Mitochondrial care in acute myocardial infarction

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This editorial refers to ‘Effect of intravenous TRO40303 as an adjunct to primary percutaneous coronary intervention for acute ST-elevation myocardial infarction: the MITOCARE study results’†, by D. Atar et al. on page 112

Rapid restoration of blood flow has the greatest impact on reducing infarct size and improving patient prognosis in patients with ST-elevation myocardial infarction (MI). However, reperfusion itself can exacerbate myocardial damage on top of the initial ischaemic damage. Lethal reperfusion injury develops when sudden restoration of blood flow causes necrosis of myocytes that—albeit injured by the preceding ischaemia—were potentially salvageable at the time of reperfusion. In animal models, reperfusion injury may account for up to 50% of the final infarct size.

Reperfusion injury is modifiable. Pre-infarct angina and repetitive episodes of ischaemia before ST-elevation MI reduce final infarct size, and are thought to be innate forms of pre-conditioning that reduce reperfusion injury. Hence, reperfusion injury is a target for improving outcomes in patients with acute MI undergoing optimal revascularization. Pre-conditioning by mechanical intervention, with repeated cycles of brief ischaemia and reperfusion before extended ischaemia, cannot be applied in acute MI due to its unpredictable nature. Repeated cycles of re-occlusion and reperfusion of the coronary artery within the first minute of reflow (post-conditioning) and repeated cycles of brief ischaemia and reperfusion in a distant organ (remote conditioning), typically the upper arm, can protect from lethal reperfusion injury and reduce infarct size by 30–70% according to experimental animal studies. Although the initial promising results with post-conditioning, which ultimately confirmed a specific intervention against reperfusion injury, have not been quite consistent in more recent studies, the intervention by remote conditioning has been translated into the clinical setting in proof-of-concept studies, and also demonstrated improvement in clinical outcome.

The demonstration of cardioprotective effects by various forms of ischaemic conditioning therapies has encouraged the pursuit of underlying mechanisms and drugs that recapitulate mechanical conditioning by specifically addressing signal transduction pathways. Mechanical conditioning activates several protective mechanisms in the target organ, including three parallel signalling cascades: the nitric oxide-dependent G-protein coupled receptor-eNOS-protein kinase G pathway, the reperfusion-injury salvage kinase (RISK) pathway and the survivor activating factor enhancement (SAFE) signalling pathway (Figure 1). The pathways interact and converge on the mitochondria to modify membrane integrity by inhibiting the opening of the membrane permeability transition pore (MPTP). The MPTP is closed during myocardial ischaemia but opens during reperfusion, causing mitochondrial swelling, loss of function and, potentially, cellular necrosis. Cyclosporine A prevents MPTP opening, provided that it is ‘on board’ at start of reperfusion. In the clinical setting, cyclosporine has been shown to reduce infarct size in patients undergoing primary PCI. Other pharmacological approaches for preventing or modifying the MPTP opening, e.g. by volatile anaesthetics or metformin, have shown cardioprotective capacity in experimental studies, but remain to be tested systematically in clinical trials.

In this light, the MITOCARE study—a proof-of-concept study investigating the cardioprotective effect of TRO40303, a new mitochondrial-targeted drug, as an adjunct to primary percutaneous coronary intervention in patients with acute ST-elevation MI—is appropriate and timely. However, the study demonstrated no protection from TRO40303 as measured by biomarker release over 3 days, cardiac magnetic resonance (CMR)-assessed myocardial salvage index, CMR-assessed infarct size or left ventricular ejection fraction.

The strength of the study is its multicentre design, inclusion of patients with totally occluded culprit vessels and large area-at-risk, use of CMR in a subgroup of patients and independent measurement of left ventricular function as secondary endpoints. The active study group started out on slightly more negative premises with respect to age, baseline biomarkers and unsuccessful revascularization. Endpoint limitations include lack of individual area-at-risk assessment using biomarkers and potential interference with the area-at-risk determination from T2-weighted oedema with CMR by any cardioprotective intervention. The study is challenged by the excellent outcomes from modern, standard therapy of ST-elevation MI and the power is borderline. The translation of the cardioprotective efficacy of TRO40303 from healthy animals to humans may be attenuated.
by conditions that are also known to attenuate protection by mechanical conditioning, such as age and co-morbidities—in particular hypercholesterolemia, diabetes, obesity and hypertension—which are common among patients suffering from acute MI. Medications may also attenuate the efficacy of cardioprotective treatment. Even so, the results imply the absence of cardioprotection. The drug may be challenged by some safety concerns, although the study was not powered for safety analysis.

Extrapolation from animal studies using 2.5 mg/kg and 0.3, 1.0, 3.0 and 10 mg/kg body weight has indicated that infarct size reduction may be achievable with a bolus injection of 6 mg TRO40303 per kg body weight. Reductions were modest and associated with variations in area-at-risk, such that interpretation may have been ambiguous. Simultaneous circulating TRO40303 concentrations after equivalent doses also appeared somewhat lower in the experimental model than in humans in a Phase 1 study using a formulation different from that used in animals, to evaluate safety. In the MITOCARE study, circulating concentrations of TRO40303 were not measured at the time of reperfusion. Also, importantly, mitochondrial-targeted drugs act differently from each other and our understanding of their mechanisms is still immature. While the properties of the MPTP are reasonably well defined, the identity of the molecules that assemble to form the MPTP remains uncertain (Figure 1). Cyclosporine A targets matrix cyclophilin D (CyD), where Ca\(^{2+}\) overload triggers opening of the MPTP. TRO40303 binds to the translocator protein 18 kDa (TSPO) in the outer mitochondrial membrane, where Ca\(^{2+}\) overload triggers MPTP opening. TRO40303 inhibits opening, mainly by displacement of CyD. Cyclosporine A inhibition of MPTP opening appears to coincide with its effects on ROS production and calcium overload, while the effects of TRO40303 occur slightly earlier, potentially creating a mismatch in mechanisms that may need to be simultaneous to elicit cardioprotection. Unlike cyclosporine A, TRO40303 has no effect on the calcium retention capacity of isolated mitochondria, even though it still seems to reduce reactive oxygen species production and subsequent calcium overload in an in vivo model. Finally, mechanical cardioprotection, e.g. by remote conditioning, induces a range of systemic effects including multi-organ protection, anti-inflammatory properties, reduced platelet activation, and increased exercise performance, perhaps indicating that this inherent protection system in mammalian species is a fundamental and complex part of the biological response to stress that may yet prove too complex to be fully recapitulated by a single pharmacological intervention.

Despite the disappointing results of the MITOCARE study, reduction in reperfusion injury remains a major target in improving outcomes after successful revascularization in patients with MI. The mechanisms underlying reperfusion injury and the increasing insight

**Figure 1** Simplified schematic presentation of the cytosol pathways that converge to prevent opening of the mitochondrial permeability transition pore (MPTP) in cardioprotection. eNOS/PKG: the nitric oxide dependent G-protein coupled receptor-eNOS-protein kinase G pathway; the reperfusion-injury salvage kinase pathway (RISK) based on protein kinase B; PI3K-Akt and glycogen synthase kinase 3 β and the survivor activating factor enhancement (SAFE) signaling pathway involving the JAK-STAT system and TNF-alpha receptors. Proteins implicated in MPTP formation include the matrix cyclophilin D (CyD), the inner membrane adenine nucleotide translocase (ANT) and the outer membrane voltage-dependent anion channel (VDAC). Additional proteins such as the translocator protein 18 kDa (TSPO), located in the outer mitochondrial membrane, interact with proteins implicated in MPTP formation. Under pathophysiological conditions, such as high Ca\(^{2+}\) concentration and increased oxidative stress, the complex forms an open pore between the inner and outer membranes that ultimately results in mitochondrial swelling, mitochondrial Ca\(^{2+}\) efflux and the release of apoptogenic proteins. Cyclosporine A targets matrix CyD, where Ca\(^{2+}\) overload triggers MPTP opening. TRO40303 binds to TSPO in the outer membrane. Abbreviations: eNOS: endothelial nitric oxide synthase; ERK: extracellular regulated kinase; GFR: growth factor receptor (insulin-like growth factor-1 and fibroblast growth factor-2); GPCR: G-protein-coupled receptor; GSK3-β: glycogen synthase kinase 3β; IMM: inner mitochondrial membrane; OMM: outer mitochondrial membrane; PKC: protein kinase C; TFN-R: tumor necrosis factor receptor.
into the mechanisms behind the cardioprotective effects of ischaemic conditioning have not only demonstrated that reperfusion injury is a true, modifiable clinical entity, but have also revealed targets for pharmacological intervention that potentially may generate effects similar to local and remote ischaemic conditioning. Intervening in ‘upstream’ events of the signalling cascade of conditioning by akt-activation with GLP-1 analogues and ‘downstream’ events, such as inhibiting MPTP opening with cyclosporine A, seem promising, while TRO40303—despite similar but not identical action—by as inhibiting MPTP opening with cyclosporine A, seem promising, while TRO40303—despite similar but not identical action—by

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