Taking lizard saliva to heart

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This editorial refers to ‘Exenatide reduces reperfusion injury in patients with ST-segment elevation myocardial infarction’, by J. Lønborg et al., on page 1491

For patients presenting with an acute ST-segment elevation myocardial infarction (STEMI), the most effective therapy for reducing myocardial infarct (MI) size, preserving left ventricular (LV) systolic function, and improving clinical outcomes is timely myocardial reperfusion by primary percutaneous coronary intervention (PPCI). Although the process of myocardial reperfusion is critical for myocardial salvage, paradoxically it can also induce cardiomyocyte death, thereby mitigating the full beneficial effects of myocardial reperfusion in terms of MI size reduction and myocardial salvage—a phenomenon which has been termed ‘lethal myocardial reperfusion injury’. The fact that a therapeutic intervention administered solely at the time of myocardial reperfusion can reduce MI size by up to half suggests that lethal myocardial reperfusion injury may actually contribute up to 50% of the final MI size.

Over the years a number of therapeutic strategies with proven efficacy for reducing lethal myocardial reperfusion injury in experimental studies [e.g. antioxidants, calcium channel blockers, anti-inflammatory agents, hypothermia, erythropoietin, protein kinase C (PKC)-δ inhibition] have produced disappointing results when investigated in the clinical arena as adjunctive therapy to PPCI. The reasons for this failure to translate cardioprotection into the clinical setting can be attributed to a number of factors including inappropriate animal MI models and poorly designed clinical studies.

However, more recently, a number of novel therapeutic strategies (such as ischaemic postconditioning, atrial natriuretic peptide, cyclosporin-A, and remote ischaemic preconditioning) have been reported in proof-of-concept clinical studies to reduce MI size when administered at the time of PPCI (see Table 1). To this expanding list of promising cardioprotective interventions, we can now add exenatide (Byetta), an agent which has been recently introduced as adjunctive therapy for improving glycaemic control in patients with type 2 diabetes.

Exenatide, which is a synthetic version of exendin-4, a peptide which was originally isolated from the saliva of the Gila monster (a venomous lizard), is a long-acting analogue of glucagon-like peptide-1 (GLP-1), a hormone released into the gastrointestinal tract which stimulates insulin secretion resulting in lower blood glucose levels. Because GLP-1 is rapidly broken down in the body by the enzyme dipeptidyl peptidase-IV (DPP-IV), its therapeutic application as a treatment for diabetes has been made possible using DPP-IV-resistant GLP-1 analogues (e.g. exenatide or liraglutide) and DPP-IV inhibitors (e.g. sitagliptin, vildagliptin, and saxagliptin). Interestingly, in addition to its metabolic effects, GLP-1 has also been reported in experimental studies to have receptor-mediated beneficial effects on the heart which include increasing myocardial glucose uptake, an inotropic effect, and protecting the myocardium against acute ischaemia–reperfusion injury (IRI), through the activation of known prosurvival signalling pathways such as phosphatidylinositol 3-kinase (PI3K)–Akt and protein kinase A (PKA).

Figure 1

Interestingy, experimental studies have also reported cardioprotective effects with the GLP-1 analogues (exenatide and liraglutide) and DPP-IV inhibitors (sitagliptin). Exenatide administered at the onset of myocardial reperfusion reduced MI size in the ex vivo rat heart and in the more clinically relevant closed-chest porcine heart, thereby providing the evidence required for investigating exenatide in the clinical setting.

Lønborg et al. have investigated the effects of exenatide administered as an adjunct to myocardial reperfusion in PPCI patients. The authors found that the administration of an intravenous 6 h infusion of exenatide initiated 15 min prior to PPCI increased the myocardial salvage index at 3 months from 0.62 to 0.71 and reduced the MI size/AAR (area at risk) ratio from 0.39 to 0.30. Interestingly, >90% of patients were not diabetic, illustrating that the beneficial effect of exenatide on myocardial salvage was observed in non-diabetic patients, broadening its potential clinical application to all patients. There were no
### Table 1  
**Some of the more promising therapeutic strategies for reducing lethal myocardial reperfusion injury in STEMI patients undergoing PPCI, which have been recently investigated in proof-of-concept clinical studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>n</th>
<th>Evidence for reduced myocardial reperfusion injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staat et al. 2005</td>
<td>Ischaemic postconditioning  Four 60 s angioplasty balloon inflations/deflations at onset of myocardial reperfusion</td>
<td>30</td>
<td>Reduced MI size by 36% (72 h AUC total CK). Increased myocardial blush grade</td>
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<tr>
<td>Thibault et al. 2008</td>
<td>Four 60 s angioplasty balloon inflations/deflations at onset of myocardial reperfusion</td>
<td>38</td>
<td>Reduced MI size by 41% (72 h AUC total CK) and 47% (72 h AUC troponin-I). Reduced MI size by 39% at 6 months (SPECT). Increased LV ejection fraction from 49% to 56% at 12 months (echo)</td>
</tr>
<tr>
<td>Lonborg et al. 2010</td>
<td>Four 30 s angioplasty balloon inflations/deflations at onset of myocardial reperfusion</td>
<td>118</td>
<td>Reduced MI size/AAR by 19% on CMR at 3 months. Increased myocardial salvage ratio by 31% on CMR at 3 months. Less heart failure (27% vs. 46%) at 3 months</td>
</tr>
<tr>
<td>Kitakaze et al. 2007</td>
<td>Atrial natriuretic peptide 72 h i.v. infusion of carperitide (an ANP analogue) started prior to myocardial reperfusion</td>
<td>535</td>
<td>Reduced MI size by 14.7% (72 h AUC total CK). Increased LV ejection fraction on echo from 42.5% to 44.7% at 6–12 months</td>
</tr>
<tr>
<td>Piot et al. 2007</td>
<td>Cyclosporin-A  Single i.v. bolus of cyclosporin-A (2.5 mg/kg) 10 min prior to myocardial reperfusion</td>
<td>58</td>
<td>Reduced MI size by 40% (72 h AUC total CK). Reduced MI size by 20% on CMR at day 5 (subgroup of 27 patients)</td>
</tr>
<tr>
<td>Botker et al. 2010</td>
<td>Remote ischaemic perconditioning  Four 5 min inflations/deflations of blood pressure cuff placed on upper arm in ambulance prior to myocardial reperfusion</td>
<td>142</td>
<td>Increased myocardial salvage index from 0.55 to 0.75 on SPECT scan performed at 30 days</td>
</tr>
<tr>
<td>Lonborg et al. 2011</td>
<td>Exenatide  6 h i.v. infusion of exenatide (25 μg in 250 ml normal saline) started 15 min prior to myocardial reperfusion</td>
<td>105</td>
<td>Increased myocardial salvage index from 0.62 to 0.71 on CMR at 3 months. Reduced MI size/AAR by 23% on CMR at 3 months</td>
</tr>
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</table>

Evidence for the existence of lethal myocardial reperfusion injury in each case is illustrated by the fact that the intervention applied at the time of myocardial reperfusion was able to reduce MI size. Large multicentre clinical trials are now needed to confirm these findings and determine if there is any benefit on major clinical outcomes.

AAR, area at risk; ANP, atrial natriuretic peptide; AUC, area under the curve; CK, creatine kinase; CMR, cardiac magnetic resonance; LV, left ventricular; MI, myocardial infarct; SPECT, single photon emission computed tomography.
reported cases of hypoglycaemia in patients treated with exenatide in this study, although hypoglycaemia is a potential risk in diabetic patients chronically treated with exenatide, particularly when used as an adjunct to other diabetes medications.

The authors are to be congratulated on the careful design and execution of this proof-of-concept clinical study which is one of the first to use cardiac magnetic resonance imaging (CMR) to assess myocardial salvage in PPCI patients. Experience obtained from previous clinical studies has highlighted several key considerations in the design of clinical studies for investigating therapeutic strategies aimed at reducing lethal myocardial reperfusion injury in PPCI patients.2

(i) Careful selection of patients. The STEMI patients most likely to benefit from an intervention administered at the time of myocardial reperfusion are those who present with: a large AAR (>30–35% of the left ventricle usually achieved in those patients presenting with proximal left anterior descending artery or large right coronary artery occlusions); TIMI 0 flow (so that myocardial reperfusion has not yet taken place); and minimal coronary collateralization to the AAR.8 Although Lonborg et al.9 selected patients with TIMI 0 coronary flow, they included all STEMI patients irrespective of the size of the AAR and the presence of coronary collateralization;

(ii) Careful timing and dosing of the intervention. The intervention must be administered prior to the restoration of blood flow within the infarct-related artery as myocardial reperfusion injury occurs in the first few minutes of coronary reflow. Lonborg et al.9 initiated the 6 h intravenous infusion of exenatide (25 µg in 250 mL of normal saline) 15 min prior to myocardial reperfusion and showed that blood plasma levels of exendin-4 (the active component of exenatide) were 0.177 nmol/L at the end of the PPCI procedure, which was found to be comparable with those used in their previous ex vivo small animal study.12 Interestingly, diabetic patients on chronic exenatide therapy receive a regular dose of 5 or 10 µg twice daily by subcutaneous injection, which gives a peak 2.1 h plasma concentration following a 10 µg dose of 211 pg/mL or 0.05 nmol/L. Therefore, whether a diabetic patient on regular exenatide treatment who presents with a...
STEMI also accrues similar beneficial effects on myocardial salvage is unknown;

(iii) Selection of relevant endpoints. An intervention which is adminis-

tered at the time of PPCI to reduce lethal myocardial reperfusion injury (as evidenced by a smaller MI size) will only impact on related endpoints such as LV systolic function, the incidence of heart failure, and cardiovascular death, and is unlikely to impact on unrelated endpoints such as rates of coronary revascularization or non-fatal MI. Lonborg et al.9 found that exenatide did not influence peak plasma troponin-T in the immediate 18 h time-frame, or MI size and LV ejection fraction 3 months post-PPCI. Whether a difference would have been seen if the area under curve (AUC) plasma troponin-T had been measured is unknown. The study also reported no difference in clinical outcomes at 30 days, although it was not powered to assess this endpoint.

CMR has emerged as a novel technique for measuring myocardial salvage (AAR minus the MI size) in PPCI patients, thereby enabling the assessment of the efficacy of a therapeutic interven-
tion for reducing lethal myocardial reperfusion injury in the STEMI patient. The AAR can be retrospectively measured in STEMI patients within 1 week of PPCI using T2-weighted CMR to detect the extent of myocardial oedema (which has been shown to correspond to the AAR).16,17 The MI size can then be measured by late gadolinium enhancement CMR, and myocardial salvage calculated. Importantly, the extent of myocardial salvage assessed by CMR has been reported to predict clinical outcomes in PPCI patients, thereby confirming its importance as a surrogate clinical endpoint.18 Lonborg et al.9 measured the AAR with a CMR scan performed 2 days post-PPCI, whereas the MI size was assessed on the CMR scan performed at 3 months. Over the course of 3 months it is well known that the extent of an MI reduces in size due to infarct remodelling and shrinkage, and their calculation of myocardial salvage may not be accurate. There has also been some concern that therapeutic interventions capable of reducing lethal myocardial reperfusion injury in PPCI patients may actually decrease the extent of myocardial oedema, thereby reducing the size of the AAR, resulting in an inaccurately calculated myocardial salvage index. However, we can be reassured that for exenatide at least there was no change in the size of the AAR.9

In summary, using CMR to assess myocardial salvage, Lonborg et al.9 have demonstrated that a single infusion of the GLP-1 ana-
logue, exenatide, administered at the time of PPCI improved myocardial salvage and reduced MI size/AAR in both diabetic and non-diabetic STEMI patients, thereby confirming the existence of lethal myocardial reperfusion injury in man and demonstrating it to be a viable target for cardioprotection. In addition, the findings from this study illustrate the potential dual actions of certain anti-diabetic drugs (such as the GLP-1 analogues and the DPP-IV inhibitors) to lower blood glucose levels on the one hand while also conferring cardioprotection on the other. Whether exenatide can improve clinical outcomes in this patient group remains to be determined in a large multicentre randomized clinical trial. Fur-

thermore, whether it is cardioprotective in other clinical settings of acute IRI such as in thrombolysed STEMI patients or in patients undergoing coronary artery bypass graft surgery needs to be explored.

Conflict of interest: none declared.

References

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17. Aletras AH, Tlak GS, Natanzon A, Hsu LY, Gonzalez FM, Hoyt RF Jr, Araci AE. Retrospective determination of the area at risk for reperfused acute myocardial
A 62-year-old male was admitted to the emergency department of our centre because of recurrent episodes of palpitations and dizziness. The patient had a history of severe blunt chest trauma with multiple rib fractures (5–10th) due to a tractor fall 2 years before. The electrocardiographic tracing at admission showed (Panel A) a wide QRS tachycardia with the right superior axis, the onset of the QRS is relatively slurred, and the interval from the QRS onset to the peak of V1 is 150 ms, consistent with an epicardial origin. The cardiac evaluation revealed a severely depressed ejection fraction and the coronary angiography excluded significant stenosis of the coronary arteries. The thoracic computed tomography showed a broken fifth rib with chips touching the lateral wall of the left ventricle (Panel B, arrow). An electrophysiological study was performed and the tachycardia was easily inducible during programmed electrical stimulation. Due to a high degree of clinical suspicion of epicardial origin, a median sternotomy that enabled access to the left lateral epicardium was performed. Isolated diastolic potentials that preceded QRS onset by 60 ms was recorded during the ventricular tachycardia. A cryoablation was performed with restoration of sinus rhythm (Panels C and D). During the electrophysiological study after epicardial ablation, no ventricular arrhythmias were inducible with the programmed electrical stimulation from the apex of the right ventricle. At 1-year follow-up, the patient’s outcome was uneventful and the left ventricular ejection fraction recovered to normal. To our knowledge, this is the first report of an epicardial ventricular tachycardia secondary to a remote blunt chest trauma.

Note: Electrocardiographic leads in the figure are taken in the operation theatre.

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