



## APPLICATION OF MILD HYPOTHERMIA IN THE TREATMENT OF ACUTE ST-ELEVATION MYOCARDIAL INFARCTION: A REVIEW

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### ABSTRACT

Reperfusion therapy is one of the most important treatments for acute ST-elevation myocardial infarction (STEMI). However, the vascular reperfusion process itself leads to myocardial reperfusion injury, so how to reduce reperfusion injury is the focus of attention. Studies have shown that hypothermia treatment before reperfusion can reduce the infarct surface and reduce the microvascular myocardial injury after reperfusion. In recent years, there are also some exploratory clinical studies will be sub-hypothermia assisted STEMI treatment.

Research conclusions in this paper, we reviewed the progress of STEMI in the treatment of hypothermia, and the purpose of this study was to elucidate the application value of mild hypothermia in STEMI therapy.

**Keywords review;** coronary artery disease; mild hypothermia; myocardial infarction

## OVERVIEW

The treatment of acute ST segment elevation myocardial infarction (STEMI) is as fast as possible, recovery of coronary flow, salvage of ischemic myocardium and reduction of infarct size, At present, the treatment of STEMI is mainly thrombolytic therapy or percutaneous coronary intervention. Admission therapy (PCI) to open the obstructed coronary artery at an early date and restore the ischemic myocardium blood supply to reduce infarct size and avoid complications. The infarct size is acute in the heart one of the major predictors of early and long-term prognosis in patients with muscle infarction (AMI) [1]. Paradox is the acute course of coronary flow that restores the ischemic myocardium, reperfusion injury may occur in [2]. Reperfusion injury can cause 4 types of heart insufficiency: (1) myocardial stunning; (2) microvascular obstruction or no reflow; (3) reperfusion arrhythmia; (4) fatal reperfusion injury; [3]. Hypothermia therapy refers to controlling the core temperature of a patient to protect organs from the impact of damage, depending on the temperature, a mild low temperature (33 °C ~ 35 °C), Moderate low temperature (28 °C ~ 32 °C), deep low temperature (17 °C ~ 27 °C) and low depth temperature (<16 °C), mild hypothermia therapy is the use of physical or pharmaceutical methods to the human body, the core temperature drops to 32 ~35. Low temperature treatment can protect myocardial function and promote the development of myocardial function Cell survival, suppression and reduction of apoptosis, [3]. Hypothermia therapy is associated with myocardial insufficiency. The protective effects of blood and reperfusion injury are strong and reproducible, and exist extensively mechanism to explain the protective effect of low temperature.

### **Animal experimental study of mild hypothermia treatment for AMI:**

In animal studies, mild hypothermia therapy is safe and reliable mild hypothermia therapy before reperfusion can relieve ischemia-reperfusion injury and decrease myocardial ischemia reperfusion injury. Infarct size in low myocardial ischemia [4, 5]. Abendschein et al [6] in more than 30 years ago, the study showed that deep hypothermic treatment (26 °C) could significantly reduce the size of the coronary artery in dogs after 5 h or 10 h myocardial ischemia damage range, so that the former myocardial infarct size a reduction of 25%, which reduced the infarct size by nearly 20%. Deep hypothermia therapy it may induce adverse effects of cardiac fibrillation, spontaneous ventricular fibrillation, and cardiac dysfunction, therefore, it is rarely used to treat patients with clear awareness. Chien et al. [7] in 1994 the first published report on the cardioprotective effects of mild hypothermia therapy on myocardial ischemia chapter. The normal temperature of the rabbit (35 ~42 min) was performed by 30 coronal rotation vein occlusion, 3 h reperfusion, by warming or physical hypothermia, was measured at the right jugular vein blood temperature was measured, and the results showed that infarct size was positively related to body temperature and decreased in temperature 1°C, the infarct size decreased by 8%, irrespective of heart rate. Hamamoto et al [8] performed a coronary occlusion of 1 h in the sheep and reperfusion at 3 h in the similar experiments were carried out in the temperature range of 35.5 ~39.5 °C in this study. The relationship between temperature and

infarct size was also found elevated temperature to 39.5 °C infarct area increases with decreasing temperature and decreasing infarct size. At 39.5°C, reperfusion leads to the most serious myocardial injury. Based on the above research, we can draw a conclusion the reduction in body temperature to 37°C can reduce infarct size, while the same increases body temperature increases infarct size. So fever for AMI patients need to be treat in time [7, 8]. Simkhovich et al [9] were given to 20 min rabbits with coronary occlusion the local hypothermia treatment reduced the myocardial temperature by an average of about 6 °C hypothermia in Minya reduces myocardial oxygen consumption and protects ischemic myocardium. Kanemoto et al. [10] 76 rabbits were treated with 30 min coronary artery occlusion after 3 h reperfusion, mild hypothermia therapy was performed at different times during myocardial ischemia / reperfusion the earlier time of hypothermia treatment, the more obvious myocardial protective effect is, the infarct size is reducing more. Subsequently, in many different animals, including dogs, pigs, rats, mice, a large number of studies have been carried out in rabbits, and most studies have shown that they are performed after myocardial ischemia mild hypothermia therapy reduces infarct size and uses sub - low during ischemia, the longer the temperature treatment, the better the effect of heart protection, the better for the clinical treatment hypothermia treatment provides a basis for [3,11-13].

Dae and his team, [14], carried out 60 min coronary artery left to pigs the anterior descending branch was occluded for 3 h after reperfusion, to study the effect of low temperature treatment (34 ~38 °C) on myocardium the influence of infarct size. The cryogenic treatment device was inserted into the inferior vena cava from the femoral vein of the pig and opened 20 min after ischemia at the beginning of hypothermia treatment, infarct size decreased by 80% in ischemic areas. This research it is important for clinical application of hypothermia therapy.

### **Clinical study of mild hypothermia therapy with STEMI:**

Small clinical trials confirmed hypothermia in conscious patients with AMI treatment is safe and reliable, [15-17]. Dixon et al [15] randomly assigned 42 patients low temperature treatment for vascular internal heat exchangers or standard PCI treatment in two groups. Hypothermia patients the treatment was well tolerated without hemodynamic instability or loss of heart rhythm there was a constant increase in risk, but there was no significant difference in infarct size between the two groups. In low temperature treatment studies, Kandzari et al [16] randomly selected 20 patients who underwent direct PCI and adjuvant hypothermia therapy to achieve a successful perioperative cooling of the blood vessels the core temperature was low and the patient was well tolerated. A multicenter study 49 patients were treated with an automatic peritoneal lavage system to induce hypothermia at low temperature after 32.5°C for 24 h, rewarming 3 h, 3 patients were excluded, and 46 patients completed the treatment, this suggests that mild hypothermia is safe and reliable for AMI patients, [17]. Ly et al [18] using hypothermia therapy was performed by using body surface cooling, and Zimmermann et al [19] were adopted endovascular cooling showed that AMI patients were treated with mild hypothermia good and safe.

The COOL-MI I trial is a low temperature treatment for negative results, STEMI bed study [20], the trial selected 392 patients with STEMI, who were randomly divided into standard PCI group PCI+ and hypothermia treatment group two groups. The latter takes blood besides receiving PCI the tube was cooled by 3 h and rewarming by 4 h for mild hypothermia treatment. The time for low temperature group balloon dilatation was 18 min, slightly longer than the direct PCI group, and 94% of the hypothermia group patients were low warm treatment was well tolerated, but the clinical endpoints, primary endpoints, and severity were between the two groups there was no significant difference in side effects. Patients were treated with single photon emission 30 days later Tomographic imaging (SPECT) assessed infarct size (group PCI: 13.8% vs, PCI+ low) temperature group: 14.1%). Further analysis was made before the onset of reperfusion at a temperature of 35°C infarct size decreased by 49% in patients with anterior wall myocardial infarction, SPECT trends (PCI group: 18.2%, N =58 vs PCI+ hypothermia, group: 9.3%, N =16). In the CHILL-MI study, 120 cases of STEMI within 6 h were selected the patients were divided into PCI group and mild hypothermia group according to the proportion of 1:1, and the latter was adopted the core temperature was reduced by 600~2000 ml 4 ice cold saline combined with intravascular cooling the infarct size was assessed by myocardial scintigraphy at 33 (4, 2) days the percentage of blood myocardium (IS/MaR) was the endpoint event, and the results showed that hypothermia treatment is safe and can be achieved quickly by freezing Saline Combined with intravascular cooling target temperature, but there was no significant difference in IS/MaR between the two groups [21]. An American, one multicenter studies included 44 patients with PCI, who were divided into group STEMI (26 patients) and mild hypothermia treatment combined with PCI group (28 cases), mild hypothermia remained at 3 PCI after h, the core temperature was 34.7°C, and the results showed that mild hypothermia therapy was safe for the patients, but the myocardial infarct size in the mild hypothermia group was not significantly less than in the PCI group less [22].

In the ICE-IT test for positive results, [23] was selected in 228 cases STEMI patients were randomly divided into PCI group and endovascular hypothermia on +PCI group two (1:1), hypothermia treatment, intravascular cooling for 6 h, rewarming for 3 h. There was no difference between the clinical end points and the severe side effects of the group, and the death in the hypothermia group rates were higher (7.89%, vs, 3.51%), possibly because of hypothermia in older subjects more, the area of myocardial infarction with SPECT assessment after 30 days, low temperature group infarct the product decreased by 23% (PCI:13.2% vs low temperature: 10.2%, P =0.14). The anterior wall myocardial infarction was analyzed before reperfusion and the body temperature dropped below 35, infarct size decreased by 43% (group PCI: 22.7%, N=38 vs hypothermia group): 12.9%, N =10, P =0.09). In the RAPID MI-ICE test, 20 cases were selected patients with AMI were divided into standard PCI group and PCI+ mild hypothermia treatment group (1:1) the hypothermia group was treated with 3 h mild hypothermia to reduce the target temperature to below 35°C in 3 h, the results showed that the infarct size decreased in the mild hypothermia group compared with the standard PCI group 38%[24]. Erlinge et al [25] performed clinical trials in 197 patients with AMI mild hypothermia was performed in 94 of the participants, and the results showed a sub low compared with the

control group the infarct size decreased by 24% in warm treatment and increased before reperfusion the infarct size decreased by 37% in patients under 35°C. After that, they chose a large area of SETMI was taken in 120 patients with COOL-MI and 20 in the MI-ICE trial the patients were further studied and all patients were treated with PCI within 6 h of the disease, mild hypothermia therapy started before PCI and continued to 1~3, h, and nucleus after reperfusion the heart temperature was controlled at 33°C, and assessed by myocardial scintigraphy at (4±2) days IS/MaR, the results showed mild hypothermia compared with the PCI group without hypothermia treatment group IS/MaR was relatively decreased (RR) 15%, and the incidence of heart failure was also decreased low. In the anterior wall STEMI patients with 0~4 h, the decrease in IS/MaR is particularly high obviously, RR is 31%[26]. Another study included 20 patients with STEMI, hypothermia treatment prior to PCI. The study showed that before direct PCI the standard temperature is <35 degrees centigrade and is safe, and there is no delay in PCI, and hypothermia treatment is performed adjuvant therapy for STEMI can reduce infarct size by 38%[27].

### **The timing of hypothermia treatment induces the rate and duration of hypothermia:**

As previously mentioned, analyses of COOL-MI and ICE-IT studies show that sub low warm treatment only starts before reperfusion and the temperature is effective. Gotberg et al [28 and 29] used pig models for hypothermia experiments, and after reperfusion they used them 1000 ml, 4°C ice cold water, gave 40~45 kg pigs a cooling of the blood vessels to make it 5 minutes the body temperature dropped below 35 min and no improvement in infarct size was seen effect. When the ischemic phase lasts 40 min, mild hypothermia is administered at least before reperfusion at the start of 15 min, the researchers found a reduction of 39% in the infarct size, which is confirmed hypothermia therapy prior to reperfusion is beneficial for the overall outcome. After that, researchers changed the ischemic period to 5 min, and the rest of the time to induce hypothermia treatment, and then the infarct size of pigs treated with hypothermic perfusion was reduced by 18%, suggesting hypothermia treatment there is an independent effect on reperfusion injury. Otaken et al, [12], Maeng et al, [13], etc. Animal studies also directly demonstrate the efficacy of mild hypothermia therapy before and after reperfusion injury the result is the same as above. Kanemoto et al [10]'s research in the rabbit experiment it was found that 5 min prior to reperfusion for hypothermia treatment resulted in the opposite conclusion. Because pig models are closer to humans than rabbits, so hypothermia therapy is used in pig models for re irrigation the positive effect of injection injury may be more desirable in patients.

There is evidence that hypothermia therapy for ischemia should be carried out as early as possible before reperfusion, but the duration of hypothermia after reperfusion remains unclear, and in the heart the answer to this question in the patient is unclear, [23]. Gotberg et al [29] pairs pig mold type II hypothermia treatment continued to 15~60 min after reperfusion and was not found in the graft the dead area has an additional protective effect and suggests that hypothermia therapy should be followed by reperfusion early finish. The researchers concluded that COOL-MI and ICE-IT worked in the study, the low temperature of 3~6 h is at least unnecessary and lasts 1 h adaptive [23]. It is also important that hypothermia therapy requires

systemic hypothermia. Single ice salt water can rapidly reduce blood temperature, but rebound quickly, making it infarct size the improvements are discounted and plenty of ice salt water is used to cool (limit 2 L) possible acute heart failure and pulmonary embolism may result in [23] in large myocardial infarction patients, therefore, it is necessary to combine intravascular cooling. Gotberg et al [24] studies confirm the blood vessel internal cooling combined with ice brine can induce cold more quickly, so low temperature + PCI the patient's body temperature dropped below 35 °C before reperfusion, the study showed rapid induction of hypothermia was safe and reliable, and infarct size decreased significantly less than 38% and the level of blood troponin decreased. Although 1.5 L ice brine cools down (4 °C) may cause heart failure and pulmonary embolism, but is low in PCI+ there was no pulmonary congestion in the warm treatment group, and the patients with heart failure were also less pneumonia the incidence was not different between the two groups. Hypothermia therapy is known to inhibit the immune system the increased risk of infection increases by 3 h, cooling induction and 3 h rewarming may increase the chance of pulmonary infection, therefore, reduces the duration of hypothermia treatment and may benefit more. Koreny et al [30] selected 111 cases of cardiac sudden hypothermia treated at the heart center the patient showed a cardiac arrest of 8 h in patients with myocardial infarction within 8 h, the target temperature and creatine kinase isoenzyme (CK-MB) were decreased the level has declined.

## CONCLUSION

Mild hypothermia therapy is a very active adjunct to STEMI in the field of study, clinical studies have shown that mild hypothermia is safe and reliable well tolerated in awake patients. The core temperature of hypothermia therapy before reperfusion is below 35 °C, which is an important component of the reduction of myocardial infarction degree in STEMI patient's hypothermia should be as early as possible, preferably before reperfusion. After reperfusion, the duration of hypothermia should be shortened as far as possible. Animal experiments confirmed mild hypothermia treatment myocardial infarct size may be reduced, and COOL-MI studies have not been found to be mild hypothermia treatment reduced infarct size in STEMI patients, but in sub trials and others clinical studies confirmed that mild hypothermia therapy reduces myocardial infarction in patients with STEMI the role of area, this point is still controversial. For mild hypothermia treatment, as there are many clinical studies of adjuvant therapies for STEMI, which require extensive clinical trials investigate and draw definite conclusions.

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