Heme oxygenase-1: An important therapeutic target for protecting against myocardial ischemia and reperfusion injury

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Myocardial reperfusion therapy (such as thrombolysis and percutaneous coronary intervention) is the optimal therapeutic strategy for acute myocardial infarction, which could preserve myocardial viability and function by reversing myocardial ischemia and reducing the infarct size and has been endorsed in clinical practice [1]. However, the subsequent ischemia and reperfusion (I/R) injury may attenuate the therapeutic benefit [1]. Although reperfusion therapy is essential for the survival of ischemic tissue, reperfusion itself could cause additional cellular injury. I/R could cause local myocardial inflammation, accompanying with apoptosis, which could result in myocardial cell damage [2].

High mobility group box 1 protein (HMGB1), a highly conserved nuclear protein that could regulate gene transcription and maintain the nucleosome structure, could be passively released from necrotic cell, apoptotic cell or actively secreted by innate immune cells (such as macrophages and monocytes) [3,4]. Present study shows that HMGB1 functions as a novel pro-inflammatory cytokine and promotes the progress of myocardial I/R injury [5]. HMGB1 could promote the release of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), whereas HMGB1 A box peptide (a specific HMGB1 antagonist) could reduce myocardial ischemia and reperfusion injury and inhibit the release of TNF-α and IL-6 [5], indicating that inhibiting HMGB1 expression could suppress the inflammatory process. Meanwhile, lots of drugs have been found to reduce myocardial I/R injury by inhibiting HMGB1 expression, including asperosaponin X [6], minocycline [7], ethyl pyruvate [8], etc. These suggested that HMGB1 may be a potential therapeutic target for myocardial I/R injury and inhibiting HMGB1 could reduce myocardial I/R injury [9].

Heme oxygenase-1 (HO-1), an inducible isoform of heme oxygenase enzymes, has been proved that it involves inhibition of early pro-inflammatory cytokines, such as TNF-α and IL-6 which could promote cell apoptosis, and induction of the anti-inflammatory cytokine-IL-10 which could inhibit cell apoptosis [10,11]. Recently, Liu et al. [12] showed that hydroxysafflor yellow A could provide a protective effect on anoxia/reoxygenation (same as I/R) -induced apoptosis and injury in H9c2 cardiomyocytes and upregulate expression and activity of HO-1, while an HO-1 inhibitor could completely suppress HO-1 enzymatic activity upregulated by hydroxysafflor yellow A and notably diminished the anti-apoptotic effect of hydroxysafflor yellow A, indicating that HO-1 may play an important protective effect on anoxia/reoxygenation or I/R injury. In addition, Takamiya et al. [13] have demonstrated that the circulating levels of HMGB1 were higher in HO-1−/− mice than HO-1+/+ mice and the HO-1−/− mice given HMGB1 neutralizing antibody showed improvement in survival compared with littermates receiving control antibody. In addition, the HO-1 induction has also been shown that it could prevent the release of HMGB1 inendotoxin-activated macrophages in vitro and septic animals in vivo [14]. These results suggested that the HO-1 induction plays an important role in anti-inflammatory effect and could prevent anoxia/reoxygenation or I/R injury by inhibiting HMGB1 release. In conclusion, upregulating HO-1 expression may provide a protective effect on myocardial I/R injury which may be associated with inhibiting HMGB1 expression; HO-1 may be an important therapeutic target for protecting against myocardial I/R injury.

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Cryoenergy is effective in the treatment of resistant hypertension in non-responders to radiofrequency renal denervation

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To the Editor,

Percutaneous catheter-based renal denervation (RDN) is a new treatment option for drug-resistant hypertension (HTN) [1,2]. Until now, radiofrequency (RF) current is the predominant energy source used for ablation of the renal nerves. However, according to the literature, about 15–20% of treated patients are non-responders to the RDN therapy, indicated by a post-interventional reduction of systolic blood pressure (BP) less than 10 mm Hg [1,2]. In the treatment of cardiac arrhythmias, it was shown that the use of cryoenergy, in comparison to RF current, is accompanied by a reduction of pain and discomfort during ablation without significant differences in the rate of effectiveness [3]. Consequently, this approach might also be used for RDN in drug resistant hypertension to reduce the pain during the procedure, achieve a more effective RDN and minimize the number of non-responders. Recently, we demonstrated that cryoablation of the renal artery is feasible and safe in a sheep model [4]. In this animal model, an almost total loss of neurofilaments in the created lesions was observed representing a surrogate marker for effective sympathetic denervation [4]. Here we describe for the first time that cryoacllation, as second-line therapy for sympathetic denervation of the renal arteries, is safe and effective in patients with ongoing resistant HTN despite optimized medical treatment and previous unsuccessful RDN with RF current.

In this pilot study, three patients with drug resistant hypertension (from a population with a responder rate of 80% [5]) who did not show the intended treatment goal with RF current (reduction of the mean 24-h ambulatory BP ≥ 10 mm Hg) underwent cryoablation for RDN. One patient with end stage renal disease (ERSD) was successfully treated initially with RF ablation of the renal artery. Twelve months later,

Table 1
Baseline patient characteristics.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>Age (y)</td>
<td>38</td>
<td>70</td>
<td>48</td>
</tr>
<tr>
<td>Time after renal denervation with RF current (months)</td>
<td>12</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Comorbidty</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>CAD</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Chronic renal insufficiency (creatinine &gt; 130 μmol/l)</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Obstructive sleep apnoea (treated)</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Body mass index</td>
<td>18.0</td>
<td>47.5</td>
<td>31.8</td>
</tr>
<tr>
<td>Number of antihypertensive medication</td>
<td>6</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Changes at three-month follow-up</td>
<td>– 3</td>
<td>– 2</td>
<td>– 2</td>
</tr>
<tr>
<td>24-h ABPM (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>189/115</td>
<td>154/81</td>
<td>187/104</td>
</tr>
<tr>
<td>At 1 month</td>
<td>104/63</td>
<td>132/73</td>
<td>128/88</td>
</tr>
<tr>
<td>At 3 months</td>
<td>106/65</td>
<td>132/69</td>
<td>161/100</td>
</tr>
</tbody>
</table>

Yr, years; RF, radiofrequency; CAD, coronary artery disease; ABPM, ambulatory blood pressure monitoring.

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References