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REVIEW ARTICLE

Therapeutic hypothermia in the treatment of myocardial infarction with ST-segment elevation – state of the art for 2014

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Abstract
Therapeutic hypothermia is a modern procedure introduced into the cardiology guidelines in 2012. The main purpose of this state of the art for 2014 is to summarize relevant information about the use of therapeutic hypothermia in ST-elevation myocardial infarction (STEMI). Authors describe the role and benefits of the procedure, and review animal models and randomized clinical trials (COOL-MI, ICE-IT, RAPID MI-ICE, CHILL-MI) relating to hypothermia in STEMI. In conclusion we emphasize that results from randomised controlled trials indicate safe use and a cardioprotective effect of therapeutic hypothermia in patients with STEMI.

Keywords
Hypothermia, STEMI, CVD, infarction, cardioprotection, cooling

The fundamental principle of therapeutic hypothermia, involving a controlled reduction of body temperature to below 35°C, has not changed since its introduction [1]. However, its role in the treatment of emergencies has changed. The first attempts at using hypothermia in the treatment of cardiovascular disease (CVD) were made in cardiac centres during cardiac surgery procedures [2]. When used intraoperatively, it enables safe conduct of surgery that requires cessation of circulation for a short period of time, thereby reducing the risk of neurological complications and secondary heart failure.

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Therapeutic hypothermia was introduced to the modern cardiology relatively late. Only in 2012, it was included in the guidelines for treating STEMI, as a method recommended for patients after cardiac arrest to prevent secondary neurological damage (class of recommendation I, level of evidence B) [3]. Lowering the temperature of the central compartment inhibits adverse metabolic reactions associated with ischaemia and reperfusion. These positive effects include: 1) inhibition of adverse enzymatic reactions, 2) suppression of free radicals, 3) protection of the lipoprotein membranes, 4) reduction of oxygen demand in the areas of reduced perfusion, 5) reduction of intracellular acidosis, 6) inhibition of biosynthesis, 7) release and uptake of activating neurotransmitters [4].

The well-documented clinical efficacy of the therapeutic hypothermia in the prevention of the central nervous system injury gave rise to a hypothesis advertising its possible protective properties in myocardial reperfusion injury resulting from a MI. This hypothesis was first confirmed in the studies involving small animals, clearly indicating that mild cooling of the ischaemic muscle (by about 2-5°C) reduced the infarct size and improved cardiac output [5]. These results were verified in a large animal model (pig). Dae et al. conducted a study on a model of a MI of anterior wall (left anterior descending occlusion) in 22 individuals [6]. Hypothermia in the study group (34°C) was achieved by means of an intravascular catheter placed in the inferior vena cava. Histopathological analysis demonstrated a significant reduction in MI zone, reaching up to 80% (9% +/- 6% vs. 45 +/- 8%, *P* <0.0001). To evaluate the effect of hypothermia on hemodynamics of the circulatory system, the researchers also monitored the heart rate, stroke volume and cardiac output (duration of hypothermia, the heating phase, 30 min after achieving the normothermia). A significant physiological reduction of the heart rate during cooling, accompanied by a compensatory increase in the stroke volume (but constant cardiac output) were observed [6]. The results confirmed the clinical efficacy and safety of initiating the therapeutic hypothermia in large mammals with a large anterior MI (Figure 1).

The COOL MI study was the first study carried out in humans, whose aim was to assess the efficacy of the therapeutic hypothermia in reducing the infarct size [7]. It included patients with anterior and inferior MI and total duration of ischaemia less than 6 hours, excluding the patients with cardiogenic shock and those who suffered from the MI within

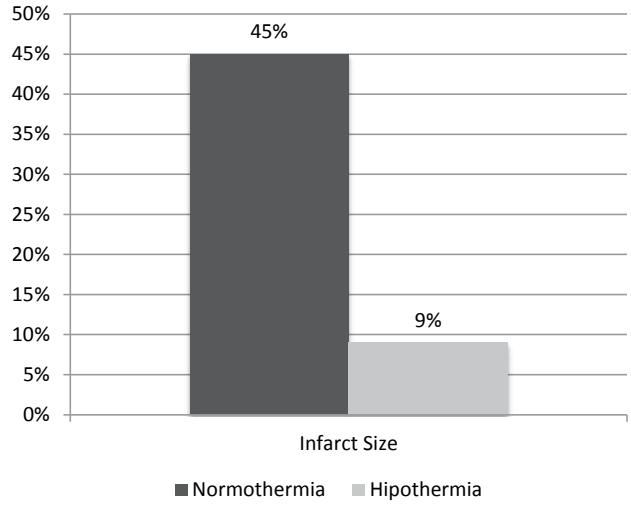

Figure 1. Effect of the therapeutic hypothermia on the size of left ventricular myocardial infarction (animal model)

the past month. Following randomisation, in half of the patients, apart from percutaneous coronary intervention (PCI), the endovascular therapeutic hypothermia was applied, using catheter of 10 French placed in the inferior vena cava (Repetitive, Radiant Medical). According to the protocol, the patients in the study arm were cooled during PCI to the target temperature of 32°C, with the intention of maintaining this temperature for a total of 3 hours. MI size was assessed by means of a single-photon emission computer tomography (SPECT) 30 days after PCI procedure. In neither of the groups an increased incidence of major cardiovascular complications (death, reinfarction, the need for repeat revascularisation, major bleeding) was observed. To the researchers' disappointment, the mean size of the MI assessed one month after the intervention did not differ between the groups (13.8% vs. 14.1%, ***P***=0.83) [7]. One year following the publication of the COOL MI study, the results of another clinical trial were reported that evaluated the clinical efficacy and safety of the therapeutic hypothermia in reducing the volume of myocardial necrosis in patients with STEMI – ICE-IT study[8]. Baseline clinical characteristics of the study group, including patients with anterior and inferior MI, were similar to the previous study. The second trial covered a total of 217 patients (108 in the hypothermia group and 109 in the control group). SPECT-based assessment of the MI size was performed on the 30th day after the intervention. However, there was still no significant improvement in the reduction of the infarction size in the patients treated with therapeutic hypothermia (10.2% vs. 13.2%, *P*=0.14) [8].

Detailed analysis of the data from these two studies provided valuable information that could help explain the differences in results between humans and animal models. In the COOL MI study, over 30% of patients did not reach the target temperature of 35°C at the time of reperfusion (balloon inflation, direct stent implantation). Only a post-hoc analysis, accounting exclusively for the patients who met this condition, confirmed a significant reduction in the size of myocardial injury (9.3% vs. 18.2%, *P*=0.05) [9]. In the ICE-IT study, the target temperature was also achieved in less than 62% of patients. Reduction of the infarct size was achieved in patients treated in the centres with high adherence to the study protocol (*P*=0.017). As shown in both studies, obtaining the hypothermia prior to a coronary reperfusion is a serious logistic problem, especially when the procedure is performed under time pressure, and is a key to a successful therapy.

Conclusions from the COOL MI and ICE-IT studies provided the basis for designing a third clinical trial called RAPID MI-ICE. The basic aim of the researchers was to cool all the patients included in the study to a temperature below 35°C before the reperfusion [10]. The study was carried out in a Swedish academic centre with extensive experience in therapeutic hypothermia treatments. It included 20 patients, half of whom were cooled using a high-performance endovascular system (RTx InnerCool, Philips). Necrosis size was assessed on the fourth day after PCI, using a nuclear magnetic resonance method (T2-weighted images). The mean temperature at the time of reperfusion was 34.7°C, and the threshold of below 35°C was achieved in all patients in the study. The time from the first contact with a medical professional to the reperfusion was longer in the group treated with hypothermia. However, the difference was only three minutes, which seems acceptable. The resonance showed a significant, 38% reduction in the size of myocardial necrosis in the cooled group. This observation was reflected in a 43% reduction of troponin concentration. The RAPID MI-ICE study provided a new impulse for further attempts at the implementation of hypothermia in the treatment of patients with STEMI and facilitated the design and introduction of so far the largest study in this field, called CHILL-MI [11]. Its results were announced on 30 October 2013, at Transcatheter Cardiovascular Therapeutics (TCT) 2013 conference in San Francisco, California (USA). The study design and methodology were based on the previous models. The patients with extensive anterior and inferior MI, lasting no longer than 6 hours, were enrolled. A temperature below 35°C at the reperfusion was achieved in 77 % of individuals (92 % < 35.4°C). The time of additional delay until PCI in the hypothermia group was +9 min. Infarct size assessed by magnetic resonance imaging on 4th day after PCI was lower in the group subjected to hypothermia, but the difference was not significant (relative reduction of the infarct size: –13%, *P*=0.15). The results were significant in the subgroup of patients at a very early stage of MI, lasting less than 4 hours, regardless of its location (relative reduction in the infarct size: -21%, *P*<0.05). Furthermore, a 30-day analysis confirmed significant reduction in death rate and heart failure in the study group (3.2% vs. 13.5%, *P*<0.05).

In conclusion, it should be emphasized that all clinical trials conducted so far clearly indicate the safety of therapeutic hypothermia in patients with acute STEMI. The benefits observed in selected subgroups of patients confirm the potential of this method to reduce the size of myocardial necrosis associated with reperfusion during PCI. Considering the lack of viable alternatives that could contribute to an improvement of reperfusion and cardioprotection of myocytes, hypothermia remains an important therapeutic option. Nevertheless, one of the factors in reducing the risk of death and serious complications is quick transportation of a patient with STEMI to the cath lab, ideally without stopping at a hospital emergency department [12]. Only by following this recommendation, together with modern methods of myocardial protection such as therapeutic hypothermia, can the chance of long-term prognosis and quality of life be optimised [3].

Conflict of interest: None declared

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