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EDITORIAL

Therapeutic hypothermia to reduce infarct size in STEMI: time to give it the cold shoulder?

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Timely reperfusion of the infarct-related coronary artery in acute ST-segment elevation myocardial infarction (STEMI) patients using primary percutaneous coronary intervention (PCI) is the gold-standard therapy for limiting myocardial infarct (MI) size[1]. However, the process of restoring coronary blood flow can, in itself, induce further cardiomyocyte death due to the detrimental effects of acute ischaemia/reperfusion injury (IRI) which include mitochondrial dysfunction, oxidative stress, calcium overload, inflammation and microvascular obstruction[1]. As such, there is still a need for new cardioprotective treatments to reduce MI size and prevent the onset of heart failure in STEMI patients treated by primary PCI.

Although a large number of cardioprotective strategies have been reported to reduce MI size in animal models of acute IRI, their translation into the clinical setting for patient benefit has been largely disappointing. The potential reasons for this failed translation of cardioprotection are multiple and include limitations with the preclinical animal IRI models, which do not accurately recapitulate the clinical setting, and issues with clinical study design, including the following: the testing of cardioprotective interventions which failed in preclinical studies, poor selection of patients, the timing of the cardioprotective intervention, concomitant use of medications (such as antiplatelet agents, nitrates and statins) and comorbidities (such as age, diabetes, hypertension) which may confound cardioprotection, the presence of collateral flow, preinfarct angina, and the choice of surrogate study endpoints[1].

The cardioprotective potential of therapeutic hypothermia to decrease myocardial oxygen requirements and reduce MI size has been the subject of research for nearly three decades, with initial small and large animal IRI studies reporting that cooling the myocardium to <35°C prior to or after the onset of ischaemia was effective in reducing MI size[2,3]. However, these studies also demonstrated that cooling the myocardium specifically at the onset of reperfusion did not reduce MI size. As such, it came as no surprise that clinical trials evaluating the cardioprotective effect of therapeutic systemic hypothermia at the onset of reperfusion using either endovascular cooling[4-6] or peritoneal hypothermia[7] failed to show any reduction in MI size in STEMI patients undergoing primary PCI, and in fact, therapeutic systemic hypothermia was associated with an increase in adverse events including paroxysmal atrial fibrillation, infection, and cardiogenic shock when compared to standard care[4-7].

In this issue of EuroIntervention, El Farissi and colleagues[8] report the results of the EURO-ICE study, which evaluated the cardioprotective effects of selective intracoronary hypothermia to achieve a rapid reduction in intracoronary temperature whilst avoiding the adverse effects of systemic cooling (such as shivering). This was a multicentre trial of 200 large anterior STEMI patients randomised to either selective intracoronary hypothermia or routine care. The primary endpoint was MI size at 3 months, quantified by cardiovascular magnetic resonance imaging (CMR; 89 patients received intracoronary hypothermia, and 97 patients received routine care). There was no reduction in MI size with hypothermia, either in the intention-to-treat or per-protocol analysis.

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The authors should be congratulated on completing such a challenging multicentre study. There are several notable strengths in the study design: (1) the intervention achieved a rapid reduction in distal intracoronary temperature of 6°C within a median time of 43 seconds using equipment readily available in most cardiac catheterisation laboratories, including an over-the-wire balloon catheter and a pressure wire that also measured temperature; (2) the study focused on STEMI patients who were most likely to benefit from a cardioprotective intervention applied at reperfusion,

namely patients with large anterior STEMI presenting <6 hours after symptom onset with pre-PCI Thrombolysis in Myocardial Infarction (TIMI) flow 0-1; and (3) the primary endpoint of MI size (as a percentage of left ventricular [LV] mass) quantified by CMR at 3 months after primary PCI is accepted to be the gold standard surrogate study endpoint for evaluating cardioprotective efficacy in STEMI patients.

There are several potential reasons to explain the neutral findings of the EURO-ICE study: (1) as mentioned previously, small and large animal IRI studies have reported that cooling the myocardium at the onset of reperfusion did not reduce MI size, with hypothermia only being effective if applied during ischaemia[2,3]; (2) the door-to-balloon time was delayed by a median of 15 minutes in the intervention arm when compared to the control arm, thereby prolonging the total ischaemic time, which may have mitigated any of the cardioprotective benefits of cooling; (3) the presence of preinfarct angina and collateral blood flow were not accounted for; and (4) the 10 minute duration of cooling during the reperfusion phase may have been too short to achieve cardioprotection in the STEMI patients. In contrast to the current study, a previously published smaller study from 2018 of 50 STEMI patients reported cardioprotection with selective intracoronary hypothermia (achieving a 6°C reduction in distal intracoronary temperature within 31±8 seconds but with a delay in door-to-flow restoration time of 13 minutes), demonstrating an improvement in myocardial salvage on CMR at 7 days although the reduction in MI size as a percentage of LV mass was not significant[9].

Unfortunately, the EURO-ICE trial joins a long list of trials – not only in the specific field of therapeutic hypothermia, but also in the field of cardioprotection in general – which have failed to reduce MI size in STEMI patients undergoing primary PCI. This highlights the challenges in targeting reperfusion injury to reduce MI size in STEMI patients. Interestingly, hyperoxaemic supersaturated oxygen therapy administered as an adjunct to primary PCI is the only cardioprotective therapy which has been awarded premarket approval from the U.S. Food and Drug Administration for reducing MI size in anterior STEMI patients presenting within 6 hours of symptom onset[10]. Whether this intervention can improve clinical outcomes is currently being evaluated in 443 patients with anterior STEMI in the AMIHOT III trial (ClinicalTrials.gov: NCT04743245).

As it stands, myocardial reperfusion injury remains a clinically important and viable target for cardioprotection, especially in higher-risk patients with large anterior STEMI presenting with or without cardiogenic shock, and the search continues for a novel cardioprotective therapy capable of reducing MI size, preserving cardiac function and improving clinical outcomes.

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Conflict of interest statement

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