Ischemic heart disease (IHD) is the leading cause of death and disability worldwide, one major manifestation of which is an acute ST-segment elevation myocardial infarction (STEMI). For these patients, the treatment of choice is timely myocardial reperfusion using primary percutaneous coronary intervention (PPCI). However, the process of reperfusion can in itself induce myocardial injury and cardiomyocyte death—a phenomenon that has been termed “myocardial reperfusion injury” and that contributes to up to 50% of the final myocardial infarction (MI) size. Therefore, novel cardioprotective therapies are required to protect the heart against myocardial reperfusion injury in order to reduce MI size, preserve myocardial function, and prevent the onset of heart failure. In this regard, a number of hormones have been reported in preclinical animal studies and early clinical trials to reduce MI size when administered at the time of reperfusion. Assessing the cardioprotective efficacy of a novel therapy requires the measurement of the area at risk (AAR) of MI and MI size, as this allows the calculation of myocardial salvage, which is a more sensitive measure of cardioprotection than absolute MI size reduction as it takes into account the AAR. Cardiac magnetic resonance imaging (MRI) is an important imaging modality for assessing myocardial salvage in reperfused STEMI patients. The recent availability of hybrid simultaneous positron emission tomography (PET)/MRI will allow one to investigate the effects of novel cardioprotective therapies in the reperfused heart on cardiac metabolism, fibrosis, angiogenesis, apoptosis, and inflammation, providing new insights into the pathophysiology of acute MI and the post-MI remodeled heart. In this article, we review the emerging role of cardiac MRI to assess myocardial salvage of novel cardioprotective therapies such as hormones.
patients going on to develop heart failure is actually increasing. Therefore, novel therapies are required to prevent myocardial reperfusion injury, reduce myocardial infarction (MI) size, and preserve cardiac function, thereby preventing the onset of heart failure. In this respect, experimental animal and early clinical studies have reported beneficial effects in terms of myocardial salvage with several different hormones administered at the time of myocardial reperfusion. The ability to assess the cardioprotective efficacy of novel therapies requires the in vivo measurement of the area of myocardium at risk of MI (the area at risk or AAR) and MI size. In this regard, T2-weighted cardiac magnetic resonance imaging (MRI) can quantify the size of the AAR by detecting areas of myocardial edema, an approach that has been used to measure myocardial salvage in clinical cardioprotection studies. In this article, we highlight myocardial reperfusion injury as a neglected therapeutic target, review the therapeutic potential of hormones as a novel cardioprotective therapy for preventing reperfusion injury, and explore the role of cardiac MRI for measuring myocardial salvage.

Myocardial reperfusion injury: a neglected therapeutic target

“Myocardial reperfusion injury” describes the myocardial injury and cardiomyocyte death that occurs on reperfusing ischemic myocardium. In STEMI patients reperfused by PPCI, the presence of myocardial reperfusion injury mitigates the benefits of reperfusion in terms of myocardial salvage, contributing to up to 50% of the final MI size (Figure 1). There are four types of myocardial reperfusion injury, the first two of which are reversible and include reperfusion arrhythmias and myocardial stunning. The second two, which are irreversible and induce cardiomyocyte death, are microvascular obstruction and lethal reperfusion injury. The existence of lethal reperfusion injury as an independent mediator of cell death had been fiercely contested in the past. This was due to an inability to directly demonstrate reperfusion inducing the death of cardiomyocytes that were viable at the end of ischemia. However, the fact that therapeutic interventions have been reported in both animal and clinical studies to reduce MI size when administered solely at the time of reperfusion has been accepted as indirect evidence for the existence of myocardial reperfusion injury. Examples of therapies that have been reported to reduce MI size when given at reperfusion include a variety of different hormones.

Hormones as novel cardioprotective therapies

A large number of hormones have been found in animal MI studies to prevent myocardial reperfusion injury and reduce MI size when exogenously administered at the time of myocardial reperfusion (Figure 2). These hormones mediate their cardioprotective effect via a number of different cell-surface receptors (including serine threonine, tyrosine kinase, G-protein coupled, natriuretic, and cytokine receptors), which activate a wide variety of intracellular cardioprotective signaling cascades (including the cyclic guanosine monophosphate–protein kinase G [cGMP-PKG], the reperfusion injury salvage kinase [RISK], and the survivor activating factor enhancement [SAFE] pathways), many of which terminate on mitochondria.
an important target of cardioprotection (Figure 2). Only an overview of hormone cardioprotection can be provided in this section; for a more comprehensive account the reader is directed to extensive reviews of this topic. A selected number of these cardioprotective hormones including atrial natriuretic peptide (ANP), insulin (glucose-insulin-potassium [GIK] therapy), and exenatide (a glucagon-like peptide 1 [GLP-1] analogue) have been translated into the clinical setting and have been reported to reduce MI size when administered at the time of reperfusion in STEMI patients receiving PPCI (Table I). Ongoing clinical cardioprotection STEMI studies are currently investigating the hormone melatonin and a number of hormones (including erythropoietin) that have failed to have any beneficial effects in the clinical setting despite reduced MI size in animal studies (Table I). The reason for the failed translation of cardioprotective therapies from bench to bedside has been extensively reviewed.

The ability to assess the cardioprotective efficacy of novel therapies administered at the time of myocardial reperfusion to prevent reperfusion injury requires the assessment of myocardial salvage, as this is a more sensitive measure of cardioprotection than absolute MI size reduction. Cardiac MRI has recently been shown to quantify myocardial salvage in clinical cardioprotection studies.

**Assessing myocardial salvage using cardiac MRI**

Following an acute coronary artery occlusion, the amount of myocardium at risk of infarction (or AAR) is a major determinant of MI size. Therefore, it is essential to take this into account when assessing the ability of a novel cardioprotective therapy to limit MI

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**Fig. 2** Signaling pathways underlying hormone cardioprotection at reperfusion. Simplified scheme illustrating the intracellular signaling pathways underlying the cardioprotection elicited by hormones investigated in animal studies and translated into the clinical setting (*). Exogenously administered hormones will bind to their respective receptor on the cardiomyocyte cell surface, activating a variety of signaling cascades, including the reperfusion injury salvage kinase (RISK; Raf-Mek1/2-Erk1/2 and PI3K-Akt), survivor activating factor enhancement (SAFE; JAK-STAT), and cyclic guanosine monophosphate–protein kinase G (cGMP-PKG) pathways, which then terminate on either mitochondria (where mitochondrial permeability transition pore [mPTP] opening is inhibited) and the sarcoplasmic reticulum (where sarco/ endoplasmic reticulum Ca²⁺ ATPase [SERCA] is inhibited), thereby inducing cardioprotection.

**Abbreviations:** Akt, protein kinase B; ANP, atrial natriuretic peptide; BAD, Bcl-2-associated death promoter; eNOS, endothelial nitric oxide synthase; GF, growth factor; GIK, glucose-insulin-potassium therapy; GLP-1, glucagon-like peptide 1; GSK, glycogen synthase kinase; JAK, Janus kinase; KATP, adenosine triphosphate–sensitive potassium channel; NO, nitric oxide; PKC, protein kinase C; ROS, reactive oxygen species; sGC, soluble guanylyl cyclase; STAT, signal transducer and activator of transcription. Modified from reference 7: Hausenloy DJ, Yellon DM. Cardiovasc Res. 2009;83(2):179-194. © 2014, Oxford University Press.
size. This is especially important in patients presenting with an acute STEMI, in whom the size of the AAR can vary from 5% to 40% of the left ventricular (LV) volume from patient to patient depending on the site of the acute coronary artery occlusion. Myocardial salvage, which takes into account the AAR, is a more sensitive measure of cardioprotective efficacy than absolute reduction in MI size, meaning that a smaller number of patients is required in clinical trials investigating novel cardioprotective therapies. Myocardial salvage, which is calculated by subtracting MI size from the AAR, represents the amount of myocardium salvaged by the novel cardioprotective therapy (Figure 3). When normalized to the AAR, the myocardial salvage index is the proportion of the AAR that has been salvaged by the novel cardioprotective therapy (Figure 3).

The ability to assess myocardial salvage in the clinical setting requires a reliable and robust in vivo measure of the AAR. In this regard, cardiac MRI has emerged as a potential approach for achieving this. Cardiac MRI has recently been reported to be beneficial in patients presenting with an acute coronary syndrome, as it can measure LV volumes and function, detect regional wall motion abnormalities, and exclude LV thrombus. Furthermore, a unique characteristic of cardiac MRI is its ability to tissue characterize the different components of the infarct. For reperfused STEMI patients, cardiac MRI can be safely performed in the first week to quantify both the AAR and the MI size, thereby enabling the calculation of myocardial salvage. Cardiac MRI performed in the first week of hospital admission has been shown to retrospectively quantify the AAR in STEMI patients. This relies on the ability of T2-weighted cardiac MRI to detect myocardial edema, a marker of reversible myocardial ischemic reperfusion injury within the AAR (Figure 3). There have, however, been several issues with using T2-weighted cardiac MRI to measure the AAR in reperfused STEMI patients including imaging artifacts, low signal-to-noise ratio, and the cardioprotective therapy reducing the circumferen-

<table>
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<th>Hormone</th>
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<tr>
<td>Erythropoietin (EPO)</td>
<td>51</td>
<td>High dose EPO (2 x 50 000 IU by IV bolus—one prior to PPCI and a further dose 24 hours later)</td>
<td>Failure to reduce MI size or improve myocardial salvage; increased incidence of MVO</td>
<td>A number of large studies have confirmed that EPO is not beneficial; some studies find it may be harmful</td>
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<tr>
<td>Insulin (GIK therapy)</td>
<td>357</td>
<td>12-hour IV GIK infusion administered in the ambulance</td>
<td>Reduced MI size and less in-hospital mortality and cardiac arrest</td>
<td>Inconclusive results in previous clinical studies with GIK therapy</td>
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<tr>
<td>Atrial natriuretic peptide (ANP)</td>
<td>569</td>
<td>72-hour IV infusion of Carperitide (an ANP analogue)</td>
<td>Reduced MI size by 15% (72 hour AUC CK) and 2.0 % increase in LVEF</td>
<td></td>
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<tr>
<td>Glucagon-like peptide (GLP-1)</td>
<td>21</td>
<td>72-hour IV infusion of GLP-1</td>
<td>Increased LVEF and less regional wall motion abnormalities</td>
<td>Only patients with severe LV impairment were included</td>
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<tr>
<td>Glucagon-like peptide (GLP-1) analogue</td>
<td>107</td>
<td>6-hour IV infusion of exenatide (a GLP-1 analogue) started 15 minutes “prior” to PPCI</td>
<td>Increased MSI (0.62 to 0.71) at 90 days by cardiac MRI Reduced MI size by 23% of AAR at 90 days by cardiac MRI</td>
<td></td>
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<tr>
<td>Melatonin</td>
<td>40</td>
<td>Melatonin Intracoronary 10 mL 0.1 mg/mL and intravenously 49 mg</td>
<td>Currently recruiting primary end point MI size and myocardial salvage on cardiac MRI at 4 days</td>
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Table I: Hormone cardioprotection at reperfusion in ST-segment elevation myocardial infarction (STEMI) patients. Abbreviations: AUC, area under the curve; CK, creatine kinase; GIK, glucose-insulin-potassium; IU, international units; IV, intravenous; LV, left ventricle; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRI, magnetic resonance imaging; MSI, myocardial salvage index; MVO, microvascular obstruction; n, number; PPCI, primary percutaneous coronary intervention. Data from references 16-21.
Measuring myocardial salvage: hormone cardioprotection

The extent of myocardial edema (and therefore the measured AAR). The very recent availability of hybrid simultaneous PET/MRI provides the opportunity to simultaneously relate changes in cardiac metabolism (myocardial $^{18}$F-fluorodeoxyglucose [$^{18}$FDG] uptake) to constituents of the reperfused myocardial infarction. It allows the PET and MRI images to be acquired simultaneously with the patient in the same position on the scanner table, facilitating accurate coregistration of fused images, and precise voxel-by-voxel comparison images of cardiac anatomy and metabolism. Using this technique, we have recently demonstrated impaired glucose metabolism as evidenced by reduced myocardial $^{18}$FDG uptake within the AAR that corresponds to that delineated by T2-mapping cardiac MRI imaging (unpublished data, Figures 4 and 5). The relationship between the colocalized areas of myocardium with impaired glucose metabolism (imaged by PET) and edema (imaged by T2 mapping) in reversibly injured myocardium within the AAR is unclear and needs further investigation. With the availability of novel tracers for detecting hypoxia, apoptosis, fibrosis, inflammation, and angiogenesis, hybrid PET/MRI of the heart should provide unique insights into the pathophysiology of acute MI and subsequent post-MI LV remodelling. This should result in the identification of novel cellular and molecular targets for treating MI and heart failure.

Summary and conclusion

Despite optimal therapy, the morbidity and mortality in patients presenting with a STEMI remains significant. One neglected therapeutic target for which there is currently no effective therapy is "myocardial reperfusion injury," which refers to the cardiomyocyte death that occurs on reperfusing acutely ischemic myocardium and that has been reported to reduce MI size by 50%. As such, novel cardioprotective therapies are required to target myocardial reperfusion injury to limit MI size, preserve cardiac function, and prevent the onset of heart failure. In this regard, certain hormones have been reported in animal studies and initial clinical trials to reduce MI size when administered at the onset of reperfusion through the activation of established intracellular cardioprotective signaling pathways. Cardiac MRI has emerged as a potential noninvasive imaging technique.

**Fig. 4** Hybrid simultaneous positron emission tomography/magnetic resonance imaging (PET/MRI) of left anterior descending (LAD) coronary artery myocardial infarction (MI). This figure shows representative long-axis fused $^{18}$F-fluorodeoxyglucose ($^{18}$FDG)-PET/MRI images (left-sided panels) and late gadolinium enhancement (LGE; right-sided panels; white arrows) cardiac MRI images of a patient presenting with a transmural MI (containing microvascular obstruction; yellow arrows) within the LAD coronary artery territory. There is an area of markedly reduced myocardial uptake of glucose, which spatially matches the distribution of LGE (left-sided panels; red arrows).

**Fig. 5** Positron emission tomography/magnetic resonance imaging (PET/MRI) of transmural and subendocardial myocardial infarction (MI). This figure shows representative short-axis images of late gadolinium enhancement (LGE) cardiac MRI (showing MI), $^{18}$F-fluorodeoxyglucose ([$^{18}$FDG]-PET (showing reduced myocardial FDG uptake in areas of MI and the area at risk [AAR]), T2-mapping MRI (increased T2 values within the AAR), and fused FDG-PET:LGE MRI in two patients with subendocardial MI ([1] and [2], with significant myocardial salvage) and two with transmural MI ([3] and [4], with minimal myocardial salvage).
technique for quantifying myocardial salvage, permitting the assessment of the cardioprotective efficacy of novel therapies targeted against reperfusion injury. The recent availability of hybrid simultaneous PET/MRI should provide important insights into the pathophysiology of acute MI and post-MI remodeling, enabling the identification of novel therapeutic targets for cardioprotection.

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REFERENCES