Heart Metab. (2016) 70:19-23

Pharmacological agents for reducing myocardial infarct size in ST-segment elevation myocardial infarction

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Abstract

Major progress has been made over the last two decades for the treatment of patients with ST-segment elevation myocardial infarction (STEMI). The major objective of this treatment is to reduce infarct size, which is the major prognostic factor in this population. Most of the efforts have been focused on improving reperfusion therapy in order to open as quickly as possible the culprit coronary artery. Recently, phase 2 trials have demonstrated that reperfusion injury exists, is of significant importance, and might be prevented by protective interventions (eg, ischemic conditioning) applied immediately before reflow. Several recent studies have addressed whether pharmacological agents can mimic ischemic conditioning. Although many past infarct size–reduction studies have not shown a reduction in size, some phase 2 studies have shown that reduction in infarct size is possible in patients with STEMI, provided the pharmacological treatment is administered before reperfusion. In contrast, the recent phase 3 CIRCUS trial (Cyclosporine to ImpRove Clinical oUtcome in ST-elevation myocardial infarction patients) did not demonstrate any benefit of cyclosporine on clinical outcome in patients presenting with anterior infarcts. Additional studies are needed to determine whether pharmacological agents targeting reperfusion injury might improve clinical outcomes in STEMI patients. ■ *Heart Metab*. 2016;70:19-23

Keywords: ischemia-reperfusion; ST-segment elevation myocardial infarction; treatment of reperfusion injury

The unmet need

Coronary heart disease remains the leading cause of death worldwide. Despite major progress in primary percutaneous coronary intervention (PCI) made during the past two decades, mortality and morbidity remain unacceptably high in ST-segment elevation myocardial infarction (STEMI). In the recent CIRCUS trial (Cyclosporine to ImpRove Clinical oUtcome in STEMI patients), nearly 20% of patients with anterior infarcts were either dead or rehospitalized for heart failure at 1 year despite more than 90% succesful reperfusion and optimal pharmacological treatments.[1] Although there is not much room to further reduce door-to-balloon time in PCI, the two following major goals, if reached, should

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Abbreviations

CIRCUS: Cyclosporine to ImpRove Clinical oUtcome in ST-elevation myocardial infarction patients; **CsA:** cyclosporine A; **EMBRACE:** Evaluation of Myocardial effects of Bendavia for Reducing reperfusion injury in patients with Acute Coronary Events; **GLP-1:** glucagon-like peptide-1; **INFUSE-AMI:** Intracoronary Abciximab and Aspiration Thrombectomy in Patients with Large Anterior Myocardial Infarction; **LV:** left ventricular; **METOCARD-CNIC:** METOprolol in CARDioproteCtioN during an acute myocardial InfarCtion; **MITOCARE:** Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Assess the Safety and Efficacy of TRO40303 for the Reduction of Reperfusion Injury in Patients Undergoing Percutaneous Coronary Intervention for Acute Myocardial Infarction; **MOVE ON!:** Impact of pre-reperfusion Metoprolol On clinical eVEnts after myocardial infarctiON; **PCI:** percutaneous coronary intervention; **PTP:** permeability transition pore; **STEMI:** ST-segment elevation myocardial infarction

continue to improve patient prognosis: first, reducing the duration of ischemia via faster access to reperfusion therapy; second, protecting the heart from reperfusion injury.[2] Both would reduce myocardial infarct size and then prevent adverse left ventricular (LV) remodeling, preserve LV function, prevent the onset of heart failure, and improve survival.

There is strong experimental evidence that reperfusion injury may be attenuated by interventions applied after the onset of ischemia, specifically by ischemic conditioning interventions.[3] Phase 2 clinical trials have demonstrated that ischemic postconditioning can reduce infarct size and improve recovery of contractile function in STEMI patients.[4,5] We will briefly review recent advances in *pharmacological* prevention of reperfusion injury.

Pharmacological prevention of reperfusion injury

Over the past three decades, although numerous experimental studies have reported myocardial protection by different pharmacological agents, the translation into clinical settings has been very challenging.[6] Several drugs have recently been tested as an adjunct to reperfusion therapy, targeting either key players of signaling pathways or mitochondria, considered to be a final effector of reperfusion-induced cell death.

Cyclosporine A and other agents targeting mitochondria

Apart from its immunosuppressive activity, cyclosporine A (CsA) is known as a potent inhibitor of the opening of the mitochondrial permeability transition pore (PTP). PTP opening is considered a crucial event in cardiomyocyte death after prolonged ischemia-reperfusion. During the past 20 years, CsA has consistently been shown to reduce cell death after an ischemic insult in a variety of experimental preparations, including in vivo models of infarction.[7-9] Some, but not all, phase 2 clinical trials have suggested that CsA can protect the heart following a prolonged ischemic insult.[10-15] Despite these encouraging results, in the 970-patient CIRCUS trial, the administration of CsA immediately before PCI failed to improve clinical outcomes (all-cause death, heart failure hospitalization, and adverse LV remodeling) at 1 year in anterior-STEMI patients.[1] The discrepancy between the neutral results of this phase 3, multicenter, randomized, placebo-controlled trial and previous phase 2 studies is unclear. Different issues may be discussed, including (i) a type I error frequently seen in small-size phase 2 studies, (ii) the nonspecific inhibition of PTP opening by CsA, or (iii) the immunosuppressive effects of CsA that might have modified a putative protective effect of inhibition of PTP opening. Probably more important are factors related to the major difference between experimental and clinical settings and between surrogate end points (eg, infarct size) and clinical outcomes (eg, heart failure or mortality). Unlike animals, patients displayed comorbidities and received treatments (β-blockers, angiotensin-converting enzyme inhibitor, antiplatelet agents, statins) that might alter the efficacy of the tested pharmacological agent. Noteworthy, the increased use of the new $P2Y_{12}$ platelet inhibitors (prasugrel, ticagrelor) may have played a role, because ticagrelor and prasugrel are known to reduce myocardial infarct size per se.[16,17] Eventually, one may also question whether CsA could actually reach its mitochondrial target under the specific conditions of its use in STEMI patients. Were the dose, route, and timing of administration appropriate for a sufficient amount of this drug to bind cyclophilin D within the just reoxygenated cardiac mitochondria and prevent PTP opening? Overall, although there is little doubt that CsA is not the pharmacological agent

that will improve cardiac protection in STEMI patients, its failure by no means questions the concept of protection against myocardial reperfusion injury.

Other agents targeting mitochondria have been tested recently. MTP-131 is a peptide that targets cardiolipin in the inner mitochondrial membrane, optimizes mitochondrial energetics, and attenuates production of reactive oxygen species. Despite encouraging preclinical data, MTP-131 failed to reduce infarct size in the phase 2 EMBRACE study (Evaluation of Myocardial effects of Bendavia for Reducing reperfusion injury in patients with Acute Coronary Events).[18-20] TRO40303, a pharmacological agent that is believed to bind to the translocator protein TSPO in the outer mitochondrial membrane—but not specifically inhibit PTP opening—was able to limit infarct size in rodents, but not in the pig model.[21,22] In the STEMI-patient MITOCARE study (Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Assess Safety and Efficacy of TRO40303 for Reduction of Reperfusion Injury in Patients Undergoing Percutaneous Coronary Intervention for Acute Myocardial Infarction), TRO40303 failed to reduce infarct size.[23]

Together, these trials question whether the noxious effects of PTP opening can be captured in the settings of STEMI.

Therapies targeting glucose metabolism

Several experimental investigations have suggested that insulin can prevent reperfusion injury. However, clinical results have been equivocal.[24] Recently, Lexis et al evaluated the effects of metformin treatment on the preservation of LV function in STEMI patients without diabetes.[25] In that double-blind, placebo-controlled phase 2 study, metformin hydrochloride (500 mg twice daily) did not improve LV function at 4 months. The antidiabetic agent glucagon-like peptide-1 (GLP-1) and the GLP-1 analog exenatide have been demonstrated in animal studies to reduce infarct size.[26,27] Intravenous administration of exenatide before PCI has been shown to reduce infarct size in STEMI patients.[28] The GLP-1 analog liraglutide, administered before PCI and continued for 7 days, improved LV function in STEMI patients; however, its impact on infarct size was not assessed in that pilot trial.[29] Phase 3 trials are needed to determine whether these agents improve clinical outcomes in STEMI patients.

Nitric oxide and nitrite

Experimental evidence suggests a role for nitric oxide (NO) in conditioning interventions.[30] Yet, intravenous administration of nitrite in animal models has produced equivocal results.[31] In STEMI patients treated by PCI, the administration of nitrite either intravenously or intracoronarily failed to significantly reduce infarct size.[32,33]

Abciximab

Glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors can prevent thrombotic events owing to their potent effect on platelets and eventually on platelet-leukocyte aggregates. In the INFUSE-AMI trial (Intracoronary Abciximab and Aspiration Thrombectomy in Patients with Large Anterior Myocardial Infarction), anterior-STEMI patients underwent PCI and received abciximab and/or thrombectomy as part of an open-label 2x2 factorial protocol. Thrombus aspiration had no effect on infarct size, but intracoronary administration of abciximab significantly reduced infarct size as measured by cardiac magnetic resonance.[34] Additional information is needed to examine whether abciximab might improve clinical outcomes in STEMI.

Adenosine

Based on experimental works, adenosine has long been considered a potent infarct-size reducing agent. Its clinical interest has been evaluated in different cardiac ischemia-reperfusion settings; unfortunately, the results have been inconsistent, with some studies reporting a reduction in infarct size (eg, with a high dose administered to patients hospitalized within 3 hours of symptom onset) and others not.[35,36] Larger clinical trials selecting patients that experienced a short period of ischemia are needed in order to examine whether adenosine might bring clinically relevant benefit to STEMI patients.

Metoprolol

Intravenous administration of metoprolol immediately before reperfusion can reduce infarct size in the pig heart.[37] In the METOCARD-CNIC trial (METOprolol in CARDioproteCtioN during an acute myocardial InfarCtion), 270 anterior-STEMI patients received in-

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travenous metoprolol in the ambulance immediately before hospital admission. In the treated group, there was a significant reduction in infarct size together with a limitation in adverse LV remodeling, an improved functional recovery, and less rehospitalization for heart failure.[38] A phase 3 trial is in preparation (the MOVE ON! trial [Impact of pre-reperfusion Metoprolol On clinical eVEnts after myocardial infarctiON]), aimed at determining whether metoprolol might improve clinical outcome (mortality and rehospitalization for heart failure) in STEMI patients.

From now on

Our inability to transfer experimental evidence to clinical conditions and the accumulation of negative results from clinical trials are a major concern, as the prognosis of "optimally treated" STEMI patients remains poor. Several factors ought to be taken into consideration, including the incomplete understanding of the mechanisms of reperfusion injury[39] and of its role in cell death, myocardial healing, and remodeling. Also, the clinical scenario may be quite different from what is extrapolated from in vivo animal studies. For example, whereas postinfarct pathophysiology suggests an underlying central role of LV remodeling in the occurrence of heart failure, rehospitalization of a STEMI patient for heart failure in real life often results from intervening unrelated events, such as infections, metabolic disorders, and even inappropriate use of some pharmacological agents. Obviously, comorbidities (eg, diabetes, hypertension) and of cotreatments at the time of infarction, which obviously do not exist in animal models, are major modifiers of effect and can impact transferability of results from animal to clinical settings. It might be naive to consider that one single drug aiming at a single molecular target might prevent such a powerful and complex phenomenon as ischemia-reperfusion injury.

Although the concept of reperfusion injury and conditioning remains very strong, new approaches are certainly needed in order to improve clinical outcomes in STEMI patients. ■

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