protecting against lethal myocardial ischemia-reperfusion injury in pigs. Am J Physiol Heart Circ Physiol 2006; 290: H1011-8.

64. Schwartz LM, Welch TS, Crago MS. Cardioprotection by multiple preconditioning cycles does not require mitochondrial K(ATP) channels in pigs. Am J Physiol Heart Circ Physiol 2002; 283: H1538-44.

65. Segawa D, Sjöquist PO, Wang QD, Gonon A, Rydén L. Time-dependent cardioprotection with calcium antagonism and experimental studies with clevidipine in ischemic-reperfused pig hearts: part II. J Cardiovasc Pharmacol 2002; 40: 339-45.

66. Kohlhauer M, Berdeaux A, Ghaleh B, Tissier R. Therapeutic hypothermia to protect the heart against acute myocardial infarction. Arch Cardiovasc Dis 2016; 109: 716-22.

67. Yamada KP, Kariya T, Aikawa T, Ishikawa K. Effects of therapeutic hypothermia on normal and ischemic heart. Front Cardiovasc Med 2021; 8: 642843.

68. Olivecrona GK, Götberg M, Harnek J, Van der Pals J, Erlinge D. Mild hypothermia reduces cardiac post-ischemic reactive hyperemia. BMC Cardiovasc Disord 2007; 7: 5.

69. Jones RN, Reimer KA, Hill ML, Jennings RB. Effect of hypothermia on changes in high-energy phosphate production and utilization in total ischemia. J Mol Cell Cardiol 1982; 14 Suppl 3: 123-30.

70. Shao ZH, Chang WT, Chan KC, Wojcik KR, Hsu CW, Li CQ, et al. Hypothermia-induced cardioprotection using extended ischemia and early reperfusion cooling. Am J Physiol Heart Circ Physiol 2007; 292: H1995-2003.

71. Dallan LA, Giannetti NS, Rochitte CE, Polastri TF, San Martin CY, Hajjar LA, et al. Cooling as an adjunctive therapy to percutaneous intervention in acute myocardial infarction: cool-MI InCor trial. Ther Hypothermia Temp Manag 2021; 11: 135-44.

72. Götberg M, Olivecrona GK, Koul S, Carlsson M, Engblom H, Ugander M, et al. A pilot study of rapid cooling by cold saline and endovascular cooling before reperfusion in patients with ST-elevation myocardial infarction. Circ Cardiovasc Interv 2010; 3: 400-7.

73. Erlinge D, Götberg M, Lang I, Holzer M, Noc M, Clemmensen P, et al. Rapid endovascular catheter core cooling combined with cold saline as an adjunct to percutaneous coronary intervention for the treatment of acute myocardial infarction. The CHILL-MI trial: a randomized controlled study of the use of central venous catheter core cooling combined with cold saline as an adjunct to percutaneous coronary intervention for the treatment of acute myocardial infarction. J Am Coll Cardiol 2014; 63: 1857-65.

74. Nichol G, Strickland W, Shavelle D, Maehara A, Ben-Yehuda O, Genereux P, et al. Prospective, multicenter, randomized, controlled pilot trial of peritoneal hypothermia in patients with ST-segment- elevation myocardial infarction. Circ Cardiovasc Interv 2015; 8: e001965.

75. Noc M, Erlinge D, Neskovic AN, Kafedzic S, Merkely B, Zima E, et al. COOL AMI EU pilot trial: a multicentre, prospective, randomised controlled trial to assess cooling as an adjunctive therapy to percutaneous intervention in patients with acute myocardial infarction. EuroIntervention 2017; 13: e531-9.

76. Erlinge D, Götberg M, Grines C, Dixon S, Baran K, Kandzari D, et al. A pooled analysis of the effect of endovascular cooling on infarct size in patients with ST-elevation myocardial infarction. EuroIntervention 2013; 8: 1435-40.

77. Erlinge D, Götberg M, Noc M, Lang I, Holzer M, Clemmensen P, et al. Therapeutic hypothermia for the treatment of acute myocardial infarction-combined analysis of the RAPID MI-ICE and the CHILL-MI trials. Ther Hypothermia Temp Manag 2015; 5: 77-84.

78. Mottillo S, Sharma K, Eisenberg MJ. Therapeutic hypothermia in acute myocardial infarction: a systematic review. Can J Cardiol 2011; 27: 555-61.

79. Villablanca PA, Rao G, Briceno DF, Lombardo M, Ramakrishna H, Bortnick A, et al. Therapeutic hypothermia in ST elevation myocardial infarction: a systematic review and meta-analysis of randomised control trials. Heart 2016; 102: 712-9.

80. Merrill TL, Mitchell JE, Merrill DR, Gorman JH 3rd, Gorman RC, Gillespie MJ. Myocardial tissue salvage is correlated with ischemic border region temperature at reperfusion. Catheter Cardiovasc Interv 2020; 96: E593-601.

81. Hale SL, Herring MJ, Kloner RA. Delayed treatment with hypothermia protects against the no-reflow phenomenon despite failure to reduce infarct size. J Am Heart Assoc 2013; 2: e004234.

82. Götberg M, van der Pals J, Götberg M, Olivecrona GK, Kanski M, Koul S, et al. Optimal timing of hypothermia in relation to myocardial reperfusion. Basic Res Cardiol 2011; 106: 697-708.

83. Tissier R, Chenoune M, Ghaleh B, Cohen MV, Downey JM, Berdeaux A. The small chill: mild hypothermia for cardioprotection? Cardiovasc Res 2010; 88: 406-14.

84. Scirica BM. Therapeutic hypothermia after cardiac arrest. Circulation 2013; 127: 244-50.

85. Kandzari DE, Chu A, Brodie BR, Stuckey TA, Hermiller JB, Vetrovec GW, et al. Feasibility of endovascular cooling as an adjunct to primary percutaneous coronary intervention (results of the LOWTEMP pilot study). Am J Cardiol 2004; 93: 636-9.

86. Testori C, Sterz F, Delle-Karth G, Malzer R, Holzer M, Stratil P, et al. Strategic target temperature management in myocardial in-

87. Otterspoor LC, Van 't Veer M, Van Nunen LX, Brueren GR, Tonino PA, Wijnbergen IF, et al. Safety and feasibility of selective intracoronary hypothermia in acute myocardial infarction. EuroIntervention 2017; 13: e1475-82.

88. Scaravilli V, Bonacina D, Citerio G. Rewarming: facts and myths from the systemic perspective. Critical Care 2012; 16: A25.

89. Tveita T, Myklebust R, Ytrehus K. Changes in myocardial ultrastructure induced by cooling as well as rewarming. Res Exp Med (Berl) 1998; 197: 243-54.

90. Testori C, Beitzke D, Mangold A, Sterz F, Loewe C, Weiser C, et al. Out-of-hospital initiation of hypothermia in ST-segment elevation myocardial infarction: a randomised trial. Heart 2019; 105: 531-7.

91. Jain A, Gray M, Slisz S, Haymore J, Badjatia N, Kulstad E. Shivering treatments for targeted temperature management: a review. J Neurosci Nurs 2018; 50: 63-7.

92. Otterspoor LC, van Nunen LX, Rosalina TT, Veer MV, Tuijl SV, Stijnen M, et al Intracoronary hypothermia for acute myocardial infarction in the isolated beating pig heart. Am J Transl Res 2017; 9: 558-68.

93. Otterspoor LC, Van't Veer M, van Nunen LX, Wijnbergen I, Tonino PA, Pijls NH. Safety and feasibility of local myocardial hypothermia. Catheter Cardiovasc Interv 2016; 87: 877-83.

94. Sessler DI. Complications and treatment of mild hypothermia. Anesthesiology 2001; 95: 531-43.

95. Urits I, Jones MR, Orhurhu V, Sikorsky A, Seifert D, Flores C, et al. A Comprehensive update of current anesthesia perspectives on therapeutic hypothermia. Adv Ther 2019; 36: 2223-32.

96. Drescher C, Diestel A, Wollersheim S, Berger F, Schmitt KR. How does hypothermia protect cardiomyocytes during cardioplegic ischemia? Eur J Cardiothorac Surg 2011; 40: 352-9.

97. Saad H, Aladawy M. Temperature management in cardiac surgery. Glob Cardiol Sci Pract 2013; 2013: 44-62.

98. Chamorro C, Borrallo JM, Romera MA, Silva JA, Balandín B. Anesthesia and analgesia protocol during therapeutic hypothermia after cardiac arrest: a systematic review. Anesth Analg 2010; 110: 1328-35.

99. Leslie K, Sessler DI, Bjorksten AR, Moayeri A. Mild hypothermia alters propofol pharmacokinetics and increases the duration of action of atracurium. Anesth Analg 1995; 80: 1007-14.

100. Tortorici MA, Kochanek PM, Poloyac SM. Effects of hypothermia on drug disposition, metabolism, and response: a focus of hypothermia-mediated alterations on the cytochrome P450 enzyme system. Crit Care Med 2007; 35: 2196-204.

101. Hostler D, Zhou J, Tortorici MA, Bies RR, Rittenberger JC, Empey PE, et al. Mild hypothermia alters midazolam pharmaco-

kinetics in normal healthy volunteers. Drug Metab Dispos 2010; 38: 781-8.

102. Fritz HG, Holzmayr M, Walter B, Moeritz KU, Lupp A, Bauer R. The effect of mild hypothermia on plasma fentanyl concentration and biotransformation in juvenile pigs. Anesth Analg 2005; 100: 996-1002.

103. Michelsen LG, Holford NH, Lu W, Hoke JF, Hug CC, Bailey JM. The pharmacokinetics of remifentanil in patients undergoing coronary artery bypass grafting with cardiopulmonary bypass. Anesth Analg 2001; 93: 1100-5.

104. Heier T, Caldwell JE, Sessler DI, Miller RD. Mild intraoperative hypothermia increases duration of action and spontaneous recovery of vecuronium blockade during nitrous oxide-isoflurane anesthesia in humans. Anesthesiology 1991; 74: 815-9.

105. Beaufort AM, Wierda JM, Belopavlovic M, Nederveen PJ, Kleef UW, Agoston S. The influence of hypothermia (surface cooling) on the time-course of action and on the pharmacokinetics of rocuronium in humans. Eur J Anaesthesiol Suppl 1995; 11: 95-106.

106. Lee HJ, Kim KS, Jeong JS, Kim KN, Lee BC. The influence of mild hypothermia on reversal of rocuronium-induced deep neuromuscular block with sugammadex. BMC Anesthesiol 2015; 15: 7.

107. Heier T, Caldwell JE, Sessler DI, Kitts JB, Miller RD. The relationship between adductor pollicis twitch tension and core, skin, and muscle temperature during nitrous oxide-isoflurane anesthesia in humans. Anesthesiology 1989; 71: 381-4.

108. Tissier R, Hamanaka K, Kuno A, Parker JC, Cohen MV, Downey JM. Total liquid ventilation provides ultra-fast cardioprotective cooling. J Am Coll Cardiol 2007; 49: 601-5.

109. Kanemoto S, Matsubara M, Noma M, Leshnower BG, Parish LM, Jackson BM, et al. Mild hypothermia to limit myocardial ischemia-reperfusion injury: importance of timing. Ann Thorac Surg 2009; 87: 157-63.

110. Hamamoto H, Leshnower BG, Parish LM, Sakamoto H, Kanemoto S, Hinmon R, et al. Regional heterogeneity of myocardial reperfusion injury: effect of mild hypothermia. Ann Thorac Surg 2009; 87: 164-71.