Reducing myocardial infarct size: myth or reality
Heart and Metabolism is a journal published three times a year, focusing on the management of cardiovascular diseases. Its aim is to inform cardiologists and other specialists about the newest findings on the role of metabolism in cardiac disease and to explore their potential clinical implications. Each issue includes an editorial, followed by articles on a key topic. Experts in the field explain the metabolic consequences of cardiac disease and the multiple potential targets for pharmacotherapy in ischemic and nonischemic heart disease.

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This year marks the 30th anniversary of the first report of “ischemic preconditioning,” which after reperfusion is the most powerful endogenous intervention for reducing myocardial infarct (MI) size. The last 3 to 4 decades have witnessed the accumulation of a huge amount of published literature in the research field of “cardioprotection”—a term used here to describe mechanical and pharmacological interventions for reducing MI size. Much of the research has focused on targeting “myocardial reperfusion injury,” which denotes the myocardial injury and cardiomyocyte death that paradoxically occur on reperfusing acutely ischemic myocardium and which has been demonstrated to contribute up to 50% of the final MI size. Despite timely reperfusion by primary percutaneous coronary intervention (PPCI), mortality and morbidity after an acute ST-segment elevation MI (STEMI) remain significant, with 7% death and 22% heart failure at 1-year follow-up. Thus, novel cardioprotective therapies are required to target myocardial reperfusion injury and reduce MI size in order to preserve left ventricular systolic function and prevent the onset of heart failure after STEMI. However, the results of a large number of clinical studies in reperfused STEMI patients have failed to demonstrate reduced MI size and improved clinical outcomes. The reasons for this are multiple and complex and have been discussed extensively in the literature; they can be attributed to problems with the design of both experimental and clinical studies used to test novel cardioprotective therapies.

In this issue of Heart and Metabolism, leading researchers in the field review some of the recent developments in the topical area of cardioprotection. The issue opens with an introduction by Gerd Heusch highlighting the importance of acute myocardial reperfusion injury as a target for cardioprotection and alluding to myocardial reperfusion as a double-edged sword. The metabolic consequences of acute ischemia and reperfusion on the myocardium are elegantly reviewed by Gary Lopaschuk in the Refresher Corner. These metabolic effects highlight opportunities for cardioprotection using metabolic modulation agents such as trimetazidine, a topic discussed in the article by Petr Widimsky.

Mechanical interventions for targeting myocardial reperfusion injury and reducing MI size, such as ischemic postconditioning (IPost) and remote ischemic conditioning (RIC), are reviewed by Hans Erik Bøtker. Of these, RIC holds the most promise for reducing MI size and improving clinical outcomes in reperfused STEMI patients (highlighted in the Hot Topics article by Luciano Candilio)—and is currently being tested in the ongoing European COND12/ERIC-PPCI trial (Effect of Remote Ischemic Conditioning on Clinical Outcomes in STEMI Patients Undergoing PPCI). Investigating the signaling pathways underlying ischemic...
preconditioning and postconditioning has unveiled numerous cardioprotective targets, many of which have been tested using pharmacological agents—a topic reviewed here by Michel Ovize. Assessing the efficacy of cardioprotective therapies for reducing MI size requires the quantification both of the area at risk and MI size. For this purpose, cardiac magnetic resonance imaging has emerged as the noninvasive imaging modality of choice, a subject that is summarized by Colin Berry in the current issue. More advanced imaging methods, such as hybrid cardiac positron emission tomography/magnetic resonance imaging (PET-MRI), have been investigated in reperfused STEMI patients to elucidate the in vivo metabolic effects of acute ischemia/reperfusion injury on the myocardium. The article by Heerajnarain Bulluck illustrates the use of PET-MRI in two case reports.

In summary, this issue of Heart and Metabolism highlights some of the recent developments in the field of cardioprotection and illustrates the challenges and opportunities faced when investigating therapies to reduce MI size and improve clinical outcomes in STEMI patients treated by PPCI.

REFERENCES

The good: reperfusion is mandatory for myocardial salvage

In acute myocardial infarction, myocardial ischemia results from the coronary occlusion resulting from the rupture of an atherosclerotic plaque in an epicardial coronary artery with superimposed thrombosis. The duration of coronary occlusion that the myocardium can tolerate before irreversible injury occurs differs between species and depends largely on the residual/collateral blood flow and on heart rate. In larger mammals, infarction begins to develop after a 20- to 40-minute coronary occlusion and spreads in a wavefront transmurally from the inner to the outer layers and laterally to the borders of the area at risk; infarction is more or less complete after 6 hours of coronary occlusion. Humans, like other primates, are relatively resistant to infarction such that even after 12 hours of coronary occlusion, parts of the ischemic myocardium survive and can still be rescued by interventional reperfusion. Reperfusion precipitates the morphological signs of irreversible injury, but is absolutely mandatory to salvage ischemic myocardium from impending infarction. The final infarct size after myocardial ischemia/reperfusion depends on (i) the size of the area at risk—ie, the coronary perfusion.
Heart Metab. (2016) 70:4-7

Reperfusion – the good, the bad, and the ugly

territory—that undergoes ischemia and reperfusion; (ii) the duration of coronary occlusion (see above); (iii) the severity of myocardial ischemia or, conversely, the amount of residual blood flow through collateral vessels; (iv) the myocardial temperature; and (v) the hemodynamic situation, notably heart rate. Myocardial infarction is largely the result of a necrotic mode of cell death, but other modes of cell death—such as apoptosis, necroptosis, and autophagy—have also been reported to contribute to myocardial infarction in a number of experimental studies. Collapse of mitochondrial function and structure, activation of intracellular proteolysis (calpain, caspases), intracellular sodium and calcium overload with subsequent edema, and excessive and uncoordinated contractile activity secondary to calcium cycling between sarcoplasmic reticulum and cytosol causally contribute to cell death. The resulting infarct size determines the process of post–myocardial infarct remodeling, the progression to heart failure, and ultimately, a patient’s prognosis. A reduction in infarct size via reopening of an occluded coronary artery was first reported in dogs in 1972, and this approach was relatively quickly translated to humans, first in the form of thrombolysis and now preferably in the form of percutaneous coronary intervention, including stent implantation. Today, the need for reperfusion to salvage ischemic myocardium from impending infarction is obvious and is no longer under scientific debate; the discussion is rather about logistics and implementation. Also, all adjunctive cardioprotective strategies known so far only work in conjunction with reperfusion.

The bad: reperfusion injury to myocardium and coronary microcirculation

Whether or not reperfusion only precipitates signs of irreversible injury or causes injury per se has been a matter of a long-lasting debate, because the precipitation of signs of injury with reperfusion could not be distinguished from true causation of injury by reperfusion. However, with the recognition of the postconditioning phenomenon—i.e., the reduction in infarct size resulting from several cycles of brief reocclusion and reperfusion of a coronary artery during the early moments of reperfusion after a prolonged coronary occlusion—it is now unequivocally clear that reperfusion per se causes irreversible injury and contributes to infarct size. Such reperfusion injury affects not only the cardiomyocytes, but also the coronary microcirculation such that myocardial infarction and coronary “no-reflow” are closely associated in reperfused myocardial infarction. The amount of reperfusion injury largely depends on the duration of the preceding ischemia and displays a typical maximum (Figure 1). Both ischemia and reperfu-
of transcription 3 [STAT3]). These signal transduction cascades converge at the mitochondria, activate mitochondrial adenosine triphosphate (ATP)-dependent potassium channels, which interact with mitochondrial connexin 43, and ultimately inhibit mitochondrial permeability transition pore opening. It is still unclear what mediator(s) transfers the cardioprotective signal from an ischemic/reperfused limb or parenchymal organ to the heart; however, neuronal and humoral mediators, including nitrite, stromal-derived factor-1, and microRNA 144 have been proposed. Reperfusion injury is also attenuated through gentle, as opposed to abrupt, reperfusion—ie, with reduced perfusion pressure or slow restoration of coronary blood flow. Finally, there are a number of drugs that engage parts of the signal transduction pathways of the mechanical conditioning strategies and reduce infarct size; examples include cyclosporine A, enantiatide, and metoprolol, each of which have reduced infarct size in proof-of-concept clinical trials. In pig experiments, the selective heart rate–reducing agent ivabradine also reduced infarct size even when given only shortly before reperfusion. The ischemia/reperfusion-induced coronary microvascular injury, manifesting as edema and microvascular obstruction during reperfusion, is multifactorial in origin. Each of the following contribute: embolization of particulate atherosclerotic debris from the epicardial culprit lesion, aggregation of platelets and of platelets/leukocytes, intense vasoconstriction in response to mediators released from the culprit vessel, extravascular coronary compression by the edema, and physical destruction of the capillaries with luminal obstruction. Ischemic pre- and postconditioning not only reduce infarct size, but also attenuate the damage to the coronary microcirculation such that myocardial edema is reduced. Cardiomyocyte necrosis/myocardial infarction is closely related to coronary microvascular injury, but microvascular injury is probably not causal for infarction.

The ugly: stunning and reperfusion arrhythmias

Even myocardial ischemia without irreversible injury leaves the myocardium stunned, ie, in a state of fully, but only slowly, reversible contractile dysfunction. The pathomechanisms of stunning involve excess reactive oxygen species formation and calcium overload which, in close interaction, impair excitation-contraction coupling and, ultimately, contractile function. Acute stunning per se rarely causes clinical problems; it predominantly affects diastolic left ventricular function and is probably more paradigmatic than clinically important. However, long-term repetitive stunning causes hibernation, ie, a persistent state of contractile dysfunction, but with preserved viability such that contractile dysfunction is reversible upon eventual revascularization. Hibernating myocardium has molecular and morphological features of both adaptation and degeneration. Reperfusion arrhythmias are frequently observed, but only rarely are a clinical problem.

REFERENCES


Mechanical interventions to reduce myocardial infarct size

Michael Rahbek Schmidt, MD, PhD; Nichlas Riise Jespersen, MD; Hans Erik Bøtker, MD, PhD, DMSc
Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark

Correspondence: Professor Hans Erik Bøtker, Aarhus University Hospital, Department of Cardiology, Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark
E-mail: heb@dadlnet.dk

Abstract
Myocardial infarction is a major cause of death and disability worldwide, and myocardial infarct size is a principal determinant of outcome. Although early and successful restoration of myocardial reperfusion after an ischemic event is the most effective strategy to reduce infarct size and improve clinical outcome, reperfusion may itself induce further myocardial damage. Mechanical interventions may limit myocardial ischemia-reperfusion injury beyond opening of the coronary artery. Several types of mechanical intervention have had cardioprotective effects in experimental studies, but few have reduced infarct size in clinical trials to a convincing degree. Remote ischemic conditioning by three or four 5-minute inflations of a blood pressure cuff interrupted by 5 minutes of reperfusion has repeatedly been shown to reduce myocardial injury in patients admitted with myocardial infarction. Similarly, intravascular cooling by infusion of cold saline has been shown to afford some protection against myocardial ischemia-reperfusion injury. Both interventions can be carried out during transport to hospital for patients with acute myocardial infarction and may provide a prognostic benefit in this group of patients. Heart Metab. 2016;70:8-13

Keywords: ischemic preconditioning; myocardial infarction; reperfusion injury

Myocardial infarction is a leading cause of death in its acute phase, but the long-term morbidity and mortality are also alarmingly high. The frequency and severity of the most detrimental early and late consequences of a myocardial infarction—heart failure and arrhythmia—are directly related to the extent of tissue death resulting from the index infarction.

While early and successful restoration of blood flow is the most effective strategy to reduce tissue injury and improve clinical outcome, the return of oxygenated blood into oxygen-deprived tissue during restoration of blood flow paradoxically induces further tissue damage by reperfusion injury, which is the tissue damage that occurs when blood supply returns to the tissue after a period of ischemia or lack of oxygen. The absence of oxygen and nutrients from blood during the ischemic period creates a condition in which restoration of circulation results in inflammation and oxidative damage through the induction of oxidative stress rather than immediate restoration of normal function. Reperfusion injury may be responsible for up to 35%
Mechanical interventions to reduce myocardial infarct size

of the final infarct size. The shorter ischemia duration achieved with today’s fast transfer to acute cardiac units, acute balloon angioplasty (primary percutaneous coronary intervention [PCI]) with stent implantation, and up-to-date antithrombotic pharmacological therapy has reduced immediate mortality dramatically. Still, morbidity, in particular due to postinfarction heart failure, remains unexpectedly high. Consequently, the focus in myocardial infarction treatment has now been directed toward reducing the reperfusion injury.

The term cardioprotection refers to interventions aimed at limiting the combined ischemia-reperfusion injury. Traditionally, cardioprotective strategies have been divided into pharmacological or mechanical ones, although recent evidence suggests that there is substantial overlap in the biological effects of the two. The current article focuses on mechanical cardioprotection, which covers all nonpharmacological interventions, spanning exercise to cutaneous electrostimulation and on to cooling and various concepts of ischemic conditioning. Below, we primarily focus on modalities with extensive experimental and clinical evidence of effect (Figure 1).

Local ischemic pre- and postconditioning

The best known and most extensively investigated mechanical method to induce cardioprotection is “training” the myocardium to withstand longer-lasting ischemia by exposing it to brief and nonlethal episodes of ischemia—local ischemic preconditioning. Local ischemic preconditioning has long been known to afford potent protection against ischemia-reperfusion injury, but the technique has inherent limitations, as it requires interruption of blood flow to the target organ and, thus, can be achieved only in the operating room or during coronary angioplasty. Furthermore, in unpredictable ischemia, such as acute myocardial infarction, local ischemic preconditioning is not feasible for obvious reasons and has not found widespread clinical use.

However, by applying the local ischemic conditioning stimulus after the ischemic event (eg, at the time of reperfusion in primary PCI)—so-called ischemic postconditioning—most of these obstacles for clinical use are overcome. In experimental models, ischemic postconditioning inhibits ischemia-reperfusion injury almost as effectively as ischemic preconditioning. Some clinical studies suggest that local ischemic postconditioning reduces myocardial injury in patients undergoing primary PCI for acute myocardial infarction, but another recently published trial could not confirm this effect. Furthermore, two large-scale trials failed to show any effect on myocardial reperfusion and clinical end points. These two trials each included approximately 700 patients admitted with ST-segment elevation myocardial infarction (STEMI) randomized to either standard primary PCI or primary PCI followed by postconditioning, with one of the trials including a third group with a combination

Abbreviations

CHILL-MI: Efficacy of Endovascular Catheter Cooling Combined With Cold Saline for the Treatment of Acute Myocardial Infarction (trial); CONDI2/ERIC-PPCI: Effect of Remote Ischemic Conditioning on Clinical Outcomes in STEMI Patients Undergoing PPCI (trial); PCI: percutaneous coronary intervention; RAPID MI-ICE: Rapid Intravascular Cooling in Myocardial Infarction as Adjuvant to Percutaneous Coronary Intervention; RIC: remote ischemic conditioning; STEMI: ST-segment elevation myocardial infarction
of remote ischemic conditioning (RIC) and postconditioning in addition to primary PCI.⁷

**Remote ischemic conditioning**

Based on the original groundbreaking observation of local ischemic preconditioning, the concept of conditioning the myocardium from afar (remote ischemic conditioning, RIC) was developed through a series of increasingly clinically applicable techniques culminating in the presently used concept of achieving organ protection by inducing brief episodes of limb ischemia⁸ with a blood-pressure cuff.

From the site of the remote stimulus, through humoral and neuronal pathways, RIC activates several protective mechanisms in the target organ similar to those activated by local preconditioning. Furthermore, RIC modifies the systemic inflammatory response and prevents endothelial dysfunction⁸ and platelet activation⁹ after ischemia-reperfusion injury.

The simple and noninvasive nature of RIC has facilitated its translation into clinical use. Since the first demonstration of its effect in humans in 2002,⁸ multiple randomized clinical trials have shown that RIC affords cardioprotection in patients admitted with acute myocardial infarction treated by either primary PCI¹⁰-¹² or thrombolysis¹³ (Table I). Moreover, a recent follow-up study by Sloth et al suggested that the reduced myocardial injury achieved by RIC treatment in the ambulance during transport to hospital of STEMI patients admitted for primary PCI may translate into improved clinical outcome.¹⁴ Although experimental evidence indicates that risk factors and comorbidity modify the efficacy of RIC, only minor attenuation by smoking and left ventricular hypertrophy has been demonstrated in the clinical use of RIC.¹⁵

To date, RIC is the most extensively investigated mechanical means to achieve cardioprotection and is the intervention showing the most consistent benefit. A large-scale clinical trial (COND2/ERIC-PPCI [Effect of Remote Ischemic Conditioning on Clinical Outcomes in STEMI Patients Undergoing PCI]) is currently investigating whether RIC provides clinical benefit to patients admitted with myocardial infarction.

**Cooling**

Moderate hypothermia induced prior to reperfusion may reduce infarct size in animal models.¹⁶ Important prerequisites include a systemic rather than regional hypothermia and a target core temperature below 35°C achieved before onset of reperfusion.¹⁷ A clinical pilot study has suggested that patients admitted with anterior STEMI and who are rapidly cooled to a body temperature below 35°C by the combination of cold saline infusion together with an endovascular cooling catheter before primary PCI develop smaller infarcts.¹⁸

The CHILL-MI study (Efficacy of Endovascular Catheter Cooling Combined With Cold Saline for the Treatment of Acute Myocardial Infarction), using a similar cooling technique as in the initial pilot study, showed that while cooling did not have an overall cardioprotective effect, it seems to reduce infarct size in patients with anterior STEMI admitted for primary PCI within 4 hours of symptom onset. In addition, cooling caused a significant reduction in heart failure events.¹⁹ Possible explanations for an overall lack of cardioprotective effect in the CHILL-MI study are a borderline statistical power and that cooling below 35°C was not achieved in all patients. Consequently, recent studies have targeted optimizing methods for fast and reliable temperature reduction.

Even with the currently applied methods, cooling may be beneficial, as a prespecified pooled analysis of another cooling study—RAPID MI-ICE (Rapid Intravascular Cooling in Myocardial Infarction as Adjunctive to Percutaneous Coronary Intervention)—and CHILL-MI indicated a reduction in myocardial infarct size and a reduction in heart failure with endovascular cooling in patients admitted with STEMI for primary PCI, predominantly in patients with a large area of myocardium at risk.²⁰

**Exercise**

Several preclinical and clinical studies have shown that exercise induces cardioprotection. Its relevance is limited in the setting of acute myocardial infarction. It is of interest, however, that mechanisms between RIC and exercise are overlapping. Both RIC and exercise induce dialyzable, bloodborne protection that can be abrogated by opioid receptor blockade (naloxone).²¹ Of note, RIC may also increase exercise capacity as shown in highly trained athletes, a concept that may have relevance in patients with post-infarction heart failure.²²
Effects of mechanical interventions on myocardial metabolism

The metabolic changes occurring in the myocardium during and after acute ischemia are described in a separate article in the current issue of *Heart and Metabolism*. Worth mentioning here is the interesting observation that mechanical cardioprotection interventions seem at least in part to exert their cardioprotective effects by activating intracellular signaling pathways, including the endothelial nitric oxide synthase (eNOS)-related system—which is recruited immediately by adenosine, bradykinin, and opioids—the reperfusion injury salvage kinase (RISK) pathway, and

Remote ischemic conditioning

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients (control/RIC)</th>
<th>RIC regimen</th>
<th>End point</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bøtker et al, 10 2010</td>
<td>69/73</td>
<td>Upper limb 4 cycles I/R (5/5 min)</td>
<td>Salvage index (SPECT)</td>
<td>20% increase in salvage index</td>
</tr>
<tr>
<td>Munk et al, 21 2010</td>
<td>110/108</td>
<td>Upper limb 4 cycles I/R (5/5 min)</td>
<td>LVEF at 30 days</td>
<td>5% increase in LVEF in anterior infarcts</td>
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<tr>
<td>Rentoukas et al, 22 2010</td>
<td>30/33</td>
<td>Upper limb 3 cycles I/R (5/5 min)</td>
<td>ST-segment resolution</td>
<td>20% increase in proportion of patients achieving full ST-segment resolution</td>
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<tr>
<td>Crimi et al, 23 2013</td>
<td>50/50</td>
<td>Lower limb 3 cycles I/R (5/5 min)</td>
<td>CK-MB (AUC 72 h after PCI)</td>
<td>20% reduction in CK-MB release</td>
</tr>
<tr>
<td>Prunier et al, 24 2014</td>
<td>17/18</td>
<td>Upper limb 4 cycles I/R (5/5 min)</td>
<td>CK-MB (AUC 72 h after PCI)</td>
<td>31% reduction in CK-MB release</td>
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<tr>
<td>Sloth et al, 14 2014</td>
<td>167/166</td>
<td>Upper limb 4 cycles I/R (5/5 min)</td>
<td>MACCE at 4 y</td>
<td>12% reduction in MACCE</td>
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<tr>
<td>Yellon et al, 13 2015</td>
<td>260/260</td>
<td>Upper limb 4 cycles I/R (5/5 min)</td>
<td>TnT (AUC 24 h after PCI)</td>
<td>17% reduction in TnT release</td>
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<tr>
<td>Eitel et al, 7 2015</td>
<td>232/232</td>
<td>Upper limb 3 cycles I/R (5/5 min) + local postC</td>
<td>Salvage index (MRI)</td>
<td>23% increase in salvage index</td>
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<tr>
<td>White et al, 26 2015</td>
<td>40/43</td>
<td>Upper limb 4 cycles I/R (5/5 min)</td>
<td>Myocardial edema (MRI)</td>
<td>27% reduction in myocardial edema</td>
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Ischemic postconditioning

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<th>PostC regimen</th>
<th>End point</th>
<th>Outcome</th>
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<tr>
<td>Staat et al, 3 2005</td>
<td>14/16</td>
<td>60 s x 4</td>
<td>CK (AUC 72 h)</td>
<td>36% decrease in CK</td>
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<tr>
<td>Sörensson et al, 27 2010</td>
<td>38/38</td>
<td>60 s x 4</td>
<td>CK (AUC 72 h)</td>
<td>No statistically significant effect</td>
</tr>
<tr>
<td>Lønborg et al, 4 2010</td>
<td>59/59</td>
<td>30 s x 4</td>
<td>Infarct size (MRI)</td>
<td>31% increase in salvage ratio</td>
</tr>
<tr>
<td>Freixa et al, 5 2012</td>
<td>40/38</td>
<td>60 s x 4</td>
<td>Infarct size (MRI)</td>
<td>No statistically significant effect</td>
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<tr>
<td>Hahn et al, 6 2013</td>
<td>350/350</td>
<td>60 s x 4</td>
<td>ST-segment resolution</td>
<td>No statistically significant effect</td>
</tr>
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Cooling

<table>
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<tr>
<th>Study</th>
<th>No. of patients (control/cooling)</th>
<th>Cooling regimen</th>
<th>End point</th>
<th>Outcome</th>
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<tr>
<td>Dixon et al, 28 2002</td>
<td>21/21</td>
<td>Endovascular cooling</td>
<td>Infarct size (MRI)</td>
<td>No statistically significant effect</td>
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<tr>
<td>Erlinge et al, 19 2014</td>
<td>59/61</td>
<td>IV cold saline</td>
<td>Infarct size (MRI)</td>
<td>No statistically significant effect</td>
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<tr>
<td>Erlinge et al, 20 2015</td>
<td>69/71</td>
<td>IV cold saline</td>
<td>Infarct size (MRI)</td>
<td>15% reduction in infarct size / area at risk</td>
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<td>Nichol et al, 29 2015</td>
<td>26/28</td>
<td>Peritoneal cold saline</td>
<td>Infarct size (MRI)</td>
<td>No statistically significant effect</td>
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Table I Major studies of the effect of mechanical conditioning in patients with acute myocardial infarction admitted for primary percutaneous coronary intervention.

Abbreviations: AUC, area under the curve; CK-MB, creatine kinase MB; I/R, ischemia/reperfusion; IV, intravenous; LVEF, left ventricular ejection fraction; MACCE, major adverse cardiac and cerebrovascular event; MRI, magnetic resonance imaging; PCI, percutaneous coronary intervention; postC, postconditioning; RIC, remote ischemic conditioning; SPECT, single-photon emission computed tomography; TnT, troponin T.
the survivor activating factor enhancement (SAFE) pathway. These pathways ultimately converge at the mitochondrial level to modify mitochondrial function. Some evidence suggests that a temporary downregulation of mitochondrial function during initial reperfusion—including not only reduced respiration, but also reduced glycolytic flux—is associated with a subsequently improved mitochondrial respiration and a reduced reactive oxygen species formation. However, the exact interplay between modification of cytosol signaling pathways and simultaneous changes in mitochondrial function has yet to be integrated into a comprehensive scheme. Similarly, the causal relation to metabolic changes associated with mechanically induced cardioprotection is unknown. After the initial activation of anaerobic glycolysis with lactate production, persistent ischemia inhibits both glycolysis and glycolgenolysis. Conditioning strategies accentuate this inhibition and also enhance posts ischemic glycogen resynthesis. A cardioprotective effect of the inhibited glycolysis by local ischemic preconditioning of hearts has been attributed to a reduction in ischemic tissue acidosis. Our previous finding that inhibition of the malate-aspartate shuttle reduces myocardial lactate accumulation during ischemia and tracer-estimated glycolytic flux during reperfusion to the same extent as classical ischemic preconditioning uncovers a potential underlying metabolic mechanism of cardioprotection that is also in accordance with an initial downregulation of mitochondrial function during initial reperfusion.30

Conclusion

A wide array of mechanical interventions to reduce myocardial infarct size have shown consistent effects in experimental models, but so far only cooling and remote ischemic conditioning have shown convincing reduction in infarct size in a clinical setting. Currently, large trials are underway to elucidate the effect of RIC and cooling on clinical outcome in patients admitted with myocardial infarction. MRS and HEB are shareholders in CellAegis Devices.

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Mechanical interventions to reduce myocardial infarct size


How to measure myocardial infarct size by cardiac magnetic resonance imaging

David Corcoran, BMedSci MRCP; Colin Berry, PhD, FACC, FESC, FRCPI
1BHF Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow
2Golden Jubilee National Hospital, Clydebank, UK

Correspondence: Professor Colin Berry, BHF Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, 126 University Place, University of Glasgow, Glasgow, G12 8TA, Scotland, UK
E-mail: colin.berry@glasgow.ac.uk

Abstract
In survivors of acute myocardial infarction (MI), the initial size of infarction is associated with long-term prognosis. This article addresses the role of contrast-enhanced cardiac magnetic resonance (CMR) imaging in determining the presence and extent of MI. Contrast-enhanced CMR is widely accepted as the reference method for imaging infarct size. The principles involved in contrast-enhanced CMR imaging of MI will be considered, including pathophysiology, gadolinium contrast kinetics, and imaging methods. The different approaches to measuring infarct size with CMR will also be discussed. Heart Metab. 2016;70:14-18

Keywords: acute myocardial infarction; CMR imaging; infarct size

Introduction
In survivors of acute myocardial infarction (MI), the initial size of infarction is associated with long-term prognosis.1-4 Myocardial infarct size can be assessed noninvasively with different methods, including measurement of cardiac biomarkers (e.g., troponin), electrocardiography, nuclear imaging, and contrast-enhanced cardiac magnetic resonance (CMR) imaging.5,6 Each of these methods have strengths and limitations; however, contrast-enhanced CMR is widely accepted as the reference method for imaging infarct size. In this article, the use of CMR to measure infarct size will be considered.

CMR for assessment of infarct size: an overview of general principles
Gadolinium chelates are extracellular contrast agents. After intravenous administration of gadolinium, the contrast agent perfuses locally through myocardium and diffuses within the interstitial compartment. In the presence of infarct tissue, the gadolinium distribution volume is increased due to the degradation of cardiac cells; the wash-in, wash-out kinetics are disturbed, and gadolinium persists within the infarct zone for a longer period of time and is revealed by a hyperintense (bright) area on T1-weighted imaging.7-10 The regional retention of gadolinium spatially reflects the
Measuring myocardial infarct size by CMR imaging

**Abbreviations**

CMR: cardiac magnetic resonance; LGE: late gadolinium enhancement; MI: myocardial infarction; MVO: microvascular obstruction; OAT: Otsu-Auto-Threshold; ROI: region of interest; SD: standard deviation; STEMI: ST-segment elevation myocardial infarction; FWHM: full width at half maximum

territory of infarct tissue fibrosis at the near-cellular level. Inversion-recovery T1-weighted methods allow optimized signal and contrast and are used in clinical practice.

**Acquisition**

A CMR scan should be conducted by appropriately trained staff in line with contemporary standardized protocols. Infarct imaging with contrast-enhanced CMR involves a wide-bore clinical scanner, typically 1.5 or 3.0 Tesla, a phased-array chest surface coil, and retrospective electrocardiogram gating. Infarct tissue is revealed by late gadolinium enhancement (LGE) imaging. The method typically involves breath-hold inversion recovery imaging 10 to 15 minutes after intravenous administration of a gadolinium-based contrast agent (0.10-0.20 mmol/kg). Scans of the entire left ventricle should be acquired sequentially with short-axis slice positions and also with orthogonal long-axis positions. The slice positions should be spatially registered with other acquisitions for mass, function, and tissue characterization. If breath-holding is poor, then a “single-shot” acquisition method may be preferred. In order to ensure that uninjured myocardium appears black, the inversion times should be individually adjusted to optimize nulling of apparently normal myocardium (typical values, 200-300 ms). In order to rule out the possibility of artefact, scans should be repeated with “phase swops.”

**Timing after acute MI**

Infarct size changes progressively after acute MI. Initially, infarct tissue is expanded because of edema, inflammatory-cell infiltrates, and hemorrhage. As healing progresses, these acute infarct pathologies resolve and are replaced with collagen scar tissue such that the size of infarction diminishes with time. CMR with LGE can track these changes because gadolinium is an extracellular contrast agent. Due to these changes over time, the size of infarction as revealed by LGE within the first week after an acute MI may overestimate the actual size of infarction; LGE may more closely approximate infarct size in the following days and weeks as injured tissue is replaced by collagen scar tissue.

The prognostic value of infarct size revealed by contrast-enhanced CMR may vary over time from the index event. A multivariable analysis carried out by Lønborg et al showed that—beyond other clinical parameters of the severity of MI, including peak troponin T concentration—final infarct size measured at 3 months was associated with all-cause mortality and heart failure hospitalization.

**Measurement of infarct size with CMR**

LGE images should be analyzed by observers who have been trained to use software that is appropriate for measurement of infarct size.

Where feasible, the presence of acute infarction should be established on the basis of abnormalities in cine wall motion, resting first-pass myocardial perfusion, and LGE imaging. If LGE imaging is used, the presence of acute infarction should be confirmed on both the axial and long-axis acquisitions. The epicardial and endocardial borders of the ventricle should be delineated by manual or semiautomated methods. The papillary muscles, trabeculae, and blood pool should be excluded from these contours. The apical short-axis slice may be excluded to rule out partial volume effects.

The myocardial mass of late gadolinium (grams) can be quantified with computer-assisted planimetry, and the approach to image analysis may be user-defined (ie, manual) or fully automated.

**Methods for estimation of infarct size**

Delineation of the infarct territory involves identifying the border of the bright infarct zone, distinguished from the lower signal intensity of neighboring unaffected tissue and the remote zone. The main approaches include manual delineation based on visual assessment, determination of the “full width at half maximum” (FWHM), use of the Otsu-Auto-Threshold (OAT) method, thresholding from the remote zone (eg, based on >5 standard deviations [SDs]),...
and automated methods. An example of how the estimated extent of infarction may differ between methods is shown in Figure 1. Comparative studies of these methods have recently been performed.

**Infarct border delineation based on thresholding (threshold set to a >5-SD difference in signal intensity versus remote-zone signal intensity)**

For infarct-size delineation based on a greater than 5-SD difference in mean signal intensity in the infarct zone versus the remote zone, a region of interest (ROI) should be manually inserted within apparently unaffected myocardium in an area distant from the infarct zone, and the area of hyperenhancement calculated as the territory defined by a signal intensity more than 5 SDs above the mean within the ROI. The size of the remote-zone ROI should be large enough to be representative; in general, a 2.0-cm² ROI is considered to be representative.

**Full width at half maximum**

The FWHM technique defines the threshold for boundary delineation as half the maximal signal within the scar. An ROI should be drawn manually in the infarct zone (taking care not to involve the dark core of microvascular obstruction [MVO], if present); hyperenhancement is then calculated as pixels where signal intensity is greater than 50% of the automatically determined maximum signal intensity in the infarct zone. The FWHM method is unaffected by ROI size as it selects the threshold based on the single pixel with highest signal intensity.

**Otsu-Auto-Threshold**

OAT automatically identifies hyperenhanced areas and has minimal user dependence. The OAT method involves automatic calculation of the signal-intensity threshold for each slice by dividing the signal-intensity histogram in each slice into two groups (enhanced, normal) according to the signal-intensity threshold that gives the least variance (lowest sum of variances) and, thus, the most homogeneity of signal intensities within each group. Endo- and epicardial contours are user defined, as is manual correction of noise artifact. OAT does not involve ROIs and so is more user independent than other approaches.

**Overview of diagnostic performance**

Flett et al demonstrated that infarct size may be reliably delineated using thresholding greater than 5-SD...
SDs above a remote reference region and expressed as a percentage of total left ventricular mass. Use of a 2-SD threshold approach leads to an overestimation of infarct size, whereas the FWHM approach has good reproducibility.

McAlindon et al. measured infarct size repeatedly in 40 patients with recent ST-segment elevation MI (STEMI). They found that the manual and FWHM methods were associated with the lowest inter- and intraobserver variability for infarct size, with similar findings for interscan variability. Khan et al. assessed infarct size in 10 STEMI patients repeatedly at 1.5- and 3.0-Tesla field strengths. They found that the FWHM method was accurate and reproducible, whereas the threshold approach (5 SD) and OAT methods overestimated infarct size at both field strengths. Vermes et al. assessed 28 patients with acute MI and found no differences between the OAT and the 5-SD threshold methods.

One of the main limitations of these analyses is the lack of reference data for measurement of the absolute amount of infarct tissue. Experimental studies have shown that infarct size can be estimated with laboratory techniques such as tissue staining with the colorless dye triphenyltetrazolium chloride (TTC). With this dye, the area of dead cells will appear pale, and viable cells—which retain NADH—will be red, due to a color change in the dye when reduced by dehydrogenases.

Microvascular obstruction

MVO revealed by contrast-enhanced CMR represents failure of the intravenous contrast agent to penetrate within the infarct core. Infract regions with evidence of MVO are usually included within the infarct area, and the area of MVO can be separately assessed and expressed as a percentage of total left ventricular mass. MVO occurs in about 40%-50% of STEMI survivors and is a prognostically important complication. Noncontrast T1-mapping has emerging potential for imaging MVO with comparable prognostic significance to contrast-enhanced CMR.

Infarct size and myocardial salvage

In survivors of acute MI, the amount of salvageable myocardium is represented by the amount of ischemically jeopardized tissue that is amenable to recovery. Myocardial salvage can be calculated by subtraction of percent infarct size from percent area at risk, as revealed by T2-weighted edema imaging.

Myocardial viability

The extent of LGE is a measure of the extent of viable myocardium after MI and predicts the potential for recovery after coronary revascularization. CMR has a Class 1A guideline recommendation for assessing ischemia and viability in STEMI survivors who have multivessel coronary disease.

Conclusion

Contrast-enhanced CMR is widely accepted as the reference method for imaging infarct size and pathology. Because of acute tissue injury and swelling, the initial size of infarction revealed by CMR in the first week after STEMI overestimates actual (final) infarct size. A threshold approach based on a 5-SD difference in signal intensity versus the remote-zone signal intensity and the FWHM method have the best diagnostic performance overall.

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

Thomas Bochaton, MD; François Derimay, MD; Michel Ovize, MD, PhD
Louis Pradel Hospital, Cardiovascular Functional Exploration Service, Clinical Investigation Center & UMR1060 (CarMeN), Claude Bernard University Lyon 1, Lyon, France

Correspondence: Michel Ovize, MD, PhD, Louis Pradel Hospital, Cardiovascular Functional Exploration Service, 59 Bd Pinel, Bron 69394, France
E-mail: michel.ovize@chu-lyon.fr

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% successful reperfusion and optimal pharmacological treatments. Although there is not much room to further reduce door-to-balloon time in PCI, the two following major goals, if reached, should...
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 P2Y12 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 MI-TOCARE 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-
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. 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 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 postischemic 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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The cardioprotective effects of trimetazidine

Petr Widimsky, MD, DrSc, FESC, FACC
Cardiocenter, Third Faculty of Medicine, Charles University Prague, Czech Republic

Correspondence: Petr Widimsky, MD, DrSc, FESC, FACC, Srobarova 50, 100 34 Praha 10, Czech Republic
E-mail: petr.widimsky@fnkv.cz

Abstract
This review summarizes the available evidence on the cardioprotective effects of trimetazidine, focusing on clinical studies in a large spectrum of patients, including those with stable angina pectoris, acute myocardial infarction, ischemic cardiomyopathy, heart failure, and those undergoing percutaneous coronary intervention. The cardioprotective effects of trimetazidine have been proven both in experimental and in clinical studies. However, the evidence for a more robust clinical benefit (hard endpoints) is still awaited. Heart Metab. 2016;70:24-27

Keywords: angina; cardioprotection; trimetazidine

Introduction – trimetazidine’s mechanism of action

Trimetazidine was described almost 50 years ago as the first cytoprotective anti-ischemic metabolic agent; it improves myocardial glucose utilization through inhibition of fatty acid metabolism. Trimetazidine inhibits $\beta$-oxidation of fatty acids by blocking long-chain 3-ketoacyl-coenzyme A thiolase (LC 3-KAT), which enhances glucose oxidation. In an ischemic cell, energy obtained during glucose oxidation requires less oxygen consumption than would the $\beta$-oxidation process. Potentiation of glucose oxidation optimizes cellular energy processes, thereby maintaining proper energy metabolism during ischemia. By preserving energy metabolism in cells exposed to hypoxia or ischemia, trimetazidine prevents a decrease in intracellular adenosine triphosphate (ATP) levels, thereby ensuring the proper functioning of ionic pumps and transmembrane sodium-potassium flow while maintaining cellular homeostasis.

One study evaluated the direct cardioprotective effect of trimetazidine on isolated rat cardiomyocytes. Pretreatment of ventricular myocytes with trimetazidine increased cell resistance to hypoxic stress. The authors concluded that this cytoprotective effect was not mediated through an antioxidant activity, but rather can be related to a modification in lipid metabolism. Another experimental study investigated whether trimetazidine reduces the ionic imbalance induced by ischemia and reperfusion. During low-flow ischemia, the major effect of trimetazidine was a significant reduction in intracellular acidosis, whereas during total ischemia, the main effect of trimetazidine was a significant reduction in sodium gain. Trimetazidine-induced attenuation of ionic imbalance was associated with a significantly improved recovery of ventricular function on reperfusion, as assessed by a lower increase in diastolic pressure and an increased recovery of developed pressure. These data provided evidence that specific myocardial metabolic modula-
tation plays a significant role in reducing ionic imbalance during ischemia and reperfusion.\textsuperscript{2} Kantor et al analyzed the effects of trimetazidine on fatty acid and glucose metabolism in isolated working rat hearts and on the activities of various enzymes involved in fatty acid oxidation. This study confirmed that the antianginal effects of trimetazidine occur due to an inhibition of LC 3-KAT activity, resulting in a reduction in fatty acid oxidation and a stimulation of glucose oxidation.\textsuperscript{3} Macllnnes et al found that trimetazidine and ranolazine improved ischemic cardiac function.\textsuperscript{4} Another study demonstrated that trimetazidine inhibition of LC 3-KAT decreases fatty acid oxidation and stimulates glucose oxidation, resulting in an improvement in cardiac function and efficiency after ischemia.\textsuperscript{5} Recently, trimetazidine pretreatment was found to inhibit microembolization-induced myocardial apoptosis and improve cardiac function. The cardioprotective effect appeared to be mediated by the blockade of the mitochondrial apoptotic pathway.\textsuperscript{6}

Clinical studies with trimetazidine

The first report on the use of trimetazidine for the treatment of angina pectoris was published in 1967.\textsuperscript{7} Trimetazidine has been shown to have an antianginal effect, increasing exercise capability without producing any significant change in heart rate or systolic blood pressure.

Two studies compared the effects of trimetazidine with two established antianginals drugs. Dalla-Volta et al compared trimetazidine efficiency with that of nifedipine in 39 male patients with effort angina. The number of weekly angina attacks and the results of exercise testing did not differ between trimetazidine and nifedipine groups.\textsuperscript{8} Detry et al compared the effects of trimetazidine with propranolol in a double-blind, parallel-group, multicenter study in patients with stable angina and positive exercise test (typical anginal pain with ST-segment depression of ≥1 mm and horizontal or downward-sloping extension of the ST segment for ≥80 ms after the J point; or ST-segment depression ≥ 3 mm and no anginal pain). After 3 months, similar antianginal efficacy and similar exercise duration were observed between the trimetazidine and propranolol groups. With both drugs, there was a trend toward decreased ischemic episodes in patients who experienced ambulatory ischemia as assessed by Holter monitoring. The results suggested that trimetazidine and propranolol have similar efficacy in patients with stable angina pectoris.\textsuperscript{9} Patients with stable angina had a clinically important improvement after combination treatment with diltiazem and trimetazidine, without adverse hemodynamic events or increased side effects.\textsuperscript{10}

The largest of similar studies, a randomized, multicenter, double-blind trial assessed the anti-ischemic efficacy and tolerability of trimetazidine in combination with metoprolol among 426 patients with stable, effort-induced angina and documented coronary artery disease. After 12 weeks, there were significantly greater improvements in the metoprolol-plus-trimetazidine group than in the metoprolol-plus-placebo group in the following: time to 1-mm ST-segment depression, total workload, time to onset of angina, maximum ST-segment depression, mean weekly number of angina attacks, mean weekly nitrate consumption, and grade of anginal pain. The tolerability of trimetazidine was excellent.\textsuperscript{11}

A small randomized, double-blind study analyzed the effects of trimetazidine on the severity of myocardial ischemia during balloon angioplasty of the left anterior descending coronary artery. Trimetazidine decreased the maximum ST-segment shift and delayed its onset. Placebo had no effect on these parameters. These results support the hypothesis that trimetazidine has a direct anti-ischemic effect on human myocardial cells.\textsuperscript{12}

The largest trial with trimetazidine was EMIP-FR (European Myocardial Infarction Project - Free Radicals\textsuperscript{13}). This prospective, double-blind trial randomized 19,725 patients with acute myocardial infarction to intravenous trimetazidine or placebo. No difference was found between trimetazidine and placebo for the main end point, 35-day (short-term) mortality. Patients undergoing thrombolytic therapy showed a tendency toward a higher short-term death rate with trimetaz-
dine than with placebo (trimetazidine, 11.3%; placebo, 10.5%; P=0.15); those not receiving thrombolytic therapy demonstrated the opposite trend (trimetazidine, 14.0%; placebo, 15.1%; P=0.14).

The long-term (2-year) effect of trimetazidine on myocardial perfusion (assessed by gated single-photon emission computerized tomography [SPECT]) was investigated in 200 patients with ischemic left ventricular dysfunction and multivessel coronary artery disease. The frequency of anginal episodes per week was lower in the trimetazidine group than in the placebo group (3.9 vs 5.7; P<0.01). With trimetazidine treatment, the duration of peak exercise increased significantly over baseline values.14

Fragasso et al analyzed the effects of trimetazidine on cardiac phosphocreatine (PCr) and ATP ratio in 12 patients with heart failure by means of 31P-magnetic resonance spectroscopy. Patients were randomized in a double-blind, crossover study to placebo or trimetazidine for two periods of 90 days. At the end of each period, all patients underwent exercise testing, echocardiography, and magnetic resonance spectroscopy. On trimetazidine, New York Heart Association (NYHA) class decreased, whereas ejection fraction and metabolic equivalents (METS) increased. The mean cardiac PCr/ATP ratio was increased by 33% with trimetazidine. Trimetazidine improved functional class and left ventricular function in patients with heart failure. These effects were associated with the observed trimetazidine-induced increase in the PCr/ATP ratio, indicating preservation of the myocardial high-energy phosphate levels.15

A single-center, prospective, randomized study evaluated the effect of preprocedural oral trimetazidine on percutaneous coronary intervention (PCI)-induced myocardial injury in 266 patients with stable angina pectoris and single-vessel disease who were randomly assigned to two groups. Cardiac troponin I (cTnI) levels were measured before and 6, 12, 18, and 24 hours after PCI. Postprocedural cTnI levels were significantly reduced at all time points and the total amount of cTnI released after PCI (calculated as the area under the curve) was significantly reduced in the trimetazidine group.16

Di Napoli et al investigated the effects of trimetazidine on exercise tolerance and on plasma levels of B-type natriuretic peptide (BNP) and cardiac troponin T (cTnT) in 50 patients with ischemic cardiomyopathy who were randomized to receive trimetazidine or placebo. After 6 months, left ventricular ejection fraction and NYHA class did not change in patients of either group. However, in the trimetazidine group, a significant increase in exercise tolerance was detected (6-minute walking test), BNP and cTnT were significantly reduced during trimetazidine treatment.17

Finally, a recent retrospective cohort study evaluated the long-term effect of trimetazidine on morbidity and mortality in 669 patients with chronic heart failure (CHF); 362 patients were on trimetazidine due to symptom persistence despite uptitration of optimal CHF therapy, whereas the remaining patients continued conventional CHF therapy alone. Trimetazidine improved global survival and reduced the hospitalization rate for cardiovascular causes.18

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<tr>
<th>Study</th>
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<td>Stable angina</td>
<td>TMZ not different from nifedipine.</td>
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<td>Detry et al.1994</td>
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<td>TMZ not different from propranolol.</td>
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<tr>
<td>Di Napoli et al.2007</td>
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<td>TMZ improved exercise tolerance and reduced BNP and troponin T levels. No effect on LVEF and on NYHA class.</td>
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<tr>
<td>Fragasso et al.2013</td>
<td>Heart failure</td>
<td>TMZ improved survival and reduced hospital admissions.</td>
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Table I Summary of clinical studies with trimetazidine.

Abbreviations: BNP, B-type natriuretic peptide; EMIP-FR, European Myocardial Infarction Project – Free Radicals; LV, left ventricular; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; TMZ, trimetazidine.
Conclusion

To summarize, small- and medium-sized studies in angina patients have shown that trimetazidine delays the onset of ischemia associated with exercise, significantly decreases the frequency of angina attacks, and leads to a significant decrease in the use of nitrates (Table I). Trimetazidine improves left ventricular function in patients with coronary heart disease. It has also been shown to be effective in patients with ischemic heart failure. With regard to mortality, only one retrospective study demonstrated a potential benefit, whereas other studies did not find differences in hard clinical endpoints. The ongoing large, international, randomized ATPСI trial (The effiAcY and safety of Trimetazidine in Patients with angina pectoris having been treated by percutaneous Coronary Intervention) may elucidate the clinical benefits of metabolic cardioprotection.

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Assessing myocardial salvage in reperfused STEMI patients by hybrid cardiac PET-MR imaging

Heerajnarain Bulluck, MBBS, MRCP
The Hatter Cardiovascular Institute, Institute of Cardiovascular Science, University College London, UK; The National Institute of Health Research University College London Hospitals Biomedical Research Center, UK

Correspondence: Dr Heerajnarain Bulluck, The Hatter Cardiovascular Institute, Institute of Cardiovascular Science, University College London, WC1E 6HX, London, UK
E-mail: h.bulluck@gmail.com

Abstract
To assess the efficacy of novel cardioprotective therapies for reducing myocardial infarct size, it is important to accurately measure the area at risk, as this is needed to assess myocardial salvage, a more sensitive measure of cardioprotection. Although T2-weighted cardiovascular magnetic resonance (CMR) imaging is a promising technique for quantifying the area at risk, this approach does have its limitations. With the availability of hybrid positron emission tomography–MR (PET-MR) imaging, we now have the unique opportunity to simultaneously combine tissue characterization by CMR imaging with the metabolic insights from PET. Two cases are presented to highlight the potential utility of hybrid PET-MR imaging in acute reperfused ST-segment elevation myocardial infarction in investigating the changes in cardiac metabolism in the area at risk and in the assessment of myocardial salvage. ■ Heart Metab. 2016;70:28-31

Keywords: myocardial salvage; PET-MR; ST-segment elevation myocardial infarction

Introduction
Myocardial salvage (MS) is a more sensitive measure than myocardial infarct (MI) size to assess the effectiveness of novel cardioprotective therapies; however, currently, there is no established technique to measure MS in the clinical setting. Accurate quantification of the area at risk (AAR) is a prerequisite for the calculation of MS. The AAR refers to the territory supplied by the infarct-related artery, which is at risk of being irreversibly damaged without prompt reperfusion. MS is the difference between the AAR and MI size. Single-photon emission computerized tomography (SPECT) is considered the gold standard for the assessment of MS, but it is logistically challenging to perform. The AAR can also be retrospectively assessed by cardiovascular magnetic resonance imaging with early gadolinium enhancement, endocardial surface area (ESA) calculation, T1 mapping, T2 mapping, and T2 short tau inversion recovery (STIR) imaging, with the latter two techniques showing the most promise. Certain cardioprotective therapies, such as ischemic postconditioning and remote ischemic conditioning, have recently been shown to reduce the extent of myocardial edema as delineated by T2
mapping and T2-weighted imaging, resulting in inaccurate estimation of the AAR. Furthermore, the evolution of edema assessed by T2 mapping has recently been shown to have a bimodal pattern the first week of an MI. Interestingly, Kim et al recently showed that T2-weighted imaging did not correspond to the AAR in a canine infarct model and in a small cohort of patients. Whether hybrid positron emission tomography–magnetic resonance (PET-MR) imaging would provide a more robust method to assess the AAR has recently attracted attention. 18F-fluorodeoxyglucose (FDG) is widely used for viability assessment; its utility in the context of acute MI is not well established. This article presents two cases that highlight the potential role of hybrid PET-MR imaging in acute reperfused ST-segment elevation MI (STEMI) to assess myocardial salvage.

Case 1

A 71-year-old gentleman presented to hospital 7 hours after onset of chest pain; electrocardiogram analysis showed anterior ST-segment elevation. He did not have any past medical history of note. A diagnosis of anterior STEMI was made, and the patient underwent prompt reperfusion by primary percutaneous coronary intervention to the proximal left anterior descending artery. The thrombolysis in MI (TIMI) flow grade was 0 before the procedure and 3 after the procedure. A hybrid PET-MR scan was performed on day 5 and repeated at 1 year as part of a research protocol. In Figure 1 (top panel), the late gadolinium enhancement (LGE)-MR image from the acute scan shows a transmural anteroseptal infarct with a large burden of microvascular obstruction (red arrow). There was a corresponding large area of reduced FDG uptake (white arrow in the FDG-PET image); this is also demonstrated in the fused FDG/LGE image. The follow-up scan at 1 year showed full-thickness LGE with no salvage (Figure 1, bottom panel, red arrow) and no recovery of glucose metabolism (observable as FDG uptake) on the FDG image (white arrow).

Case 2

A 66-year-old gentleman presented to hospital within 1 hour of onset of chest pain; electrocardiogram analysis showed inferior ST-segment elevation. He was previously fit and well. A diagnosis of an inferior STEMI was made, and the patient promptly underwent primary percutaneous coronary intervention to the midright coronary artery. He had a TIMI flow grade of 1 before the procedure and 3 after the procedure. A hybrid PET-MR scan was performed on day 4 and repeated at 1 year as part of the same research protocol used for the patient above. In Figure 2 (top panel),
the acute scan shows complete MS with no infarct (red arrow in the LGE-MR image) but reduced FDG uptake in the inferior wall (white arrow in the FDG-PET image) within the AAR. The follow-up scan at 1 year showed normalization of FDG uptake in the inferior wall (white arrow in the FDG-PET image).

Discussion

These two cases demonstrate that FDG uptake observed by an acute scan within one week of an MI is reduced not only in irreversibly injured and nonviable myocardium, but also in the salvaged myocardium, for which FDG uptake subsequently normalizes on the follow-up scan. FDG, a glucose analog with a half-life of 109.8 minutes, is widely used for viability assessment. However, FDG uptake has also been shown to be affected in the reversibly injured salvaged and stunned myocardium of animal models of ischemia-reperfusion. The mechanism for this abnormal FDG uptake in areas of salvaged myocardium is not clear, but may be due to the fact that the reversibly injured but stunned myocardium preferentially takes up more glucose than free fatty acid following a period of fasting than does normal myocardium, but has delayed glucose metabolism. Therefore, after a glucose load, the reversibly injured myocardium has a reduced FDG uptake.

Nensa et al., estimating the AAR based on ESA calculations, recently showed that the area of reduced FDG uptake was larger than the AAR in 18 of the patients included in the study. However, ESA is known to underestimate the AAR when compared with T2-weighted imaging. Our group recently compared FDG-PET with T2-mapping in order to delineate the AAR in 21 reperfused STEMI patients. The area of reduced FDG uptake was larger than the MI size and matched the AAR. The limits of agreement on Bland-Altman analysis were quite wide and could be due to differences in spatial resolution and acquisition of images at different phases of the cardiac cycle between the two techniques.

Conclusion and future directions

Hybrid PET-MR imaging is particularly appealing for acute STEMI patients because only one examination is required to obtain data in parallel from PET for the AAR and from cardiovascular magnetic resonance imaging for MI size; these can be used to assess MS. However, more work needs to be done to improve upon current attenuation correction techniques and to improve coregistration of regions of interest in order to minimize partial volume effects. More importantly, the dynamic changes of reduced FDG uptake within the salvaged myocardium within the first week of an MI needs to be assessed so that the optimum timing for FDG imaging to accurately delineate the AAR can be determined. There is also the opportunity to explore other ligands, not only for quantification of the AAR, but also to obtain more in-depth metabolic insight into the evolution of acute MI and the pathophysiology of adverse left ventricular remodeling.

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Metabolic changes in the acutely ischemic heart

Gary D. Lopaschuk, PhD
Mazankowski Alberta Heart Institute, Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada

Correspondence: Dr Gary D. Lopaschuk, 423 Heritage Medical Research Centre, Department of Pediatrics, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, T6G 2S2, Canada
E-mail: gary.lopaschuk@ualberta.ca

Abstract
The onset of ischemia is associated with dramatic alterations in cardiac energy metabolism. A mismatch between oxygen demand and oxygen supply to the heart muscle results in a decrease in mitochondrial oxidative metabolism, leading to an energy deficient state in the heart muscle. Glycolysis (which does not require oxygen) accelerates during ischemia in an attempt to increase adenosine triphosphate (ATP) production, although this is associated with the accumulation of by-products of glycolysis, including lactate and hydrogen ions (H⁺). During ischemia, there are also changes in the source of energy substrate used to support residual mitochondrial oxidative metabolism. These metabolic changes include an increase in the contribution of cardiac fatty acid oxidation to residual mitochondrial oxidative metabolism and a decrease in glucose oxidation. Low glucose oxidation accompanied by increased glycolysis results in an uncoupling of glycolysis from glucose oxidation, and the accumulation of lactate and H⁺. Reperfusion after ischemia lessens the mismatch between oxygen demand and oxygen supply to the heart muscle. However, fatty acid oxidation as a source of energy increases at the expense of glucose oxidation. This continues to uncouple glycolysis from glucose oxidation, resulting in a continued decrease in cardiac efficiency, which can contribute to myocardial injury. Therapeutic strategies that inhibit fatty acid oxidation and increase glucose oxidation can decrease the severity of ischemic injury.

Keywords: glycolysis; ischemia; reperfusion

Introduction
The heart has a very high energy demand, due to the need to continuously produce energy (in the form of adenosine triphosphate [ATP]) to sustain contractile function. The majority of this energy is obtained from mitochondrial oxidative phosphorylation, a process requiring a considerable amount of oxygen. Indeed, although the heart normally makes up less than 0.5% of the body weight, it uses more than 5% of the oxygen consumed by the body. Mitochondrial oxidative phosphorylation in the heart utilizes various energy substrates—which include fatty acids, glucose, lactate, amino acids, and ketone bodies—to generate ATP. The contributions of each energy substrate to ATP generation are tightly regulated, and there is a significant degree of plasticity and interdependence between energy substrates. Under normal physiological conditions, fatty acids and carbohydrates (i.e., glucose and lactate) represent the primary metabolic fuels that sustain cardiac function, and upwards of 95% of ATP production is attributable...
to mitochondrial oxidative phosphorylation (Figure 1). The remainder of this ATP production (approximately 5%) originates from glycolysis, which can produce ATP without the consumption of oxygen.

Myocardial ischemia in the heart arises as a result of a decreased oxygen supply to the heart (e.g., such as by a blockage of a coronary artery) and/or an increased demand of oxygen to the heart (i.e., increased workload) that outstrips the oxygen supply to the heart. Both during and after ischemia there are dramatic alterations in energy metabolism in the heart.

### Energy metabolism in the ischemic heart

In the ischemic myocardium, mitochondrial oxidative phosphorylation decreases, and because there are essentially no reserves of energy in the heart, there is a depletion of high energy phosphates. Although there is an initial transfer of phosphates from phosphocreatine to ATP (via creatine kinase) in an attempt to preserve ATP levels, this is not enough to maintain ATP levels, and in severely ischemic hearts, a depletion of myocardial ATP occurs.

During ischemia, glycolysis accelerates and becomes a very important source of energy, owing to its ability to generate ATP in the absence of oxygen ($O_2$) (Figure 1B). Glucose from intracellular intramyocardial stores of glycogen is also mobilized during ischemia. Although this additional ATP production from glycolysis may be sufficient to maintain/correct ionic homeostasis during mild to moderate ischemia, the hydrolysis of glycolytically derived ATP uncoupled from subsequent pyruvate oxidation leads to the increased generation of hydrogen ions ($H^+$’s), which can result in a decrease in intracellular pH within the ischemic myocardium.

Because pyruvate cannot be oxidized by the mitochondria, it is converted to lactate, resulting in an increased lactate production by the heart. In the presence of severe ischemia, the $H^+$’s and lactate production increases, leading to a decrease in intracellular pH and cardiac efficiency.

**Fig. 1** Alterations in myocardial energy metabolism during and after ischemia.

(A) In the aerobic heart, mitochondrial fatty acid oxidation and glucose oxidation are the major sources of energy production. In contrast, glycolysis provides less than 5% of ATP production. (B) During ischemia, mitochondrial oxidative metabolism decreases and glycolysis becomes a more important source of energy production. Fatty acids dominate as the substrate for residual oxidative metabolism. The increase in glycolysis and decrease in glucose oxidation results in the production of both lactate and $H^+$’s. (C) During reperfusion, mitochondrial oxidative metabolism recovers, but fatty acid oxidation dominates as the source of ATP production, due to increased plasma levels of fatty acids and decreased control of mitochondrial fatty acid uptake. Glucose oxidation rates remain low in reperfusion. Since glycolysis remains elevated, the uncoupling of glycolysis from glucose oxidation persists during reperfusion, leading to an increase in $H^+$ and lactate production, which can decrease cardiac efficiency and cardiac function.

Abbreviations: ADP, adenosine diphosphate; ATP, adenosine triphosphate; CoA, Coenzyme A; $H^+$, hydrogen ion; $H_2O$, water; NADH, NADH dehydrogenase subunit 2; $O_2$, oxygen; TCA, tricarboxylic acid.
tate produced from glycolysis are not removed, which eventually leads to an inhibition of glycolysis in order to prevent further accumulation of these glycolytic by-products.\textsuperscript{1,2} These effects can further aggravate disturbances in ionic homeostasis. As glycolysis only provides a small fraction of ATP compared with that provided by the oxidation of carbohydrates and fatty acids, its ability to maintain ionic homeostasis during ischemia is finite.

Mitochondrial ATP production during ischemia decreases in proportion to the decrease in oxygen supply to the heart. However, the source of energy substrate for any residual mitochondrial oxidative metabolism can dramatically change. Due to increased fatty acid supply to the heart and alterations in the control of mitochondrial fatty acid uptake, the oxidation of fatty acid dominates as the main residual source of ATP production, and glucose oxidation decreases.\textsuperscript{5} This decrease in glucose oxidation, coupled with the increase in glycolysis, results in a further uncoupling of glycolysis from glucose oxidation, which increases the production of both lactate and H\textsuperscript{+}\textsuperscript{,6,7} This contributes to a decrease in cardiac efficiency, as ATP is directed away from contractile processes to deal with the intracellular H\textsuperscript{+} accumulation.\textsuperscript{7} As a result, myocardial ischemia not only compromises cardiac ATP production, but also decreases the efficiency of using ATP for muscle contraction.

Energy metabolism during reperfusion after ischemia

If previously ischemic myocardium is reperfused in a timely manner (such as by mechanical revascularization or by use of thrombolytic agents), the increased delivery of oxygen to the heart results in a recovery of mitochondrial oxidative phosphorylation. However, during this period, rates of fatty acid oxidation recover to a greater extent than rates of glucose oxidation.\textsuperscript{7,8} This occurs because the heart is exposed to elevated circulating levels of fatty acids (a consequence of ischemic stress) and due to alterations in the subcellular control of fatty acid oxidation.\textsuperscript{1} These high levels of fatty acid oxidation decrease the rate of recovery of glucose oxidation, due to a phenomenon called the “Randle Cycle” (Figure 1C)\textsuperscript{,9} At the same time, glycolysis rates remain high in the early period of postischemic reperfusion.\textsuperscript{7} This results in a continued uncoupling of the rates of glycolysis and glucose oxidation, despite the restoration of coronary flow and hence O\textsubscript{2} delivery. This results in a continued production of both H\textsuperscript{+}’s and lactate in the reperfusion period (Figure 1C). The continued production of H\textsuperscript{+}’s during reperfusion\textsuperscript{7} contributes to the altered ionic homeostasis and decreased cardiac efficiency that occurs after ischemia.\textsuperscript{6,7,10,11} In addition to high fatty acid oxidation rates during reperfusion contributing to an uncoupling of glucose oxidation from glycolysis, high rates of fatty acid oxidation are less efficient as an energy substrate (in terms of O\textsubscript{2} consumed/ATP produced),\textsuperscript{12} which also contributes to a decrease in cardiac efficiency seen during reperfusion.\textsuperscript{1,6} This decrease in cardiac efficiency contributes to a decreased contractile function during the reperfusion period.

Switching from fatty acid to glucose oxidation during and after ischemia

Optimizing energy substrate metabolism both during ischemia and during reperfusion after ischemia is a novel strategy to preserve mechanical function and efficiency and to enhance the recovery of postischemic function. This includes pharmacological approaches that shift the balance from the oxidative utilization of fatty acid toward carbohydrate oxidation. In particular, inhibition of fatty acid oxidation and direct stimulation of glucose oxidation are potentially promising anti-ischemic interventions. Inhibition of fatty acid oxidation during ischemia can switch any residual oxidative metabolism from fatty acid oxidation to glucose oxidation, and inhibition of fatty acid oxidation during reperfusion after ischemia decreases the high rates of fatty acid oxidation seen after ischemia.\textsuperscript{5,7,13} During both ischemia and reperfusion after ischemia, inhibition of fatty acid oxidation results in a stimulation of glucose oxidation, which can improve the coupling between glycolysis and glucose oxidation.\textsuperscript{7} This decreases both H\textsuperscript{+} and lactate production, leading to an increase in cardiac efficiency, a decrease in tissue injury, and an increase in contractile function.

Presently, there is only one clinically available drug that uses a direct metabolic approach to inhibit fatty acid oxidation and stimulate glucose oxidation in the heart. Trimetazidine inhibits the fatty acid oxidation enzyme 3-ketoacyl CoA thiolase, resulting in an inhibition of fatty acid oxidation.\textsuperscript{13,14} Inhibition of fatty acid oxidation by trimetazidine has been observed in both...
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Conclusions

Dramatic alterations in energy metabolism occur in the heart during and after ischemia. High glycolysis rates accompanied by low mitochondrial glucose oxidation rates result in a decrease in cardiac efficiency and depressed contractile function. Stimulating glucose oxidation by inhibiting fatty acid oxidation can improve both cardiac efficiency and function, and therefore protect the ischemic heart.

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Reducing myocardial infarct size by remote ischemic conditioning

Luciano Candilio, MD(Res)
The Hatter Cardiovascular Institute, University College London, London, UK

Correspondence: Dr Luciano Candilio, The Hatter Cardiovascular Institute, University College London, 67 Chenies Mews, WC1E 6HX, London, UK
E-mail: luciano.candilio@nhs.net

Abstract
Ischemic heart disease is the leading cause of death and morbidity in the world, and ST-segment elevation myocardial infarction (STEMI) remains associated with a significant mortality rate and complications noted at 1-year follow-up, despite prompt coronary reperfusion achieved with either thrombolysis or primary percutaneous coronary intervention (PPCI). It is therefore clear that novel cardioprotective strategies are required to improve clinical outcomes in these subjects; in this regard, remote ischemic conditioning (RIC), a phenomenon by which brief episodes of transient limb ischemia-reperfusion are able to protect a distant or “remote” organ or tissue from a sustained period of ischemia, has been demonstrated as a promising low-cost therapeutic strategy in order to reduce myocardial injury and improve clinical outcomes in these patients. In the current article, we provide an updated review of randomized clinical trials investigating the effects of RIC in patients presenting with STEMI. ■ Heart Metab. 2016;70:36-39

Keywords: cardioprotection; myocardial infarction; remote ischemic conditioning

Background
Following an ST-segment elevation myocardial infarction (STEMI), timely restoration of blood flow with primary percutaneous coronary intervention (PPCI) or thrombolysis is the most effective strategy for reducing myocardial infarct (MI) size, heart failure (HF), ventricular arrhythmias, and mortality. Despite a significant reduction in case fatality in the last three decades, the mortality rate post-STEMI remains as high as 2.5%-10%, with an overall estimated rate of 10% of in-hospital HF or shock, 6%-7% of reinfarction at 1 year, 1.8% of in-hospital major bleeding, and 1.8%-2% stroke at 1 year.1 Crucially, restoration of coronary perfusion has been demonstrated to paradoxically induce myocardial damage, and this phenomenon, termed myocardial ischemia-reperfusion injury (IRI), has been demonstrated to account for up to 50% of the final MI size in animal studies2; therefore, novel cardioprotective strategies are required to reduce IRI after MI and to improve patient outcomes. Numerous strategies that have been investigated—including pharmacological agents, mechanical cardioprotection, and endovascular cooling—have not demonstrated a significant benefit. However, one promising approach consists of enhancing the innate mechanisms of cardioprotection from IRI by “conditioning” the heart before, during, or after the ischemic insult. Remote ischemic conditioning (RIC) offers the advantage of applying the conditioning stimulus to a “remote” or distant organ/tissue, such as the limb, thereby obviating the
Cardioprotection in acute myocardial infarction by remote ischemic conditioning

**Abbreviations**

AUC: area under the curve; CK-MB: creatine kinase–MB; ERIC-PPCI: Effect of Remote Ischemic Conditioning on Clinical Outcomes in STEMI Patients Undergoing PPCI (trial); HF: heart failure; IRI: ischemia-reperfusion injury; LV: left ventricular; MI: myocardial infarct; PPCI: primary percutaneous coronary intervention; RIC: remote ischemic conditioning; STEMI: ST-segment elevation myocardial infarction.

need to invasively intervene on the heart in order to achieve cardioprotection. In the current review, we will focus on the main studies evaluating the effects of RIC in the setting of STEMI treated with PPCI or thrombolysis and will discuss the ongoing multicenter study, the results of which should ultimately provide a conclusive answer about the potential beneficial impact of RIC on clinical outcomes.

**RIC and PPCI**

The application of RIC in patients presenting with STEMI represents the closest translation of experimental models to the clinical scenario: acute and complete coronary occlusion in the context of STEMI resembles the direct coronary artery ligature in animal studies, and typically, STEMI subjects have no pre-existing comorbidities and are on no regular medications, similarly to the preclinical settings.

Rentoukas et al. evaluated the effects of RIC in the setting of STEMI and found that the rate of full ST-segment resolution was highest in patients receiving RIC (three 4-minute cycles of transient upper-arm ischemia-reperfusion beginning 10 minutes before the estimated time of the first balloon inflation) or RIC plus morphine, compared with PPCI alone; there was no significant difference between the two conditioned groups. Additionally, subjects receiving RIC plus morphine presented the lowest troponin-I peak and the highest degree of ST-segment return to baseline.

Bøtker and colleagues demonstrated that in patients with evolving STEMI, RIC—comprising four 5-minute cycles of upper-arm ischemia-reperfusion during transport to hospital and before PPCI—improved the myocardial salvage index at 30 days; no difference was found in final infarct size, troponin-T concentrations, ST-segment resolution, death, re-infarction, left ventricular (LV) function, and hospital admission for HF within 30 days. Subsequently, the same group showed that a similar conditioning stimulus was also able to reduce the rate of major adverse cardiovascular and cerebral events (MACCE)—a composite end point of all-cause mortality, nonfatal MI, readmission for HF, and stroke/transient ischemic attack—for a median follow-up of 3.8 years.

Munk et al. failed to demonstrate that LV function could be improved by a similar RIC stimulus, although the majority of patients presented a small-to-moderate area at risk, thus small differences in LV function changes may not have been detected on echocardiography. However, importantly, in a subgroup of high-risk patients—for which the study was not adequately powered—RIC improved LV function at 30 days. In addition, Manchurov et al. showed improved endothelial function up to 1 week post-PPCI, and more recently, Crimi and colleagues found that a standard conditioning stimulus reduced total creatine kinase (CK)-MB release and improved T2-weighted edema volumes and ST-segment elevation resolution in patients with an occluded left anterior descending artery.

In a large cohort of 323 STEMI patients, our group demonstrated that four 5-minute cycles of upper-arm ischemia-reperfusion reduced infarct size (measured by cardiac magnetic resonance) 6 days after admission, total troponin-T release at 24 hours, and myocardial edema, and improved myocardial salvage.

Intriguingly, there was no difference in CK-MB area under the curve (AUC) in patients receiving PPCI alone, PPCI plus RIC (three 5-minute cycles of upper-arm ischemia-reperfusion), or PPCI plus RIC and local ischemic conditioning, although positive effects were identified in the RIC and RIC plus local ischemic group when infarct size was corrected for the area at risk. More recently, it has been demonstrated that used in addition to PPCI, three 5-minute cycles of upper-arm ischemia-reperfusion significantly reduced contrast-induced acute kidney injury, and combined RIC and local postconditioning improved the myocardial salvage index at 3 days, though there was no difference in infarct size, microvascular obstruction, and clinical outcomes at 6 months.

**RIC and thrombolysis**

A recently published multicenter, single-blinded trial evaluated the effects of RIC in STEMI patients treated...
by thrombolysis with streptokinase. This trial, conducted in Mauritius, is particularly relevant for those areas where PPCI service has limited availability. Preconditioned subjects (four 5-minute cycles of upper-arm ischemia-reperfusion, initiated before and continued during thrombolysis) sustained significantly less myocardial IRI than controls (troponin-T AUC was 32% lower and CK-MB AUC was 19% lower), thereby showing for the first time that RIC could be beneficial in this therapeutic context also and that it provides similar cardioprotective effects to those obtained in the setting of RIC-PPCI.

Conclusions

In the current review, we have briefly evaluated the application of RIC in the context of STEMI, where emergency coronary reperfusion was achieved with PPCI or thrombolysis. Crucially, all of the above-mentioned studies used surrogate biomarkers of myocardial IRI (such as troponin or CK-MB), microvascular reperfusion, LV function, and acute kidney injury as their primary end points and did not include clinical outcomes among their objectives or were not adequately powered to detect significant differences in clinical outcomes. Two large multicenter studies recently completed in the United Kingdom and Germany demonstrated no significant beneficial effect of RIC on clinical outcomes in patients undergoing elective coronary artery bypass grafting (CABG) with or without valve surgery. This could be explained by the relatively small additional cardioprotection provided by RIC to patients already receiving optimized medical therapy with more advanced surgical and anesthetic techniques and by the potential interference of intravenous anesthetics with RIC effects; crucially, the level of myocardial IRI during cardiac surgery is significantly inferior to that observed in reperfused STEMI patients, and myocardial IRI in cardiac surgery is secondary to multiple factors, with ischemia-reperfusion being one of these. It is therefore conceivable that RIC might provide more significant beneficial effects than cardiac surgery in STEMI patients: currently, a large multicenter randomized controlled trial is being conducted in the United Kingdom, Denmark, and Spain (ERIC-PPCI, NCT02342522 [Effect of Remote Ischemic Conditioning on Clinical Outcomes in STEMI Patients Undergoing PPCI]) in order to investigate whether RIC, given with four 5-minute cycles of upper-arm ischemia-reperfusion, reduces the combined primary end point of cardiac death and hospitalization at 12 months post-PPCI. This study is expected to provide a conclusive answer to whether RIC has a beneficial impact on major cardiac events in STEMI patients.

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Area at risk
The area of myocardium at risk of myocardial infarction after an acute coronary artery occlusion.

Cardiac magnetic resonance imaging (MRI)
An imaging technology that noninvasively assesses function and structure of the cardiovascular system. The technology uses magnetic field and pulses of radio wave energy to image the heart and vasculature.

Cardioprotection
Strategies and treatments for protecting the heart against the detrimental effects of acute ischemia/reperfusion injury on the myocardium.

Heart failure
The inability of the heart to pump enough blood to meet the body’s demand. In heart failure, the organs and other tissues do not receive enough oxygen and nutrients to function properly. Common contributing factors in the inability of the heart to adequately function include hypertension and ischemic heart disease.

Ischemic postconditioning
An endogenous cardioprotective phenomenon in which brief cycles of ischemia and reperfusion applied at the onset of reperfusion render the myocardium tolerant of acute myocardial reperfusion injury.

Ischemic preconditioning
An endogenous cardioprotective phenomenon in which brief cycles of nonlethal ischemia and reperfusion render the myocardium tolerant of a subsequent, otherwise lethal, episode of acute ischemia/reperfusion injury.

Myocardial salvage
Amount of myocardium salvaged after an acute coronary artery occlusion by means of reperfusion or a therapeutic intervention applied at the onset of reperfusion in order to reduce myocardial infarct size.

Positron emission tomography–magnetic resonance imaging (PET-MRI)
Imaging that uses a combination of technologies to assess both morphology and function of the heart and vasculature. Magnetic resonance imaging is used to assess tissue morphology, while positron emission tomography is used to assess function.

Primary percutaneous coronary intervention (PPCI)
A nonsurgical procedure aimed at restoring blood flow to an occluded or obstructed coronary vessel in acute coronary syndromes. This involves the insertion of a balloon or other device on a catheter through a femoral or radial artery to the occlusion site, where the artery is then opened to restore blood flow.

Remote ischemic conditioning
An endogenous cardioprotective phenomenon in which brief cycles of nonlethal ischemia and reperfusion applied to an organ or tissue remote from the heart render the myocardium tolerant of a subsequent, otherwise lethal, episode of acute ischemia/reperfusion injury.

ST-segment elevation myocardial infarction (STEMI)
Acute myocardial infarction caused by complete acute coronary artery occlusion, most often due to a thrombotic occlusion forming at the site of a ruptured atherosclerotic plaque in one of the major coronary arteries.