Effect of ischemic postconditioning on microvascular obstruction in reperfused myocardial infarction. Results of a randomized study in patients and of an experimental model in swine

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A R T I C L E   I N F O
Article history:
Received 28 November 2013
Received in revised form 22 April 2014
Accepted 5 May 2014
Available online 10 May 2014

Keywords:
Myocardial infarction
Perfusion
Ischemic postconditioning

A B S T R A C T

Background: Ischemic postconditioning (PCON) appears as a potentially beneficial tool in ST-segment elevation myocardial infarction (STEMI). We evaluated the effect of PCON on microvascular obstruction (MVO) in STEMI patients and in an experimental swine model.

Methods: A prospective randomized study in patients and an experimental study in swine were carried out in two university hospitals in Spain. 101 consecutive STEMI patients were randomized to undergo primary angioplasty followed by PCON or primary angioplasty alone (non-PCON). Using late gadolinium enhancement cardiovascular magnetic resonance, infarct size and MVO were quantified (% of left ventricular mass). In swine, using an angioplasty balloon-induced anterior STEMI model, MVO was defined as the % of area at risk without thioflavin-S staining.

Results: In patients, PCON (n = 49) in comparison with non-PCON (n = 52) did not significantly reduce MVO (0 [0–1.02]% vs. 0 [0–2.1]% p = 0.2) or IS (18 ± 13% vs. 21 ± 14%, p = 0.2). MVO (N1 segment in the 17-segment model) occurred in 12/49 (25%) PCON and in 18/52 (35%) non-PCON patients, p = 0.3. No significant differences were observed between PCON and non-PCON patients in left ventricular volumes, ejection fraction or the extent of hemorrhage. In the swine model, MVO occurred in 4/6 (67%) PCON and in 4/6 (67%) non-PCON pigs, p = 0.9. The extent of MVO (10 ± 7% vs. 10 ± 8%, p = 0.9) and infarct size (23 ± 14% vs. 24 ± 10%, p = 0.8) was not reduced in PCON compared with non-PCON pigs.

Conclusions: Ischemic postconditioning does not significantly reduce microvascular obstruction in ST-segment elevation myocardial infarction.

Clinical Trial Registration

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1. Introduction

In ST-segment elevation myocardial infarction (STEMI) timely coronary reperfusion is the primary therapeutic goal to reduce left ventricular infarct size and improve patients' outcome [1]. Unfortunately, despite successful reperfusion of the epicardial blood flow an impairment of microvascular perfusion persists in a significant number of patients, a phenomenon referred to as microvascular obstruction (MVO)
In recent years MVO has shown to be a powerful and independent predictor of a poor outcome [3–5]. Availability of cost-effective and easy-to-implement therapies that could reliably reduce MVO and subsequently may optimize the beneficial effects of timely primary percutaneous intervention would be of utmost importance [6,7]. In recent years ischemic postconditioning (PCON) has emerged as a promising option. PCON permits a progressive rather than a brisk restoration of blood flow to the jeopardized myocardium by means of consecutive cycles of inflation and deflation of the angioplasty balloon used to open the acute coronary occlusion [6–8]. Previous experimental evidence [8–11] and preliminary clinical data [12–18] suggest that this simple strategy exerts a number of protective myocardial effects in comparison with the immediate reperfusion achieved by means of a standard primary angioplasty approach. Nevertheless, the effect of PCON on MVO has not been specifically addressed.

In the present study we aimed to analyze the effect of PCON on cardiovascular magnetic resonance-derived MVO in a randomized series of patients with a first STEMI treated with primary angioplasty and on myocardial samples obtained from a highly controlled anterior STEMI swine model. Additionally, the effect of PCON on infarct size was also evaluated in the same scenarios.

2. Methods

2.1. Study group in patients

From October 2011 to July 2012, consecutive patients of age ≥18 years who were admitted to two university hospitals for a first STEMI within the first 12 h of chest pain onset and for whom the clinical decision to treat with percutaneous coronary intervention was made, were considered for inclusion. STEMI diagnosis was established on the basis of current guidelines [19].

The exclusion criteria were as follows: documented history of previous infarction; primary percutaneous revascularization not attempted; severe clinical or hemodynamic deterioration; left main stem disease; thrombolysis in myocardial infarction (TIMI) 2–3 or Rentrop collateral flow grade ≥1; death, re-infarction, cardiac surgery or severe clinical deterioration before cardiovascular magnetic resonance study; patients who denied participation in the registry; any contraindications to cardiovascular magnetic resonance.

The institutional ethics committees of the participating institutions approved the research protocol and written informed consent was obtained from all subjects. The study was conducted in accordance with the Declaration of Helsinki.

Fig. 1. Flow chart of patients. Reasons for exclusion of patients before randomization and before cardiovascular magnetic resonance are exposed in the flow chart. Abbreviations: CMR = cardiovascular magnetic resonance imaging; STEMI = ST-segment elevation myocardial infarction; TIMI = thrombolysis in myocardial infarction.
2.2. Reperfusion therapy in patients

In total, 243 STEMI patients were admitted to the institutions participating in the present study during the study period. Of these, 111 patients were excluded and 132 were randomly allocated to either the PCON or the non-PCON group. Randomization was performed using a computer-generated randomization sequence. In summary, once diagnostic coronary angiography had been carried out and the decision to undertake primary angioplasty had been made, operators acceded with their personal codes to a web page specifically developed for the present study (Universitat Politècnica, Valencia, Spain) where the patient was recorded and the study group assignment was obtained. Of the 132 randomized patients, 31 were excluded before cardiovascualar magnetic resonance. Accordingly, the final study group to explore the effect of PCON on cardiovascular magnetic resonance-derived MVO consisted of 101 patients (49 PCON and 52 non-PCON). Reasons for exclusion of 111 patients before randomization and of 31 randomized patients before cardiovascular magnetic resonance are exposed in the flow chart (Fig. 1).

Baseline characteristics, clinical data and the TIMI risk score [20] were prospectively recorded in all cases. The percentage of sum ST-segment resolution 90 min after reperfusion and the peak value was recorded.

Management of patients in the catheterization laboratory was left at the discretion of the attending Interventional cardiologists; 300 mg aspirin plus 600 mg clopidogrel oral load doses were administered. Regarding the antiagulant drug used, 40 patients (40%) received bivalirudin and 61 (60%) were treated with IIb/IIIa inhibitors plus intravenous unfractionated heparin (Table 1). The radial approach was performed using a computer-generated randomization sequence. In summary, of the 132 randomized patients, 31 were excluded before randomization and of 31 randomized patients before cardiovascular magnetic resonance are exposed in the flow chart (Fig. 1).

Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PCON</th>
<th>Non-PCON</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>101</td>
<td>49</td>
<td>52</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60 ± 13</td>
<td>60 ± 12</td>
<td>59 ± 13</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>64 (81)</td>
<td>43 (87)</td>
<td>41 (79)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>27 (27)</td>
<td>10 (20)</td>
<td>17 (33)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>51 (51)</td>
<td>25 (51)</td>
<td>26 (51)</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>53 (53)</td>
<td>23 (47)</td>
<td>30 (58)</td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>60 (59)</td>
<td>29 (59)</td>
<td>31 (60)</td>
</tr>
<tr>
<td>Anterior infarction (%)</td>
<td>41 (41)</td>
<td>19 (39)</td>
<td>22 (42)</td>
</tr>
<tr>
<td>Heart rate (beats per min)</td>
<td>75 ± 18</td>
<td>78 ± 19</td>
<td>73 ± 16</td>
</tr>
<tr>
<td>Systolic pressure (mm Hg)</td>
<td>134 ± 31</td>
<td>134 ± 30</td>
<td>135 ± 32</td>
</tr>
<tr>
<td>Killip class I (%)</td>
<td>70 (69)</td>
<td>30 (61)</td>
<td>40 (77)</td>
</tr>
<tr>
<td>Killip class ≥ II (%)</td>
<td>31 (31)</td>
<td>19 (39)</td>
<td>12 (23)</td>
</tr>
<tr>
<td>Time to reperfusion (min)</td>
<td>190 [136–352]</td>
<td>190 [129–300]</td>
<td>190 [150–416]</td>
</tr>
<tr>
<td>TIMI risk score</td>
<td>3 ± 2</td>
<td>3 ± 2</td>
<td>3 ± 2</td>
</tr>
<tr>
<td>ST-segment resolution (%)</td>
<td>84 [58–100]</td>
<td>77 [55–100]</td>
<td>86 [69–100]</td>
</tr>
</tbody>
</table>

Cardiac catheterization

Proximal left anterior descending (%) | 18 (18) | 9 (18) | 9 (17) | 0.9 |
Multivessel disease (%)               | 38 (38) | 21 (43) | 17 (33) | 0.3 |
Thrombus aspiration (%)               | 54 (53) | 25 (51) | 29 (56) | 0.8 |
Number of implanted stents            | 1.3 ± 0.7 | 1.4 ± 0.7 | 1.3 ± 0.6 | 0.6 |
Treatment with drug eluting stent (%) | 65 (64) | 31 (63) | 34 (65) | 0.8 |
TIMI flow grade 3 post-stent (%)      | 97 (96) | 48 (98) | 49 (94) | 0.6 |
Blush grade 2–3 post-stent (%)        | 83 (82) | 42 (86) | 41 (79) | 0.4 |

In-hospital medical treatment

Aspirin (%)                           | 101 (100) | 49 (100) | 52 (100) | 0.9 |
Clopidogrel (%)                       | 101 (100) | 49 (100) | 52 (100) | 0.9 |
Bivalirudin (%)                       | 40 (40) | 19 (39) | 21 (40) | 0.9 |
Ilibilla inhibitors and heparin (%)   | 61 (60) | 30 (61) | 31 (60) | 0.9 |
Beta-blockers (%)                     | 81 (80) | 37 (76) | 44 (85) | 0.3 |
ACE/AR inhibitors (%)                 | 84 (81) | 44 (90) | 40 (77) | 0.2 |
Statins (%)                           | 90 (89) | 41 (84) | 49 (94) | 0.3 |
Diuretics (%)                         | 22 (22) | 10 (20) | 12 (23) | 0.8 |

Abbreviations. ACE/AR = angiotensin converting enzyme/angiotensin receptor. PCON = postconditioning. TIMI = thrombolysis in myocardial infarction. Creatine-kinase MB mass is expressed as times over the upper reference limit. Continuous variables with a normal distribution are expressed as mean (SD) and those without a normal distribution are expressed as median (percentiles 25th–75th).

Cardiovascular magnetic resonance study in patients

Cardiovascular magnetic resonance (1.5-T, Sonata Magnetom, Siemens, Erlangen, Germany) was performed at a median of 6 days (range 5–8 days) after STEMI according to our laboratory protocol [43,22]. All images were acquired by a phased-array body surface coil during breath-holds and were ECG-triggered. Information about cardiovascular magnetic resonance sequences can be consulted in the Supplementary material.

Cardiovascular magnetic resonance studies were quantified in a central lab (Cardiac Imaging Unit, INCLIVA, Valencia, Spain) using customized software (QMASS MR, 6.1.5, Medis, Leiden, The Netherlands) by an experienced operator (F Ch, 10 years of experience in the quantification of cardiovascular magnetic resonance studies) who was blinded to the assigned treatment and to all patient data.

In cine imaging, left ventricular ejection fraction (%), end-diastolic and end-systolic volume indexes (ml/m²) and mass (g/m²) were calculated by manual planimetry of endocardial and epicardial borders of all short-axis views (Fig. 2A).

Myocardial edema was manually quantified as areas of high T2 signal intensity with respect to remote non-infarcted myocardium (Fig. 2B). Myocardial hemorrhage was manually defined as hypointense areas in the core of edema (Fig. 2B). Myocardial edema and hemorrhage were expressed as percentage of left ventricular mass.

Delayed gadolinium enhancement was manually quantified as areas of hyperenhancement in delayed gadolinium enhancement imaging. Infarct size was regarded as myocardium showing delayed enhancement (Fig. 2C) and expressed as percentage of left ventricular mass. Myocardial salvage index was defined as the percentage of myocardium with edema not displaying delayed gadolinium enhancement (Fig. 2C).

MVO was visually defined as a lack of contrast uptake in the core of tissue showing delayed gadolinium enhancement (Fig. 2D); the extent of MVO was manually defined and expressed as percentage of left ventricular mass. In order to avoid artifacts and based on the prognostic value previously demonstrated by our group [4,5], significant MVO was considered to be present if it was detected in more than one segment and in more than one view using the 17-segment model [23].

The intra-observer variability for the quantification of all cardiovascular magnetic resonance parameters in our core lab has been previously determined and is less than 5% [5].
2.4. Experimental study

In the experimental study, fourteen juvenile domestic female pigs weighing 25–30 kg were used. The Animal Care and Use Committee of the University of Valencia approved the study and it conforms to the Guide for the Care and Use of Laboratory animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1993). The entire study protocol has been described elsewhere [24].

In short, ischemia was induced by inflating a 2.5 × 10 mm angioplasty balloon at four atmospheres in the mid-left anterior descending coronary artery after the first diagonal branch in anesthetized pigs. Coronary artery occlusion was confirmed by contrast injection and by electrocardiographic ST-segment elevation. After 90 min, the balloon was deflated and restoration of normal coronary flow was documented by angiography; 7 pigs were assigned to non-PCON and 7 underwent (1 min after reperfusion) the same 4-cycle PCON protocol defined in humans using the angioplasty balloon used for provoking the infarct. The animals were allowed to recover. No coronary dissection or closure was detected at reperfusion or at 72 h angiogram.

After 72 h, pigs were anesthetized again and 20 ml of 4% thioflavin-S solution was selectively infused into the left anterior descending coronary artery using an over-the-wire catheter. Hearts were then arrested with potassium chloride and excised. The left ventricle was sectioned into 5-mm thick short-axis slices. In order to detect thioflavin-S stained areas, each slice was viewed from the apical side under ultraviolet light and photographed. Afterwards, slices were incubated into 2,3,5-triphenyltetrazolium chloride 2% solution for 20 min at 37 °C. Finally, they were viewed under room light and photographed. Images were digitized and manual definition of endocardial and epicardial borders of 4 short-axis slices (mimicking the 17-segment model in patients) were carried out offline by an independent experienced investigator using dedicated software (MATLAB 6.5, The Mathworks, Inc., Nattick, MA, USA).

The left anterior descending artery-perfused area (area at risk) was defined as the percentage of the LV volume showing thioflavin-S staining. Infarct size was defined as the percentage of the area at risk that failed to stain with 2,3,5-triphenyltetrazolium chloride. MVO was interpreted as the percentage of the area at risk that did not stain either with

![Fig. 2. Cardiovascular magnetic resonance imaging indexes. Images illustrate the cardiovascular magnetic resonance imaging indexes evaluated in the present study. A. In cine imaging, manual planimetry of endocardial and epicardial borders of all short-axis views was carried out in order to quantify left ventricular ejection fraction, end-diastolic and end-systolic volume indexes and mass. B. In T2 sequences, myocardial edema was defined as those areas showing high T2 signal intensity (arrow, left panel). Myocardial hemorrhage was regarded as hypointense areas in the core of edema (arrow, right panel). C. In delayed gadolinium enhancement sequences, infarct size was defined as the percentage of myocardium with edema (right panel, top, myocardium located between dashed lines) not displaying delayed gadolinium enhancement (right panel, bottom, red squares). D. Microvascular obstruction was defined as a lack of contrast uptake in the core of tissue showing delayed gadolinium enhancement (arrows).](image-url)
2,3,5-triphenyltetrazolium chloride or with thioflavin-S (Fig. 3). MVO was considered to be present if it affected >1 segment based on the 17-segment model.

2.5. Endpoint

The primary endpoint of the present study was to assess the effect of PCON on the occurrence and extent of MVO in STEMI patients treated with primary angioplasty and in the experimental swine model.

The secondary endpoint was to explore the effect of PCON on infarct size in STEMI patients treated with primary angioplasty (using CMR) and in the experimental swine model (as derived from the quantification of myocardial samples).

2.6. Statistical methods

The target sample size was calculated to assess the effect of PCON on the occurrence of MVO measured by cardiovascular magnetic resonance imaging. The expected effect was a 50% reduction in MVO with a statistical power of 80% and a probability of a type I error of 0.05 with a 2-sided test. Assuming a drop-out rate of 25%, the total sample consisted of 98 patients randomized equally to the two groups. For security reasons we finally randomized 132 patients.

Continuous variables were tested for normal distribution using the one-sample Kolmogorov–Smirnov test. Continuous normally distributed data were expressed as the mean ± standard deviation and compared using the Student’s t-test. Non-parametric data were expressed as the median with the interquartile range [percentiles 25th–75th] and were compared with the Mann–Whitney U-test. Group percentages were compared using the chi-square test or Fisher’s exact test where appropriate.

A multivariate logistic regression model was used to find out the effect of PCON on the occurrence of MVO once adjusted for those baseline characteristics that were available upon patients’ presentation and showed an association with MVO with a p-value <0.2. Odds ratios [95% confidence intervals] were determined.

Statistical significance was considered for two-tailed p < 0.05. SPSS 13.0 (SPSS Inc., Chicago, Illinois, USA) was used.

3. Results

3.1. Study in patients

The baseline characteristics, angiographic data and in-hospital medical treatment of the 101 patients included in the study are displayed in Table 1. The majority of patients were male (n = 84) with a mean age of 60 ± 13 years. The median time from pain onset to revascularization was 190 [136–352] min. All patients underwent primary angioplasty with stent placement, 49 patients were allocated to a PCON strategy and 52 underwent primary angioplasty alone. No significant differences were detected between PCON and non-PCON patients regarding baseline characteristics, angiographic data or in-hospital medical treatment (Table 1).

Cardiovascular magnetic resonance characteristics of the whole study group as well as of PCON and non-PCON patients are displayed in Table 2. Overall, no significant differences existed between PCON and non-PCON patients in terms of left ventricular ejection fraction, volume indexes or mass. PCON was not associated with a reduced extent of myocardial edema or hemorrhage and did not increase the myocardial salvage index.

Infarct size was comparable in PCON and non-PCON patients (18 ± 13% vs. 21 ± 14% of LV mass, p = 0.2, Table 2, Fig. 4).

In total, MVO (>1 segment) occurred in 30 patients (30%) with a mean extension of 0 [0–0.5]% of left ventricular mass. The extent of MVO (0 [0–1.02]% vs. 0 [0–2.1]% of left ventricular mass, p = 0.2) was similar in PCON and non-PCON patients (Table 2, Fig. 4). MVO
(>1 segment) was present in 12 (25%) PCON and 18 (35%) non-PCON patients, p = 0.3 (Fig. 5).

The relationship between baseline characteristics upon patients’ presentation and the occurrence of MVO is displayed in the Supplementary material (Table S1). Once adjusted for variables showing a p-value < 0.2 in Table S1 (previous history of hypertension, heart rate, Killip class upon presentation and proximal left anterior descending artery disease), PCON was not associated with a lower probability of MVO (odds ratio [95% confidence intervals]: 0.6 [0.2–1.5], p = 0.3).

In parallel to the whole study group, no significant difference between PCON and non-PCON patients in terms of the extent and occurrence of MVO was observed when subgroup analyses based on time to reperfusion (more or less than median), anterior vs. non-anterior infarction, use of thrombus aspiration and infarct size (more or less than median) were carried out (Supplementary material, Table S2).

### Table 2

Cardiovascular magnetic resonance characteristics of the whole study group and of patients treated with and without ischemic postconditioning.

<table>
<thead>
<tr>
<th>Study group</th>
<th>PCON</th>
<th>Non-PCON</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>101</td>
<td>49</td>
<td>52</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>51 ± 12</td>
<td>52 ± 12</td>
<td>50 ± 13</td>
</tr>
<tr>
<td>End-diastolic volume index (ml/m²)</td>
<td>78 ± 19</td>
<td>77 ± 18</td>
<td>78 ± 20</td>
</tr>
<tr>
<td>End-systolic volume index (ml/m²)</td>
<td>39 ± 16</td>
<td>39 ± 16</td>
<td>39 ± 16</td>
</tr>
<tr>
<td>Left ventricular mass (g/m²)</td>
<td>70 ± 17</td>
<td>71 ± 18</td>
<td>69 ± 15</td>
</tr>
<tr>
<td>Myocardial edema (% of mass)</td>
<td>0.8 ± 2.6</td>
<td>0.8 ± 2.8</td>
<td>0.7 ± 2.5</td>
</tr>
<tr>
<td>Myocardial hemorrhage (% of mass)</td>
<td>28 ± 26</td>
<td>31 ± 23</td>
<td>28 ± 29</td>
</tr>
<tr>
<td>MVO (% of mass)</td>
<td>0 [0–0.5]</td>
<td>0 [0–1.02]</td>
<td>0 [0–2.1]</td>
</tr>
</tbody>
</table>

Abbreviations. MVO = microvascular obstruction. PCON = postconditioning. Myocardial edema, myocardial hemorrhage, infarct size and microvascular obstruction are expressed as % of left ventricular mass.

Fig. 3. Macroscopic samples obtained from the swine model. Thioflavin-S and 2,3,5-triphenyltetrazolium chloride staining. Top panels correspond to an entire swine heart photographed after excision. On the left panel, the left anterior descending artery perfused area (stained with thioflavin-S) can be easily detected under ultraviolet light. On the right panel, the infarcted area can be observed (arrow) in the mid-apical anterior area even before 2,3,5-triphenyltetrazolium chloride staining. Bottom panels correspond to a transversal slice of the same heart. Extensive areas of microvascular obstruction (lack of thioflavin-S staining, left panel, arrows) and infarction (lack of 2,3,5-triphenyltetrazolium chloride staining, right panel, arrows) were detected both in the right and left ventricles. Abbreviations: LV = left ventricle; RV = right ventricle.

Fig. 4. Effect of ischemic postconditioning in patients and in experiments. Schemes represent the effect of ischemic postconditioning on infarct size and on the extent of microvascular obstruction. Ischemic postconditioning did not reduce infarct size and the extent of microvascular obstruction neither in patients (top panels) nor in the swine model (bottom panels). Results are expressed as percentage of left ventricular mass (in patients) and percentage of area at risk (in swine). In patients, MVO was a non-parametric variable. In this figure, values are presented as mean ± SD. Abbreviations: MVO = microvascular obstruction. PCON = ischemic postconditioning.

Fig. 5. Effect of ischemic postconditioning on the occurrence of microvascular obstruction in patients and in experiments. Bars represent the percentage of cases with microvascular obstruction (in >1 segment according to the 17-segment model). Ischemic postconditioning did not significantly reduce the occurrence of microvascular obstruction neither in patients (left panel) nor in the swine model (right panel). Abbreviations: MVO = microvascular obstruction. PCON = ischemic postconditioning.
3.2. Experimental study

Left anterior descending artery occlusion was performed in 14 pigs, of which two died during balloon inflation due to refractory ventricular fibrillation. Experiments were successfully conducted in the remaining 12 cases although ventricular defibrillation was required in 6 during left anterior descending artery occlusion. No significant complications were recorded during the 72 h reperfusion period.

Thioflavin-S staining (corresponding to the left anterior descending artery-perfused area, 65 ± 24% of left ventricular volume) and absence of 2,3,5-triphenyltetrazolium chloride staining (corresponding to the presence of infarcted tissue, 25 ± 9% of left ventricular volume) were detectable in all cases. Overall, MVO (defined as a lack of thioflavin-S staining in the core of the infarcted tissue) was present in 8 cases (66%) and comprised 10 ± 7% of the left ventricular volume.

Pigs treated with PCON (n = 6) compared with non-PCON experiments (n = 6), did not display a significant reduction in the extent of MVO (10 ± 7% vs. 10 ± 8% of left ventricular volume, p = 0.9) nor in infarct size (23 ± 14% vs. 24 ± 10% of left ventricular volume, p = 0.8) (Fig. 4).

MVO (>1 segment) was present in 4 (67%) PCON and in 4 (67%) non-PCON pigs, p = 0.9 (Fig. 5).

Thus similar findings in terms of extent and occurrence of infarct size and MVO were observed in PCON and non-PCON experiments. 2,3,5-Triphenyltetrazolium chloride and thioflavin-S staining of all experiments are displayed in Fig. 6.

4. Discussion

MVO can be visualized by cardiovascular magnetic resonance in a single session with accurate and reproducible measurements of left ventricular ejection fraction and infarct size, using a gadolinium based contrast agent. Patients with cardiovascular magnetic resonance-derived MVO are more likely to demonstrate wall thinning and less likely to demonstrate systolic recovery during follow-up study. Moreover MVO is an important predictor of a worse prognosis [2–5]. Additional therapies aiming to minimize MVO and consequently avoid its detrimental effects would be appreciated [2]. In this scenario PCON appears as a simple, cost-effective, widely available and easy-to-use approach to complement primary angioplasty in the management of STEMI [6,7]. However,
its effect on the occurrence of MVO has not been specifically analyzed so far. The main finding of the present study is that, in reperfused myocardial infarction, PCON did not significantly reduce the occurrence of MVO. This therapy did not exert any significant reduction of infarct size either.

4.1. Ischemic postconditioning and infarct size

A number of experimental works suggested that PCON, consisting of short periods of transient coronary occlusion during myocardial reperfusion, associated to a significant reduction of infarct size [6–11]. On the basis of this promising experimental data, several clinical studies aiming at analyzing the effect of PCON on infarct size reduction were undertaken. The first series included a small number of patients and showed that surrogates of infarct size were significantly diminished when PCON was used [12–14]. These positive results encouraged the execution of randomized trials focused on the effect of PCON in reducing cardiovascular magnetic resonance-derived infarct size yielding controversial results: whereas some studies reported a beneficial effect of PCON on myocardial salvage [12,15,16], others [17,18] did not. The disparity of results in these recent series probably reflects a high variability in study groups as well as the difficulty of achieving further reductions in infarct size beyond that derived from timely coronary reperfusion.

Regarding infarct size our data parallel recent studies that failed to detect a significant reduction in infarct size with PCON [17,18]. It is noteworthy that, although we did not detect any benefit, we did not see any harm with this treatment either.

4.2. Ischemic postconditioning and microvascular obstruction

In patients with reperfused STEMI, MVO is present in around 30% of patients and it is caused by a number of factors including distal embolization, inflammation, ischemia and reperfusion injury [1,2]. It has been suggested that PCON exerts a number of beneficial effects such as preservation of mitochondria, a certain anti-inflammatory action on neutrophils, and a delay of the rapid re-alkalinization of the heart during reperfusion. All these mechanisms could potentially result in a significant attenuation of MVO [6,7]. Moreover, in comparison with necrosis, MVO has a more progressive pathophysiological time course [2]; theoretically, this would offer an additional time window to PCON to exert its effects. Thus it is plausible to consider that reduction of MVO represents a suitable and realistic objective in order to explore the therapeutic impact of PCON in STEMI patients beyond routine coronary reperfusion.

The present study is the first randomized clinical trial specifically designed to analyze the effect of PCON on MVO as a primary outcome. Our results in patients strongly indicate that PCON does portend a significant reduction neither in the occurrence nor in the extent of MVO. In STEMI patients there is a high case-to-case variability. This could, at least in part, explain the inconsistency of results regarding the role of PCON in this scenario. To solidly demonstrate the effect of PCON on MVO, this should be consistent both in the clinical scenario (with a high inter-individual variability) and in a controlled experimental model. For that reason, in parallel with the randomized clinical study, we analyzed the same endpoint in a highly controlled swine model. In this context confounding factors can be minimized and variations in MVO should be attributed to the only differing variable, namely PCON.

We used a large animal model, focused on MVO and evaluated the resulting damage not immediately but 72 h after infarction. Results in the experimental branch were even more consistent than in the clinical study. The occurrence of MVO was exactly the same in PCON and non-PCON experiments and, in terms of extension, an almost identical percentage of left ventricular volume displaying MVO and necrosis was detected in both groups.

It cannot be definitively excluded that PCON may exert a beneficial effect in a very specific subset of patients or situations. For example, Newton et al. in a short series of 25 STEMI patients which included primary and rescue angioplasty all of them treated with primary stenting (a strategy not always possible in routine practice) suggested a reduction in MVO in PCON patients [25]. Vilahur et al. in an experimental study where swine were sacrificed soon hours after infarction observed that PCON associated with a reduction in infarct size [26]; MVO was not evaluated. These recent studies seem to suggest that PCON could exert a beneficial effect in a short-term perspective. However, in our study and in parallel to the whole study group, PCON did not associate to a lesser extent or a lower occurrence of MVO in subgroups with a higher probability of myocardial salvage: patients with a short revascularization time, those treated with thrombus aspiration and patients with non-anterior or small infarctions (Supplementary material, Table S2).

4.3. Study limitations

As in all studies with neutral results, a possible limitation could be the number of patients studied. The present study yielded a non-significant difference regarding the extent of MVO in PCON patients versus non-PCON patients [mean difference 0.6% of LV mass, SD 3.25%]. Based on these results, and if we aimed to re-calculate the sample size of the study group necessary to determine if the true difference between the PCON and non-PCON groups is 0.6, we would need to study 1236 subjects (618 subjects per group) to be able to reject the null hypothesis. This figure, along with the almost identical extent and occurrence of MVO in PCON and non-PCON pigs in the experimental branch, further illustrates that PCON does not appear as a promising option to reduce MVO in unselected STEMI patients.

4.4. Clinical implications

Ischemic postconditioning does not significantly reduce the occurrence of microvascular obstruction in reperfused ST-segment elevation myocardial infarction. This, along with the inconsistent benefit of ischemic postconditioning in attenuating infarct size reported in recent literature and the neutral effect detected in the present study, suggests that the use of this therapy cannot be recommended in the routine reperfusion of STEMI patients.

Acknowledgments

The present study was supported by the “Instituto de Salud Carlos III” (PI1102323 grant), FEDER, the “Conserveria de Educacio, Cultura i Esport de la Generalitat Valenciana” (PROMETEO/2013/007 grant) and by the Regensburger Forschungsförderung in der Medizin (ReForM).

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2014.05.003.

References


