Review Article

Yonsei Med J 2016 Mar;57(2):291-297
http://dx.doi.org/10.3349/ymj.2016.57.2.291

Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

Therapeutic Hypothermia for Cardioprotection in Acute Myocardial Infarction

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Mild therapeutic hypothermia of 32–35°C improved neurologic outcomes in outside hospital cardiac arrest survivor. Furthermore, in experimental studies on infarcted model and pilot studies on conscious patients with acute myocardial infarction, therapeutic hypothermia successfully reduced infarct size and microvascular resistance. Therefore, mild therapeutic hypothermia has received an attention as a promising solution for reduction of infarction size after acute myocardial infarction which are not completely solved despite of optimal reperfusion therapy. Nevertheless, the results from randomized clinical trials failed to prove the cardioprotective effects of therapeutic hypothermia or showed beneficial effects only in limited subgroups. In this article, we reviewed rationale for therapeutic hypothermia and possible mechanisms from previous studies, effective methods for clinical application to the patients with acute myocardial infarction, lessons from current clinical trials and future directions.

Key Words: Hypothermia, induced; myocardial infarction; myocardial reperfusion injury

INTRODUCTION

Acute myocardial infarction (AMI) is a leading cause of deaths; governments and patients have to carry big economic burden in both developed and developing countries from the disease itself and post-infarction heart failure (HF) in this post-drug eluting stenting era.[1-5] The medicine has been focusing on the timely reperfusion therapy and decreasing infarction size to reduce the mortality and morbidity.[6-8] Due to these efforts, the mortality rate fell in recent three decades by half since late 1980's.[7,9] Despites of timely myocardial reperfusion therapy, AMI still remains a major disease to threat human health: almost 25% of AMI patients develop HF after optimal reperfusion therapy.[2,10] Progressive dilatation of heart after AMI is related with high mortality.[11]

Lethal reperfusion injury, myocardial injury induced by restoring blood flow to ischemic myocardium, can cause myocardial cell death and increase infarct size which may account for 25% of total injury.[10] From the recent timely and costly efforts, the myocardial injury from delayed revascularization was successful to reduce infarct size. In contrast, previous challenges to reduce the reperfusion injury were disappointing, and there have been no available practical strategies to date.[12,13] We need, therefore, new strategies in addition to optimal reperfusion therapy to improve clinical outcomes of AMI.

Therapeutic hypothermia (TH) has been used to improve neurologic outcome of outside hospital cardiac arrest survivor.[14-16] Even delayed and slow induction of TH upto 8 hours after the return of spontaneous circulation (ROSC) improved survivals and resulted in favorable neurologic outcomes in these patients.[16] Regarding AMI, experimental results of TH before reperfusion demonstrated reduction of infarct size.[17-20] Contrary to neuroprotection, delayed TH at the time of reperfusion failed to show reduction of infarct size but only limited no-reflow.[21] Hence, rapid and safe strategies to initiate and maintain TH for cardiac protection are important in improving AMI

Received: December 31, 2015
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•The authors have no financial conflicts of interest.

prognosis.

Recent clinical trials failed to prove the infarct size reduction of mild TH in AMI patients.[22-25] Nonetheless, negative results from clinical trials could not ignore cardioprotective effect of TH which has been consistently proved in experimental studies.

In this review, we focusd on the TH for cardioprotection in myocardial infarction and discussed the results of past attempts to reduce ischemia-reperfusion injury by using hypothermia, rationale for TH, possible mechanisms from experimental studies and lessons from current clinical trials and future directions.

BEST TARGET TEMPERATURE IN THERAPEUTIC HYPOTHERMIA

Hypothermia, core body temperature <35°C, can be a life-threatening emergency but can be induced therapeutically in special medical conditions.[26,27] TH is classified according to the target body temperature; 1) mild; 32–35°C, 2) moderate; 28–32°C, 3) severe; 20–28°C, or 4) profound; <20°C.[27]

Experimental data showed strong correlation with target temperature and infarct size; every 1°C of temperature reduction results in 10–20% decrease of infarct size in swine and ovine.[17,28] Hence, lower temperature is better in reducing infarct size. However, less than 30°C of hyperthermia frequently develops atrial fibrillation, and spontaneous ventricular fibrillation is induced at <28°C in most mammalian species.[26,27] Mild hypothermia may induce decreasing heart rate without deviation of stroke volume and mean artery pressure, and is well tolerated in experimental animals and human.[27] Mild hypothermia of 32–34°C is generally accepted goal of TH.

RATIONALE FOR MILD HYPOTHERMIA

Ischemia-reperfusion injury

Irreversible myocardial damage after AMI is divided into ischemic and reperfusion injury, but they share some mechanisms and sometimes hard to clearly separate two components.[29] Of course, longer duration of coronary artery occlusion (CAO) leads to larger infarct size, and therefore, early reperfusion improves prognosis by reducing infarct size and morality.[30-32] Current guidelines strongly recommends within 90 minutes coronary angioplasty as timely reperfusion for ST elevation AMI.[33]

However, timely reperfusion is not enough to solve the reperfusion injury related problems. About 40–50% reduction of infarct size can be achieved by timely reperfusion and half of the remaining infarct size is contributed by reperfusion injury.[10,34] So, successful prevention of reperfusion injury possibly reduces infarct size additional 25%.

As for the underlying mechanisms about reperfusion injury, myocardial damages resulted from restoring epicardial coronary blood flow, are multifactorial and not fully understood to date.[29,35-37] TH is one of the promising strategies to prevent reperfusion injury,[20,38] and we focused TH and its mechanism for cardioprotection in this review.

Possible mechanism of TH

Major concept of cooling-induced cardioprotection is energy preservation; 1) reduced metabolic demands of myocardium and preserved adenosine triphosphate and glycogens, 2) enhanced cellular membrane stability from reduced acidosis, 3) reduction of Na^+ and Ca^{2+} overload,[17,19,39] and 4) enhanced mitochondrial membrane stability by inhibition of calcium induced mitochondrial permeability transition pore (MPTP) opening; maintained ion homeostasis during ischemia and reperfusion, and preserved microvascular structures.[19]

The beneficial effect of cooling was observed in mitochondria from non-reperfused as well as reperfused myocardium. Tissier, et al.[19] reported that in non-reperfused conditions, Ca^{2+} concentration required to open MPTP was slightly decreased in hypothermic hearts (-16%), whereas -49% drop in normothermic hearts. In hearts subjected to ischemia-reperfusion, a significant decrease was observed in both hypothermic (-37%) and control (-68%) hearts, although the decrease was greater in the latter.[19] Proposed protective signal transduction is via enhancing ERK pathway during ischemia,[40] while pre/post conditioning-related protection is dependent on activation of ERK in the first minutes of reperfusion.[27,41]

TIMING, SPEED, AND DURATION

Delayed and slow TH up to 8 hours after ROSC showed favorable neurologic outcome and reduced mortality in the patients experienced with outside hospital cardiac arrest.[16] Contrary, rapid early initiation before revascularization is essential to reduce infarct size in the conscious patients with AMI. Experimental studies consistently showed that rapid and earlier initiation of TH is better for reducing infarct size.[42,43] Although not feasible in clinical settings, initiation of TH even before CAO showed maximum infarct size reduction.[18,43] Pre-perfusion TH in ischemic model showed about 40% infarct size reductions, although there were some discrepancies between studies.[43,44] Hence, induction of TH before reperfusion is accepted as an essential element.

Induction of TH during reperfusion failed to reveal statistically significant reduction of infarct size, but limited no-reflow by improving microvascular resistance.[21,43-45] Microvascular resistance is one of important predictors of clinical outcomes in patients with AMI.[46-48] To attenuate reperfusion injury and microvascular alteration, maintenance of TH after revascularization is an another important issue needed to be addressed.[15,16,38]

http://dx.doi.org/10.3349/ymj.2016.57.2.291

METHODS OF THERAPEUTIC HYPOTHERMIA

Experimental studies have used various methods to induce hypothermia in AMI models; surface cooling, endovascular cooling, cold saline infusion into coronary artery, pericardioperfusion, extracorporeal blood cooling, total liquid ventilation and peritoneal lavage.[15,20] Although the critical parameters determining benefit would be early cooling initiation and rapid cooling rate, some of those methods are too invasive for clinical use. So-called ultra-fast cooling methods, including extracorporeal blood cooling, total liquid ventilation and pericardial perfusion are too invasive and have a chance to delay reperfusion procedures.[27]

Some of the methods are relatively safe and were applied to the patients with cardiac arrest or myocardial infarction (Table 1). Surface cooling can be used for total body cover or partial body pad. Conventional method had limitation of slow cooling rate, especially in obese patients.[16] Newer surface cooling device with convective-immersion method improved the cooling rate,[49] however, it might be difficult to perform coronary intervention with this device which requires covering entire body. A pilot study introduced a pad type topical surface cooling device which covers trunk of a patient with AMI eligible for primary percutaneous coronary intervention (PCI) and proved its safety but showed slow cooling rate as 79 minutes to target <34.5°C (1.5°C/hr).[50] Hence, technical evolution or combined use with other method may be necessary to achieve rapid cooling.

Transnasal evaporative cooling is to spray a liquid coolant-oxygen mixture into nasal passage and brain.[51] It is a portable device, easy to apply and relatively safe, however, can induce severe epistasis in patients with coagulopathy.

Intravenous infusion of cold saline (4°C) clearly brings about rapid cooling at first one hour with large volume infusion.[52] However, it can result in respiratory problems related to volume overloading and worsened ejection fraction.

Endovascular cooling catheter of heat-exchange with a balloon at the tip is positioned inferior vena cava through a femoral vein.[53] Basic method is heat exchange by long cold balloon without infusion of cool saline to patients. Even though rapid cooling rate of pilot study,[53] registry data failed to present rapid cooling rate (Table 1).[54] Endovascular catheter alone might be insufficient to achieve target temperature before reperfusion for AMI without delaying PCI.[15] Recently published clinical trials, which combined the use of endovascular cooling with intravenous cold saline infusion, showed about 6°C/hr cooling rate.[24]

Automated peritoneal lavage can rapidly achieve target temperature due to large surface area, however, it is an invasive procedure.[15] Peritoneal lavage with large fluid volume may induce respiratory distress due to diaphragm elevation, and has a chance of major organ bleeding with peritoneal puncture and limited candidate due to abdominal pathology or morbid obesity.

RESULTS FROM CLINICAL TRIALS AND POOLED ANALYSIS

Initial two randomized clinical trials (RCTs) were presented at scientific meetings but not yet published, and both trials adopted combination hypothermia of intravenous cold saline infusion and endovascular cooling catheter.[55,56] The Cooling as an Adjunctive Therapy to Percutaneous Intervention in patients with AMI (COOL-MI trial, n=392) showed no significant reduction of infarct size at 30 days, evidenced by heart single-photon emission computed tomography (control vs. hypothermia: 14.1% vs. 13.8%, p=0.86) but anterior AMI (18.2% vs. 9.3%, p=0.05).[27,55] The Intravascular Cooling Adjunctive to Percutaneous Coronary Intervention for AMI (ICE-IT trial, n=228) presented similar result with the COOL-MI; no difference in overall, except for reduction of infarct size in anterior myocardial infarction subgroup.[56]

Summary of published three RCTs, including one pilot study

Table 1. Summary of Clinical Studies Using Variable Strategies of Therapeutic Hypothermia

Method of cooling	Rate of cooling	Patient population	Comments
Surface cooling			
Conventional[16]	0.9°C/hr	ROSC after OHCA	Slow cooling rate
Topical trunk pad[50]	79 min to target <34.5°C (1.5°C/hr)	AMI	Pilot study
Convective-immersion[49]	37 min to target <34°C (3°C/hr)	ROSC after OHCA	
Transnasal evaporative cooling[51]	1.3°C/26 min, before hospital arrival	Cardiac arrest	Performed by emergency responder
Intravenous infusion of cold saline (4°C)[52]	4.0±0.3°C/first 1 hr	Patients with neurologic injury	Rapid induction but problems related to cold fluid overloading
Endovascular cooling-catheter[53,54]	3°C/hr in pilot study 1°C/hr in registry data	AMI Cardiac arrest	Induce and maintain TH without infusion cold fluids to patients
Automated peritoneal lavage[15,25]	8°C/hr Median 17 min to ≤34.9°C (5.6°C/1 hr)	Witnessed cardiac arrest AMI	 Increased MACE

ROSC, return of spontaneous circulation; OHCA, out of hospital cardiac arrest; AMI, acute myocardial infarction; TH, therapeutic hypothermia; MACE, major adverse cardiac event within 30 days.

for cardioprotection of AMI, is presented in Table 2. The Rapid Cooling by Cold Saline and Endovascular Cooling Before Reperfusion in Patients with ST-Elevation Myocardial Infarction: Rapid MI-ICE[22] (n=18) was a small number pilot study and showed reduction of infarct size/area at risk % (38%, p=0.04). Strength of this pilot study is no delay in TH group of door to balloon time and 100% achievement of hypothermia <35°C at the time of reperfusion. Additionally, HF at 45 days developed only in control group (n=3). There was no major bleeding in both groups, but TH group was related with 3 cases of infection.

A pooled analysis of ICE-IT and rapid MI-ICE trials, pre-Chill-MI, showed overall 37% relative reduction of infarct size in TH group who actually achieved core temperature ≤35°C at the time of reperfusion for both anterior (p=0.03) and inferior infarcts (p=0.04).[57]

After pilot study, Chill-MI trial[23] was performed using similar combined hypothermia method. However, in this multicenter RCT, total cooling maintenance time was shorter than the pilot study (1 hr vs. 3 hrs in rapid MI-ICE) and only 76% patients achieved core temperature ≤35°C at the time of reperfusion. Furthermore, TH group showed increased door to balloon time of 9 min. Their results failed to show overall reduction of infarct size, but revealed anterior wall infarct-related reduction of infarct size (33%, p=0.046) and decreased incidence of HF in 45 days (3% vs. 14% of control, p=0.047). These half successful results, compared to pilot study[22] and pooled analysis,[57] might have been due to shorter cooling maintenance time, lower achievement rate of hypothermia at the time of perfusion, and slightly delayed door to balloon time in TH group.

Another pool analysis[24] from Rapid MI-ICE and Chill-MI demonstrated that TH is more effective in large myocardium at risk, anterior wall infarction and reduced post infarction-HF, however, patients with myocardium at risk <30% show no benefit.

The Evaluation of Ultrafast Hypothermia Before Reperfusion in STEMI Patients (VELOCITY) trial[25] was performed by using automated peritoneal lavage device. Despite of rapid cooling rate of peritoneal cooling device, this RCT presented disappointed results; 1) delayed door to balloon time of median 15 minutes in TH group, 2) failed to show reduction of infarct size and microvascular obstruction, and 3) increased 30 days major adverse cardiac event (MACE) in TH group; stent thrombosis was evident only in TH group.

The association of TH with stent thrombosis was an important question in this RCT. It might be related to peritoneal cooling methods; delayed gastric absorption and reduced bioavailability of oral antiplatelet agents[25] or direct effect.[58] Although not certain, the delayed reperfusion in the hypothermia group might have attenuated the effect of hypothermia on infarct size. Furthermore, peritoneal cooling system may be related to several safety concerns; respiratory distress due to decreased diagram excursion coupled with use of sedation, major organ bleeding after peritoneal puncture, and limited candidate due to abdominal pathology or previous surgery.

Besides the VELOCITY trial, other RCTs and pooled analyses showed that combined hypothermia of intravenous cold saline infusion and endovascular cooling catheter was feasible and safe for cardioprotection in AMI. Similar to experimental studies, RCTs showed effectiveness of rapid and early achieved TH at the time of reperfusion to reduce infarct size and even slightly delayed TH was also effective for decrease of HF incidence. In addition, TH is more effective on large myocardium at risk and anterior wall infarction.

CONSIDERATIONS FOR CLINICAL USES

Most important issue is how to achieve target temperature rapidly without delaying door to balloon time: such as simple and easy method to start at emergency department or even before hospital. Most RCTs adopted methods combined intravenous cold saline infusion and endovascular cooling catheter, and small pilot study was successful but multicenter RCT. Experienced team approach may improve the cooling rate without increasing infection. In this method, hypothermia was induced by rapid infusion of 600–2000 mL of cold saline under physicians decision.[22-24] Consequently, cooling rate depends on the volume of administration and may have variation according to the volume. However, a large volume infusion of cold saline is inadequate for some patients and has a chance

Table 2. Summary of Randomized Clinical Trials of Therapeutic Hypothermia in Patients with Acute Myocardial Infarction

Clinical trials (yrs) number	Cooling method	Target °C (cooling rate)	Cooling duration & rewarming	Door to balloon time control vs. study (min)	Results (IS/Δ at risk)
Rapid MI-ICE[22] (2010) n=18	IV cold saline with endovascular catheter	33°C (4.3→8.4°C/hr)*	Total 3 hrs, passive rewarming; 3 hrs	43±7 vs. 40±6	p=0.04 (by 4 days MRI) HF; 0 vs. 3
CHILL-MI[23] (2014) n=120	IV cold saline with endovascular catheter	33°C (2.8→6°C/hr)*	Total 1 hr, passive rewarming; 3 hrs	33±12 vs. 42±16	p=0.15 (by 4 days MRI) HF; p=0.047
VELOCITY[25] (2015) n=54	Automated peritoneal lavage system	≤34.9°C (9°C/hr)	3 hrs after PCI, active rewarming; 0.5°C/hr	47 (37.55)† vs. 62 (51.81)	p=0.43 (by 30 days MRI) Higher MACE

IS/Δ at risk, infarct size/area at risk; IV, intravenous; MRI, magnetic resonance image; HF, 45 days heart failure; MACE, major adverse cardiac event within 30 days.
*Means (total mean→mean catheter) cooling rate, †Means median (interquartile range).

http://dx.doi.org/10.3349/ymj.2016.57.2.291

of pulmonary edema and worsened ejection fraction.[52] A pad type topical surface cooling, transnasal evaporative cooling or other methods can be considered as a substitute of a large volume cold saline infusion in that case.

Rapid induction of TH in conscious AMI patients may cause physical and psychological discomfort, including fear, resist and shivering.[15] Competent medical treatment is important; neuromuscular blocker for shivering and meperidine with or without oral buspirone.[15,16,22,50]

Cooling should be maintained during the first one hour of reperfusion, even though cooling had been instituted early in the ischemic period,[27] since TH during reperfusion prevents microvascular damage, obstruction and no-reflow phenomenon.[44] However, there is a lack of information regarding how long cooling should be maintained after reperfusion to achieve maximal cardioprotective effect. According to the result of Chill-MI, one hour cooling may not be enough; although they continued cooling longer than one hour until the end of the procedure, if the PCI procedure takes longer than one hour. Topics regarding the effect of prolonged cooling need to be further investigated.

FUTURE DIRECTIONS

Concerning effectiveness of reducing infarct size, lower temperature gains better result. Mild TH, which ranges from 32 to 35°C, is generally well tolerated in mammalian and human. Hence, to obtain target temperature as low as 32°C is important to achieve maximum infarct size reduction in patients with AMI. 1) Invention of clinically applicable devices and medications, 2) optimization of protocols and medical support during cooling and rewarming periods, and 3) diversification of cooling devices and dealing with safety issues; e.g., local cooling device are important topics to achieve target 32°C.

CONCLUSIONS

Most RCTs and pooled analyses have been conducted with combined methods of intravenous cold saline infusion and endovascular cooling catheter. They showed feasibility and safety of TH for cardioprotection in AMI. Similar to experimental studies, the RCTs showed effectiveness of rapid and early achieved TH at the time of reperfusion to reduce infarct size, and that even slightly delayed TH is also effective to decrease incidence of post-infarction HF. In addition, TH is more effective in large myocardium at risk and anterior wall infarction.

Hence, rapid cooling without delaying reperfusion therapy is the most important for successful outcomes. Diversification of cooling devices and experienced team approach may improve the cooling rate without increasing complications and also achieve target temperature of 32°C. A topical surface cooling, transnasal evaporative cooling or other methods can be considered as an initial cooling induction combined with rapid cooling devices, e.g., endovascular catheter. Furthermore, more experimental studies for developing ideal strategies, including clinically applicable devices and medications, are needed. Finally, well conducted larger RCTs in AMI patients are needed.

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