European Heart Journal
Acute Cardiovascular Care
EUROPEAN SOCIETY OF CARDIOLOGY®

Original scientific paper

European Heart Journal: Acute Cardiovascular Care
1–12
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DOI: 10.1177/2048872615624242
acc.sagepub.com
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Editor's Choice- Inside the cold heart: A review of therapeutic hypothermia cardioprotection

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Abstract

Targeted temperature management has been originally used to reduce neurological injury and improve outcome in patients after out-of-hospital cardiac arrest. Myocardial infarction remains a major cause of death in the world and several investigators are studying the effect of mild therapeutic hypothermia during an acute cardiac ischemic injury. A search on MEDLINE, Scopus and EMBASE databases was conducted to obtain data regarding the cardioprotective properties of therapeutic hypothermia. Preclinical studies have shown that therapeutic hypothermia provides a cardioprotective effect in animals. The proposed pathways for the cardioprotective effects of therapeutic hypothermia include stabilization of mitochondrial permeability, production of nitric oxide, equilibration of reactive oxygen species, and calcium channels homeostasis. Clinical trials in humans have yielded controversial results. Current trials are therefore seeking to combine therapeutic hypothermia with other treatment modalities in order to improve the outcomes of patients with acute ischemic injury. This article provides a review of the hypothermia effects on the cardiovascular system, from the basic science of physiological changes in the human body and molecular mechanisms of cardioprotection to the bench of clinical trials with therapeutic hypothermia in patients with acute ischemic injury.

Keywords

Acute myocardial infarction, hypothermia, cardiac arrest, dysrhythmias

Date received: 20 October 2015; accepted: 6 December 2015

Introduction

The use of targeted temperature management (TTM) has increased in the last few decades due to the development of safe and practical techniques to implement mild therapeutic hypothermia as a protective measure after cardiac arrest and in other clinical scenarios.[1–4] Clinical evidence currently supports the use of TTM after cardiac arrest in order to preserve neuronal integrity and diminish the amount of irreversible neuronal damage caused by the hypoxemic event.[5–7]

The role of therapeutic hypothermia (32–34°C) applied after out-of-hospital cardiac arrest was supported by the Hypothermia after Cardiac Arrest Study Group trial results, which showed an improvement in neurological recovery and survival in the therapeutic hypothermia group patients.[5] However, Nielsen and coworkers in the TTM trial reported no significant improvement in neurologic function when comparing therapeutic hypothermia at 33°C with TTM at 36°C.[8] The feasibility of using percutaneous coronary intervention (PCI) in combination with therapeutic hypothermia in patients after out-of-hospital cardiac arrest caused by an acute myocardial infarction opened the pos-

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sibility of aiming therapeutic hypothermia to improve cardiac function in addition to the neurological benefit.[9]

Ischemic heart disease (IHD) remains a major cause of death worldwide and investigators proposed the use of therapeutic hypothermia in patients with acute ischemic injury to protect the myocardium and minimize global cardiac dysfunction.[10–12] Several studies have established that therapeutic hypothermia may decrease infarct size.[13–16]

Therapeutic hypothermia first gained recognition as a potential myocardial protective measure for open heart surgery. In the 1950s, Bigelow and associates demonstrated in animal studies that hearts undergoing therapeutic hypothermia tolerated the cessation of blood flow for longer periods of time when compared with normothermic hearts.[17,18] This was followed by widespread use of therapeutic hypothermia before the ischemic period during cardiac surgery in humans.[19,20] Subsequent animal and human trials have increased our knowledge of cardiovascular physiology during therapeutic hypothermia.[21–25] However, the fine molecular changes that occur during cooling have yet to be fully elucidated.[13,26,27]

Recent animal experiments of therapeutic hypothermia during ischemic myocardial injury confirm the existence of a cardioprotective effect.[13,28,29] Although the specific mechanisms of cardioprotection are unclear, pre-clinical studies demonstrate that these mechanisms involve more than just a simple reduction in the cardiac metabolic rate and many molecular signaling pathways have been proposed.[14,18,30]

This review adds knowledge of therapeutic hypothermia cardioprotection at molecular and physiological levels. The primary aim of this article is to summarize the effects of therapeutic hypothermia on the heart, from the basic science of physiological changes and molecular mechanisms to the bench of clinical trials in patients with acute ischemic injury.

Methods

Data sources and search approach

We searched MEDLINE, Scopus and EMBASE for all review articles, randomized studies, pre-clinical and clinical studies published from 1950 to 2015 using the keywords "hypothermia", "therapeutic cooling", "mild hypothermia", "therapeutic hypothermia", "myocardial ischemia", "acute myocardial infarction", "cardioprotection", "reperfusion injury". Inclusion criteria for data abstraction were to contain information regarding history of therapeutic hypothermia, cardiovascular physiology during hypothermia (mild, moderate, and deep), and preclinical and clinical studies of therapeutic hypothermia applied on acute ischemic injury. Abstracts were read, and if considered pertinent for the purpose of this review, the complete articles were obtained. We also performed a manual search of the references of all selected articles. The search initially generated 188 references; we excluded 67 articles that did not contain the above-mentioned data of interest. The final number of articles for data abstraction was 121, including review articles, case reports, preclinical studies and randomized control trials.

Identification of clinical trials

Through the US National Institutes of Health clinical trials registry (clinicaltrials.gov) we searched for studies of therapeutic hypothermia in myocardial ischemia. "Hypothermia" was used as the main keyword. Studies were selected by the topic of "Myocardial infarction". Twelve studies were identified. Inclusion criteria for data abstraction were a "Completed" or "Terminated" study status. Five studies fulfilled inclusion criteria (three completed and two terminated). The unique identifiers for these studies were NCT00248196, NCT00417638, NCT01379261, NCT01864343 and NCT01655433. We also included two trials that had been presented in the Transcatheter Cardiovascular Therapeutics meetings in 2003 and 2004 (COOL-MI and ICE IT respectively), neither of which was found in the US National Institutes of Health clinical trials registry. We thus identified overall seven human clinical trials. Data were then abstracted on study objective, size, primary study endpoint, as well as the feasibility of therapeutic hypothermia and its effect on infarct size reduction. We describe the findings; meta-analytic techniques were not used.

Historical development of therapeutic cooling

Body cooling as a therapy for different medical conditions has been described in historical medical literature over centuries.[21] Hippocrates, in the Classical Greece period, recognized the importance of temperature management by inducing cooling during hyperthermia.[31] The surgeon-in-chief of the Napoleonic army, Dominique Jean Larrey, used cold temperatures as therapy, and was the first to advocate gradual rewarming.[32] His observations on frostbite in the Russian front led him to implement immersion in cold water rather than rewarming by direct heat in this type of injury.[32] In 1937 Dr. Temple Fay applied total body cooling to a patient with cancer and reported the first human physiological changes on the subject.[33,34] But it was not until Bigelow and associates applied therapeutic hypothermia during cardiac surgery, that the potential implications of therapeutic hypothermia for myocardial protection were recognized.[17,18]

In 1958, Benson and coworkers first described the use of therapeutic hypothermia in a non-surgical setting on human patients after cardiac arrest.[35] In the early studies patients were cooled to 30–32°C. This degree of hypothermia was associated with an increased risk of ventricular fibrillation and infections, thus in the three following decades the use of therapeutic hypothermia decreased as complications

out-weighed the benefits of this innovative therapy.[36,37] In the 1990s the introduction of mild therapeutic hypothermia (32–35°C) and fine temperature control reduced the number of complications, allowing the reinstatement of therapeutic hypothermia into modern medicine in the past two decades.[38–42]

Extreme hypothermia and the heart

Patients rescued from prolonged periods of time in freezing conditions provided basic information of the intrinsic cardiovascular changes that occur during cooling.[21,43] The lowest temperature from which an adult person has been documented to survive after accidental hypothermia is 13.7°C.[44] This 29-year-old female fell into icy water and had a cardiac arrest after being trapped for approximately 2 h in the water. She was successfully resuscitated after receiving cardiopulmonary resuscitation for 2 h and gradually rewarmed.[44] Another report described a case of a 31-year-old man who survived after being in subzero conditions for approximately 12–15 h.[45] He was found with a core temperature of 16°C, a heart rate (HR) of 24 beats/min, and a respiratory rate of 2 breaths/min.[45] In the setting of therapeutic hypothermia, a case report in 1955 described a 51-year-old woman with terminal ovarian cancer who was cooled down to 9°C and rewarmed successfully.[46]

A variety of cardiovascular changes occur as the body temperature falls below 36°C (see Table 1[6,21,26,47,48]). Below 30°C, cardiac arrest becomes a real concern due to an increased risk of ventricular fibrillation.[49] Contractility is also affected; at 25°C cardiac output decreases to approximately 45% of normal values.[50]

The effects of therapeutic cooling on the heart

When inducing hypothermia in a controlled environment, continuous monitoring of hemodynamic parameters enables the physician to anticipate changes in cardiac function.[51] Both the pacemaker and the cardiac contractile unit are affected by therapeutic hypothermia.[52,53]

The cardiac pacemaker and cardiac conduction

Although cardiac conduction is modified during therapeutic hypothermia, clinical studies show no significant increase in the risk of dysrhythmias when cooling to 32–35°C.[54–57] The first effect that therapeutic hypothermia has on cardiac function is a decrease in HR.[58] Recently, bradycardia during therapeutic hypothermia has even been associated with better outcomes.[59,60] The reduction of HR observed during hypothermia is attributed to a prolongation of the action potential and a decrease of spontaneous repolarization of the cardiomyocyte.[54,61] Sinoatrial node triggering is modified and a conduction delay may be registered in the electrocardiogram (EKG).[62] Prolongation of the QT interval, QRS, and PR segments have all been observed.[62,63]

A characteristic EKG abnormality described in association with hypothermia are the so-called "J" waves or Osborn waves (see Figure 1).[47,64] Osborne waves are less commonly seen in mild therapeutic hypothermia and if found clinicians should look for alternative causes (i.e. ischemia, aneurysmal subarachnoid hemorrhage).[55,65]

Table 1. Significant cardiovascular changes in humans from 36°C to 30°C core temperature.

Degrees Celsius	Significant cardiovascular changes[6,21,26,47,48]
36–35	Increase in blood pressure.
34	Tachycardia followed by progressive bradycardia.
33	Increase in renal flow ("cold diuresis"). Increase in peripheral vascular resistance (up to two-fold the baseline).
32	Decrease in myocardial oxygen consumption up to 25%.
31–30	Conduction abnormalities, dysrhythmias and significant decrease in the cardiac output.

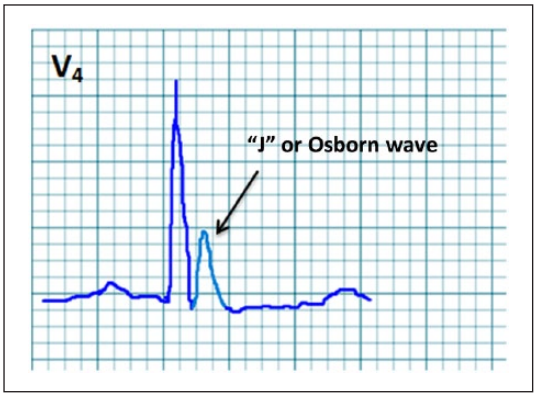

Figure 1. Classic therapeutic hypothermia "J" wave or Osborn wave in the electrocardiogram.

The cardiac contractile unit

When bradycardia occurs during therapeutic hypothermia, left ventricular filling time increases and confers a positive inotropic effect.[66] Mild therapeutic hypothermia improves systolic function by an increase in the ejection fraction (EF) and in contraction velocity; while diastolic function is preserved.[67] Weisser and collaborators demonstrated in a study of five human and eight porcine muscle strips that cooling the myocardium increased the isometric twitch force in both samples. At the same time, no significant

change was shown in intracellular calcium (Ca^{2+}).[68] In another study, Lewis and coworkers evaluated the heart contractility of 10 patients during hypothermia (33°C) using left ventricular pressure volume measurements throughout a coronary artery bypass procedure. The results showed an impaired contractility when the HR was artificially sustained during hypothermia, demonstrating that an elevated HR during hypothermia has a negative effect on contractility in humans.[69]

In parallel, the decrease in body temperature is accompanied by an upsurge of catecholamine release into the blood stream. This increases the stroke volume (SV), leading to an initial improvement in cardiac output (CO).[70] However, as body temperature continues to decrease, the overall effect on CO becomes negative, because of the predominant effect of the decrease in HR.[71] During the decline of CO, mean arterial pressure (MAP) is maintained due to the rise in peripheral vascular resistance (PVR) caused by the vasoconstrictive effect of hypothermia.[50] Mild therapeutic hypothermia (32–35°C) is therefore usually accompanied by a normal or slightly elevated MAP.[72] When a patient develops hypotension during therapeutic hypothermia, causes unrelated to hypothermia should be sought (i.e. sepsis, tension pneumothorax, tamponade, intracranial hypertension).

Cardiac perfusion

Frank and collaborators showed that the increase in catecholamine levels occurring during mild therapeutic hypothermia improves myocardial perfusion by inducing coronary artery vasodilation.[73] This improvement in perfusion increases oxygen delivery to cardiac tissue, where basal oxygen demand has already been reduced by the low temperatures.[72,74]

Mixed venous oxygen saturation (SvO2) is a better indicator of organ perfusion than cardiac index (CI) during therapeutic hypothermia.[75] In hypothermic conditions a decrease in CI does not necessarily mean that organ perfusion is reduced as well.[76] Monitoring of SvO2 is therefore recommended in order to avoid overtreatment. If the CI is "corrected" using pharmacological support when there is no evidence of organ failure, the risk of aberrant ventricular dysrhythmias and decreased cardiac contractility rises.[77]

The ischemic heart and therapeutic hypothermia cardioprotective mechanisms

Ischemia/reperfusion (I/R) injury affects the three major elements of the heart: the pacemaker, by reperfusion-induced dysrhythmias; the endothelium, through microvascular obstruction; and the myocardial contractile apparatus, by "myocardial stunning" due to calcium overload.[78–81]

The ischemic heart

Most cardiomyocyte injury occurs immediately after ischemia.[82] During acute myocardial infarction (AMI), I/R injury causes endothelial dysfunction followed by a pro-inflammatory state in the reperfusion phase.[83] Inflammatory mediators and increased production of free oxygen radicals activate apoptosis pathways in the myocardium.[84] During initial reperfusion, cellular death pathways are activated and proteases initiate destruction of the mitochondrial membranes.[85] The loss of cytosolic Ca^{2+} control and the cytoskeletal imbalance lead to a reperfusion-induced necrosis.[83] This is followed by endothelial dysfunction which impairs nitric oxide (NO) production and causes additional microvascular injury.[86] Both calcium overload and cell membrane instability have a "domino effect", propagating destruction from cell to cell via gap junctions.[87,88]

Preclinical studies of the cardioprotective mechanisms of therapeutic hypothermia

Most animal studies show a decrease in cardiac infarct size and attenuation of the myocardial ischemic/reperfusion injury when therapeutic hypothermia is induced.[13,89,90] Few investigators have analyzed signaling pathways on different animal models in the hope of providing plausible explanations for the reduction of infarct size when using therapeutic hypothermia.[91,92]

The most simple explanation is that reduction in metabolic demand of the heart during therapeutic hypothermia conserves the pool of adenosine triphosphate (ATP), thus protecting the integrity of cellular and mitochondrial membranes.[92,93] However, reperfusion-induced necrosis may be ameliorated by therapeutic hypothermia at different levels of the I/R pathology.[82] The cardioprotective effects of therapeutic hypothermia include mitochondrial permeability stabilization by survival molecular pathways, nitric oxide production with reactive oxygen species equilibrium, and calcium channel (Na^{+}/Ca^{2+}) homeostasis.[84,87,93] It has also been proposed that different pathways may be utilized when therapeutic hypothermia is implemented at different times in relation to the ischemic damage (pre-ischemia, during ischemia, or during/after reperfusion).[93,94,95] Most likely a global interaction of multiple pathway components co-exists.

Reduction of the whole I/R injury load involves deep protective mechanisms, such as the activation of survival kinases and heat-shock proteins.[14,89,96] These mechanisms have been shown to decrease the detrimental effect of the reperfusion-induced cell destruction phase, and to reduce myocardial tissue damage.[93,96] The most convincing mechanism of myocardial preservation after I/R injury with therapeutic hypothermia is the phosphorylation of the survival kinase serine/threonine kinase (Akt), whose activation is mediated probably by specific heat-shock proteins (HSP27, HSP70) induced at hypothermic temperatures (32°C).[89,93]

Activation of an anti-apoptotic pathway mediated by heat-shock protein 70 (HSP70) has been proposed during pre-ischemic induction of therapeutic hypothermia.[89,93,97] In one study, therapeutic hypothermia increased HSP70-1 mRNA levels and conserved ATP levels when the myocardium temperature was decreased to 31°C before ischemia and maintained at 34°C during ischemia.[93]

When therapeutic hypothermia is applied during the ischemic phase of I/R injury, the survival kinase Akt-1 and the MAPK/ERK signaling pathway are activated.[28,96] Ning and coworkers showed the cardioprotective role of the "oxygen-sensitive transcription factor", hypoxia inducible factor-1 (HIF-1), when therapeutic hypothermia at 30°C was applied during ischemia.[96] Therapeutic hypothermia boosted the HIF-1 cardioprotective effects by non-hypoxic pathways related to the PI3-K pathway and Akt-1 activity.[96,98]

Preclinical studies of induction of therapeutic hypothermia in the reperfusion phase in animal models suggest involvement of the survival kinase Akt.[89] Therapeutic hypothermia activates phosphorylation of HSP27 together with double phosphorylation of Akt.[89] Once HSP27-Akt is activated, nitric oxide synthetase-3 increases the production of NO. Elevated circulating amounts of NO increase mitochondria protein nitrosylation, which later modulates generation of reactive oxygen species[89,95] (see Figure 2).

Both preclinical and clinical studies of therapeutic hypothermia in myocardial ischemia have had conflicting results.[99–101] Studies have shown a decrease in cardiac infarct size in rabbits, dogs, sheep and swine.[13,92,102–107] However, Maeng and coworkers failed to reduce infarct size in swine myocardium when therapeutic hypothermia 33°C was applied during reperfusion.[100]

Notably, animal studies suggest that even when initiated too late to reduce infarct size, therapeutic hypothermia may reduce no-reflow and confer protection at the level of the microvasculature (which suffers most from endovascular damage during reperfusion injury).[108]

Induction of therapeutic hypothermia locally rather than systemically has been suggested by several researchers. Otake and coworkers studied transcoronary induction of local therapeutic hypothermia in treatment of myocardial ischemia in a swine model (rather than total body induction of therapeutic hypothermia) and demonstrated infarct size reduction.[29,100] The authors concluded this may be a feasible approach for induction of therapeutic hypothermia during myocardial ischemia.[29] An alternative approach was suggested by Dave and coworkers, who used pericardioperfusion in preclinical settings and achieved the goal of a myocardial temperature of 34°C successfully without incurring complications.[109]

Clinical studies of therapeutic hypothermia in acute ischemic injury

The COOL-MI and ICE-IT trials in humans aimed to assess the effect of mild therapeutic hypothermia on infarct size in patients with ST elevation acute myocardial infarction (STEMI).[110,111] The COOL-MI was a prospective, randomized, multicenter trial which included 357 patients with <6 h of symptoms. Patients with a prior MI or with cardiogenic shock were excluded.[111] Endovascular cooling was applied for 3 h followed by 1 h of rewarming.[111]

The ICE-IT trial included 228 patients with symptoms lasting < 6 h. Patients were treated with endovascular cooling for 6 h followed by 3 h of rewarming.[112,113]

Initially both studies showed disappointing results; no significant reduction was observed in infarct size in the therapeutic hypothermia group compared with the control group. However, a later data review revealed that patients recruited to these trials had undergone prolonged initial ischemia without induction of therapeutic hypothermia. Delayed induction of therapeutic hypothermia has been associated with loss of cardioprotection.[90] The results of these trials were reanalyzed with a correction for this contributing factor, and the adjusted results demonstrated a reduction in infarct size in anterior MI.[113]

The RAPID-MI ICE trial used therapeutic hypothermia as an adjunctive therapy with PCI in 20 patients with STEMI.[16] This single-center, prospective, randomized trial assessed the safety and feasibility of rapid induction of therapeutic hypothermia with endovascular cold saline. A significant reduction of infarct size was observed while the door-to-balloon time was increased by only 3 min. A follow-up multicenter study, the CHILL-MI trial (N=120) confirmed the safety and feasibility of rapid endovascular cooling before PCI.[11] However, the finding of a significant reduction in infarct size in the therapeutic hypothermia group did not repeat itself (see Table 2[11,16,99,114]).

Combined analysis of the RAPID MI-ICE and CHILL-MI data showed that endovascular cooling for 1–3 h associated with PCI for acute STEMI decreased the infarct size and lowered the incidence of heart failure mainly in patients with a large area of myocardium at risk.[115] However, results should be interpreted with caution since they represent post-hoc analyses, and further randomized control trials are encouraged.

A recent study of patients undergoing PCI for AMI with cardiogenic shock (N=145) also compared platelet reactivity during treatment with a $P2Y_{12}$ receptor inhibitor (clopidogrel, prasugrel and ticagrelor) with and without therapeutic hypothermia.[101] Although no significant difference in drug pharmacodynamics was observed between the groups, there were more major bleeding events and stent thrombosis in the therapeutic hypothermia group. However, this difference was not significantly higher and mortality was similar in both groups.[101]

The ongoing STATIM trial (ID: NCT01777750) is an interventional study, currently in the last period of recruiting patients with AMI undergoing induction of therapeutic hypothermia pre-hospital. The main study goal is to evaluate infarct size in patients treated with therapeutic

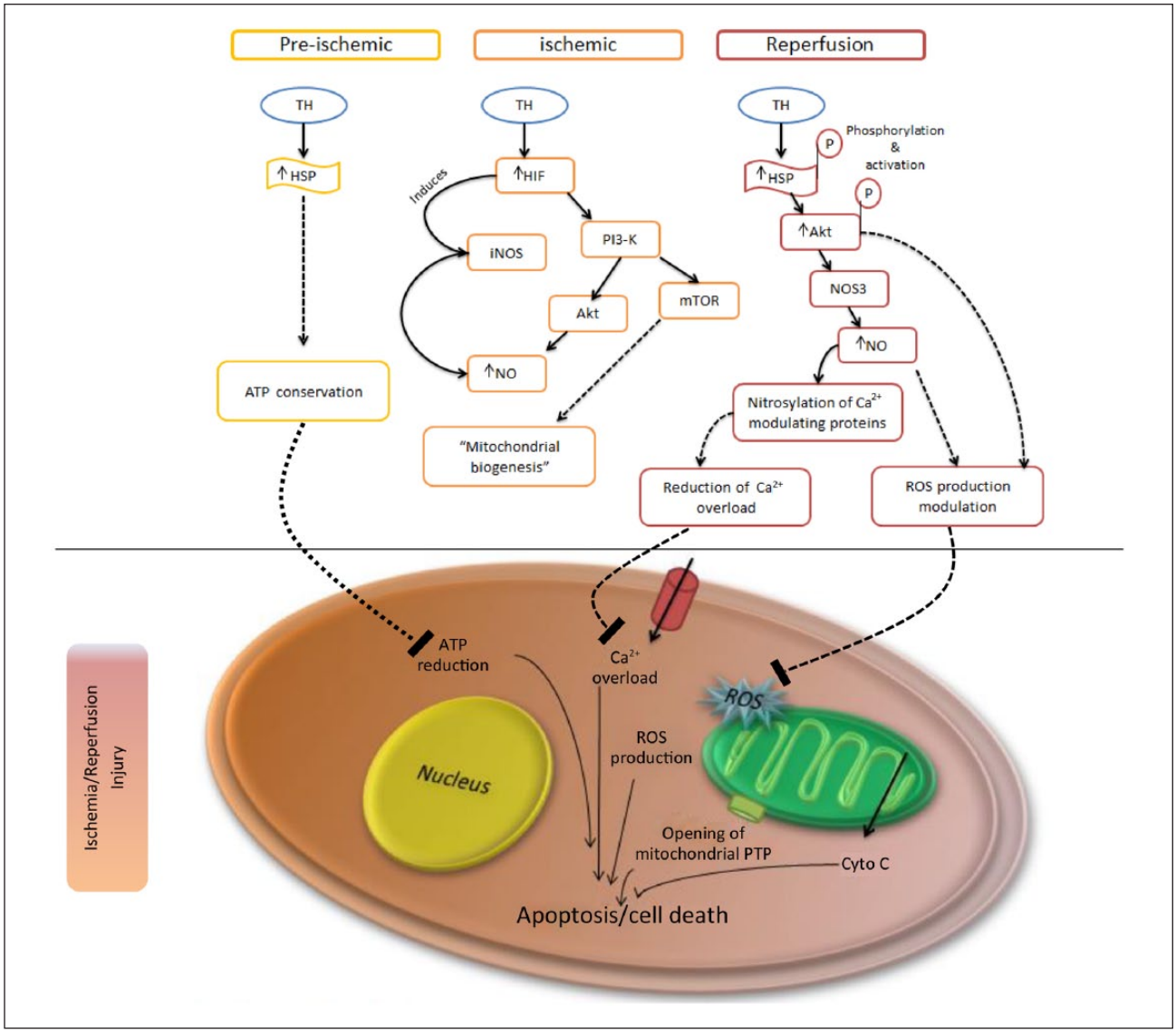

Figure 2. Proposed mechanisms of cardioprotection of therapeutic hypothermia applied at pre-ischemic, ischemic, and reperfusion phases.
TH: therapeutic hypothermia; HSP: heat-shock protein; ATP: adenosine triphosphate; HIF: hypoxia inducible factor; iNOS: inducible nitric oxide synthase; NO: nitric oxide; Ca^{2+}: calcium; NOS3: nitric oxide synthase 3; ROS: reactive oxygen species; PTP: permeability transition pore; Cyto C: Cytochrome C; mTOR: mammalian Target of Rapamycin; Akt: Serine/Threonine Kinase; P: Phosphate.

hypothermia versus those who are not. Two other currently ongoing trials are the SHOCK-COOL trial (ID: NCT01890317), an interventional study, and the COOL-AMI EU Case Series Clinical study (ID: NCT02070913), an observational study. Both studies intend to assess the feasibility and efficacy of therapeutic hypothermia as an adjunctive therapy for MI through measurement of physiologic parameters such as the cardiac power index and infarct size.

Conclusions

As therapeutic hypothermia induction techniques improve, the application of this treatment modality in many cardiac conditions is becoming more feasible. Preclinical studies of therapeutic hypothermia in animals often show a cardioprotective effect, but specific mechanisms remain unclear. Most likely a global interaction of multiple pathway components co-exists and different therapeutic hypothermia induction times may be associated with activation of different mechanisms.

In the clinical setting, human trials are inconsistent regarding reduction of infarct size, heart failure and mortality. Since the timing of therapeutic hypothermia induction may determine its effectiveness in patients with cardiac ischemic injuries, there is growing interest in this topic.

Post-hoc analyses should be carefully interpreted and further randomized controlled clinical trials are required to

Table 2. Clinical trials of therapeutic hypothermia in acute myocardial infarction.

Investigator and date	Trial	Objectives	Sample size (*N*)	Primary study endpoint	Results
O'Neill WW,[a] 2003, Grines CL[110] and O'Neill[111]	**COOL MI-I**	Test the effectiveness of TH (3 h) with adjunct PCI in patients with AMI	*N*= 357	Reduction of IS measured with SPECT imaging	IS at 30 days: Control: 13.8% Hypothermia: 14.1% *p*-value =0.83
Grines CL,[a] 2004 and O'Neill[111]	**ICE-IT**	Evaluate TH as adjuvant therapy for AMI prior to PCI	*N*=228	Reduction of IS measured with SPECT imaging	204 patients measured with SPECT 1. IS at 30 days: Control: 13.2% Hypothermia: 10.2% relative reduction: 23% *p*-value=0.14 2. Analysis by MI location: Anterior MI: Control: 20.9% Hypothermia: 15.3% *p*-value= 0.15 relative reduction: 27%
Carrozza JP and Dixon SR. October 2005 to August 2007	**COOL-MI –II**	Evaluate TH as adjuvant therapy for AMI prior to PCI	**Study terminated**	Reduction of IS measured with SPECT imaging	**Study terminated.** **Results unavailable**
Götberg et al.[16] January 2007 to October 2009	**Rapid MI-ICE-Pilot.**	Safety and efficacy of rapid endovascular cooling in patients with anterior infarctions in the setting of acute PCI	*N*=20	Myocardium at risk measured with cardiac MRI IS was assessed by late gadolinium enhancement imaging	1. IS normalized to myocardium at risk was reduced by 38% in the hypothermia group versus the control group (29.8 ± 12.6% *vs.* 48.0 ± 21.6%) *p*-value=0.041 2. Peak of troponin T was significantly decreased in the TH group *p*-value=0.01 3. Cumulative troponin T was significantly decreased in the TH group *p*-value=0.03

(Continued)

Table 2. (Continued)

Investigator and date	Trial	Objectives	Sample size (*N*)	Primary study endpoint	Results
Erlinge D et al.[11] June 2011 to November 2013	**CHILL-MI**	Confirm findings of RAPID MI-ICE trial with a larger multicenter trial	*N*=120	IS as a percentage MaR, assessed by cardiac MRI	1. Median IS/MaR: Control: 46.6% Hypothermia: 40.5% Relative reduction: 13% *p*-value=0.15 2. Analysis by MI location: Anterior MI: Reduction in IS/MaR: 33% *p*-value <0.05.
Testori C.[114] September 2011 to May 2013	**STATIM-Pilot**	To assess feasibility and safety of a combined cooling strategy (cooling pads started out of the hospital and endovascular TH) for pre-reperfusion hypothermia in patients with acute STEMI	*N*=19	Time of reperfusion of the lesion in STEMI (expected average 120 min)	Core temperature below 35.0°C at reperfusion was achieved in 11 patients (78%) within 100 min Inter-quartile range: 90–111 min
Nichol et al.[99] November 2012 to March 2014	**VELOCITY**	To assess feasibility and efficacy of TH induced by an automated peritoneal lavage system in patients with STEMI undergoing primary PCI	*N*= 54	IS assessed by cardiac MRI (days 3–5)	TH ⩽34.9°C before PCI achieved in 24/27 hypothermia patients (88.9%) at median 17.0 min after cooling onset IS by MRI at days 3–5: Control: 16.1% Hypothermia: 17.2% *p*-value=0.54

Clinical trials found in the US National Institutes of Health clinical trials registry.
[a]Not found in the US National Institutes of Health clinical trials registry. Presented at: Transcatheter Cardiovascular Therapeutics.
TH: therapeutic hypothermia; AMI: acute myocardial infarction; PCI: percutaneous coronary intervention; IS: infarct size; SPECT: single photon emission computed tomography; MRI: magnetic resonance imaging; MaR: myocardium at risk; MI: myocardial infarction; STEMI: ST elevation myocardial infarction.

establish what clinical circumstances promote the effectiveness of the cardioprotective mechanisms of therapeutic hypothermia in acute myocardial infarction. Ongoing trials are aiming to achieve a significant reduction in ischemic size using therapeutic hypothermia as an adjuvant therapy. Once these trials have been completed, a complete meta-analytic study of their compiled data may provide important information regarding the cardioprotective effect of therapeutic hypothermia in humans.

Conflict of interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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