No post-conditioning in the human heart with thrombolysis in myocardial infarction flow 2–3 on admission

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Aims

Proof-of-concept evidence suggests that mechanical ischaemic post-conditioning (PostC) reduces infarct size when applied immediately after culprit coronary artery re-opening in ST-elevation myocardial infarction (STEMI) patients with thrombolysis in myocardial infarction 0–1 (TIMI 0–1) flow grade at admission. Whether PostC might also be protective in patients with a TIMI 2–3 flow grade on admission (corresponding to a delayed application of the post-conditioning algorithm) remains undetermined.

Methods and results

In this multi-centre, randomized, single-blinded, controlled study, STEMI patients with a 2–3 TIMI coronary flow grade at admission underwent direct stenting of the culprit lesion, followed (PostC group) or not (control group) by four cycles of (1 min inflation/1 min deflation) of the angioplasty balloon to trigger post-conditioning. Infarct size was assessed both by cardiac magnetic resonance at Day 5 (primary endpoint) and cardiac enzymes release (secondary endpoint). Ninety-nine patients were prospectively enrolled. Baseline characteristics were comparable between control and PostC groups. Despite comparable size of area at risk (AAR) (38 ± 12 vs. 38 ± 13% of the LV circumference, respectively, \( P = 0.89 \)) and similar time from onset to intervention (249 ± 148 vs. 263 ± 209 min, respectively, \( P = 0.93 \)) in the two groups, PostC did not significantly reduce cardiac magnetic resonance infarct size (23 ± 17 and 21 ± 18 g in the treated vs. control group, respectively, \( P = 0.64 \)). Similar results were found when using creatine kinase and troponin I release, even after adjustment for the size of the AAR.

Conclusion

This study shows that infarct size reduction by mechanical ischaemic PostC is lost when applied to patients with a TIMI 2–3 flow grade at admission. This indicates that the timing of the protective intervention with respect to the onset of reperfusion is a key factor for preventing lethal reperfusion injury in STEMI patients.

Clinical trial number

NCT01483755.

Keywords

Acute coronary syndrome • Myocardial infarction • Post-conditioning • Cardioprotection

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Introduction

Acute myocardial infarction (AMI) is a leading cause of heart failure and death.1,2 Timely reperfusion is recommended as soon as possible for attenuating ischaemia-related myocardial damage.1,3 However, reperfusion itself has the potential to cause additional lethal injury to the heart.4–7 Zhao et al.8 demonstrated in the dog model that four cycles of (1 min of ischaemia/1 min of reperfusion) performed immediately after reflow following a prolonged coronary artery occlusion dramatically reduces infarct size: they named this phenomenon ‘ischaemic post-conditioning’ (PostC). In STEMI patients with a fully occluded coronary artery [0–1 thrombolysis in myocardial infarction (TIMI) flow grade], several groups have reported that repeated cycles of brief inflations of the angioplasty balloon with short intervening deflations were able to significantly reduce infarct size and further improve the recovery of myocardial contractile function.9–12

One important limitation of ischaemic PostC in animal models is however the very narrow time window for cardioprotection.3–15 Kin et al.16 reported in an experimental model that the beneficial effect of PostC was lost when post-conditioning algorithm was delayed by more than 1 min after reperfusion. However, Roubille et al. recently challenged these findings. They showed that the application of ischaemic PostC was still protective even when delayed by up to 15 min after reperfusion following a 40 min ischaemia in the mouse model.17 Whether cardioprotection could be offered by delayed ischaemic PostC remains unknown in the clinical setting.

A significant proportion of STEMI patients exhibit an opened culprit coronary artery at the time of the admission coronary angiography. In recent reports, nearly one-third of STEMI patients treated by primary percutaneous coronary intervention (PCI) presented with a 2–3 TIMI grade flow at admission coronary angiography.18–20 PostC cannot then be applied in the early minutes of reflow, but instead in a delayed manner. This population of patients therefore represents a ‘clinical model’ for ‘delayed’ PostC (Figure 1).

The main objective of this trial was to assess the effect of delayed mechanical ischaemic PostC on infarct size measured by contrast-enhanced magnetic resonance imaging and myocardial enzymes release in patients with acute STEMI presenting with spontaneous reperfusion of the culprit coronary artery.

Methods

The study was performed according to the Declaration of Helsinki (revised version of Somerset West, Republic of South Africa, 1996) and according to the European Guidelines of Good Clinical practice (version 11, July 1990) and French laws. The study protocol was approved by our Institution’s Ethics Committee. All subjects gave written informed consent before inclusion.

Study population

Male and female patients > 18 years of age, presenting within 12 h after chest pain onset, with ST-segment elevation ≥ 0.1 mV in two contiguous leads on 12-lead electrocardiogram and referred for PCI were eligible for enrolment. Patients with cardiac arrest, cardiogenic shock, or previous AMI were not included. The culprit coronary artery (either the left anterior descending or right coronary artery) had to be patent at the time of PCI with a TIMI flow grade ≥ 2. Patients with evidence of coronary collaterals to the risk region (Rentrop grade ≥ 1) and patients with obvious contra-indication for cardiac magnetic resonance scan (CMR scan) were not included or excluded from the study.

Coronary angioplasty

All patients received aspirin and a clopidogrel or prasugrel loading dose and heparin prior to the coronary intervention, as reported in Table 3. Coronary angiography was performed using a standard Seldinger technique. Coronary angiography allowed identification of the culprit coronary artery and checked that spontaneous reperfusion had occurred before PCI (i.e. TIMI ≥ 2 flow grade) and that no collateral filling from ipsi- or contra-lateral coronary vessels was present.19 Acute biplane LV angiography was performed just before stenting (30° right anterior oblique, 60° left anterior oblique). Coronary angioplasty was performed according to the direct stenting technique of the culprit coronary artery lesion, as described elsewhere.9–11

The area at risk (AAR) was estimated by measuring the abnormally contracting segments (ACSs) according to the method previously

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**Figure 1** Natural clinical setting of delayed post-conditioning. ST-elevation myocardial infarction patients with a thrombolysis in myocardial infarction 2–3 flow grade at coronary angiography have necessarily undergone spontaneous reperfusion prior to hospital admission. This early reflow caused lethal reperfusion injury well before PostC could be applied. These clinical settings can be considered as a ‘natural’ model of delayed PostC.
We used the BARI score as an additional technique to measure the AAR size. The BARI score is based upon an individualized assessment of the length and calibre of coronary arteries for the assessment of the jeopardized myocardium, as previously described. The AAR was expressed as a percentage of the left ventricular myocardium.

**Experimental design**

This was a multi-centre, prospective, randomized, single-blinded, controlled study. After the patients had given informed consent, they were randomly allocated to either the control or the PostC Group through pre-established sealed envelopes (Figure 2). All patients underwent direct stenting of the culprit lesion. After stenting, control patients underwent no further intervention, except clinically relevant additional treatments as described in Table 3. In PostC patients, the angioplasty balloon was re-inflated four times during 1 min (with a 1 min intervening reperfusion period) within 1 min after direct stenting. Re-inflation was performed at a site proximal to the stent implanted into the culprit lesion. Eight minutes after stenting, coronary angiography was performed in both groups to assess coronary patency.

**Treatment allocation**

Randomization was performed with the use of a computer-generated randomization sequence. Numbered, sealed envelopes that contained the study group assignment were distributed to each catheterization laboratory and were opened after informed consent had been obtained. Imaging investigators, statistical team, and also patients were blinded to the allocated group.

**Measurement of infarct size**

**Cardiac magnetic resonance imaging study**

All CMR studies were performed on a 1.5 T MAGNETOM Avanto TIM system (Siemens, Erlangen) 48–96 h after admission. Localizers and LV functional assessment with complete LV coverage were performed using steady-state, free-precession images. Delayed enhancement for infarct size and micro-vascular obstruction (MVO) was determined using a breath-hold 3D inversion recovery gradient-echo pulse sequence (TR, 1.0 ms; TE, 3.4 ms; flip angle, 20°; typical spatial resolution, 1.4 x 1.4 x 5 mm) covering the whole ventricle performed 10 min after i.v. administration of 0.2 mmol/kg of gadolinium (Dotarem®, Guerbet France). Inversion times were adjusted to optimize nulling of normal myocardium (typical values, 270–300 ms).

All images were transferred to a dedicated OsiriX workstation (OsiriX Foundation, Geneva, Switzerland) for analysis and measurement. Left ventricular volumes, ejection fraction, mass measurements, and segmental thickening were performed from the cine images with dedicated software (Argus, Siemens Medical Solutions, Malvern, PA, USA). Micro-vascular obstruction (MVO) was measured at 10 min on delayed enhanced images by manual delineation of the hypo-enhanced areas within the hyper-intense infarcted myocardium. Infarcted myocardium was measured by manual delineation of the hyper-intense myocardium on delayed enhanced images at 10 min. The main endpoint was the infarct size reported to the AAR.

**Cardiac enzymes release during the first 72 h after postC**

Blood samples were taken at admission, every 4 h after PostC during Day 1, and every 6 h on Days 2 and 3. Area under the curve (AUC; arbitrary units) of serum creatine kinase (CK) release and troponin I (Beckman Kit)
was measured in each patient by computerized planimetry (GraphPad Prism v.5.00, San Diego, CA, USA) and used as a surrogate marker of infarct size. Peak of release for CK and troponin I were also evaluated.

**Clinical outcome**

All patients enrolled had a clinical follow-up at 6 months, and all cause death, myocardial infarction, unplanned coronary revascularization, or heart failure events were reported.

**Statistical analysis**

Calculation of sample size was performed according to previous studies.\(^{11,22,23}\) Considering an expected reduction in 30% in infarct size, an average absolute infarct size of 26 g, and a SD of 13.5 g, we calculated a total sample size of 90 patients for each group as independent variables. Spearman’s test was used to study the correlations between infarct size and the AAR.

Both CMR infarct size and CK AUC were significantly or fairly correlated with the area at risk size (as estimated either by the ACS) (\(R = 0.36; P = 0.005\) for CMR infarct size and \(R = 0.19; P = 0.11\) for CK AUC respectively) in the whole population study.

Multivariate regression analyses of infarct size by different surrogates (CMR and biomarkers) adjusting for the AAR by the ACS are reported in Table 4.

**Results**

**Population**

Between August 2008 and January 2012, 99 patients were recruited in five French University Hospitals. As depicted in Figure 2, and according to pre-specified criteria, nine patients were not included on account of significant collateral flow as visible on admission coronary angiogram (four in the Control group and five in the PostC group).

There was no difference between the two groups with respect to the baseline population characteristics, and usual risk factors were well distributed between Control and PostC groups (Table 1). Duration of ischaemia, coronary angiography features and treatments administered either before and during PCI or at discharge were comparable between both groups (Tables 2 and 3).

**Area at risk and infarct size**

Area at risk (ACS, expressed as % of the LV circumference) averaged \(38 \pm 12\%\) in the control vs. \(38 \pm 13\%\) in the PostC group (\(P = 0.89\)). The BARI score averaged \(31 \pm 8\%\) in the control group vs. \(32 \pm 8\%\) in the PostC group (\(P = 0.79\)).

Mean CMR infarct size was comparable between the two groups, averaging \(23 \pm 17\) and \(21 \pm 18\) g in the control and PostC groups, respectively [mean difference = \(1.40\) g; 95% CI (−6.84 to 9.64), \(P = 0.64\); Figure 3]. Micro-vascular obstruction mass was not significantly different between the two groups [mean difference = −0.06 g; 95% CI (−2.71 to 2.58), \(P = 0.51\)]. Left ventricle mass and volumes were not different between the two groups as reported in Table 2.

The AUC or the peak release of both CK (\(P = 0.49\) and \(P = 0.41\), respectively) and troponin I (\(P = 0.52\) and \(P = 0.45\), respectively) confirmed the absence of a significant difference between both groups (Table 2).

Both CMR infarct size and CK AUC were significantly or fairly correlated with the area at risk size (as estimated either by the ACS) (\(R = 0.36; P = 0.005\) for CMR infarct size and \(R = 0.19; P = 0.11\) for CK AUC respectively) in the whole population study.

**Clinical outcomes**

There was no adverse event related to the post-conditioning procedure. At 6 months of follow-up, in the Control group, two unplanned revascularizations were reported, whereas in the PostC group one death, one re-infarction, and two unplanned revascularizations were reported. There were no significant differences in clinical outcomes between groups at 6 months by univariate logistic regression [\(OR = 2.26; 95\% CI (0.39 – 13.00); P = 0.36\)].

**Discussion**

In this multi-centre, prospective, randomized, single-blinded clinical trial, we report that ischaemic post-conditioning does not reduce infarct size in patients presenting with TIMI flow grade 2–3 (equivalent to spontaneous reperfusion) at the time of the hospital admission coronary angiography.

**Post-conditioning does not reduce infarct size in 2–3 TIMI flow grade patients**

In contrast with our previous studies in 0–1 TIMI flow grade STEMI patients, we report that ischaemic post-conditioning does not reduce infarct size in 2–3 TIMI flow grade patients. Despite this different feature in the patency of the culprit coronary artery at the time of admission, it is worth noting that the baseline characteristics of the
present study population, the treatments received before PCI, and the algorithm of ischaemic PostC, were comparable with that of the populations of our previous trials in STEMI patients with a fully occluded culprit coronary artery at the time of catheterization.9–11 This suggests that these population profile factors likely did not play a confounding role in the absence of protection by PostC.

Both the AUC and the peak release of CK and troponin I showed that ischaemic PostC did not reduce infarct size in the present study. Since reflow had occurred before admission in the catheterization laboratory (i.e. timing of the initial blood sampling for cardiac enzyme release) in TIMI 2–3 flow grade patients, one might question whether missing the initial part of the release curve of cardiac enzymes could have biased our results. This was likely not the case since CMR studies confirm that infarct size was comparable between both groups.

The duration of ischaemia is a critical determinant of infarct size in animal models.24,25 As expected, mean time from onset of symptoms to intervention, delay to hospital admission, and door-to-balloon times were similar between the two groups and cannot explain the absence of effect of ischaemic PostC in the present study (Table 2). A key point here, in contrast to previous studies in 0–1 TIMI flow grade STEMI patients, is that the real ischaemia time was shorter than the time from onset of symptoms to PCI. By definition, STEMI patients that exhibited a TIMI 2–3 flow at admission coronary angiography had necessarily undergone a spontaneous reperfusion during the time elapsed from first medical care to coronary angiography. This might explain why the average infarct size in the control group was smaller in the present study compared with our results in previous trials performed in TIMI 0–1 patients.9–11 Unfortunately, the exact reperfusion timing in these TIMI 2–3 flow grade patients cannot be accurately determined. One might however question whether a shorter ischaemia time might contribute to a reduced protection effect of post-conditioning. In the rat model, Manninveldt et al.26 have suggested that ischaemic PostC may be inefficient or even detrimental when the duration of ischaemia is short. In the present study, ischaemia duration was at least 2 h in the two groups since this was the observed delay between the onset of symptoms to the first medical care. One cannot fully rule out that the absence of protection by ischaemic PostC in the present study was due to the selection of patients with short ischaemia time. On the other hand, the lack of protection could also be due to a more gentle reperfusion through a residual stenosis.27 In an experimental pig model, gentle (low flow or low pressure) reperfusion was demonstrated to reduce infarct size.28 In our study, several patients might have undergone spontaneous thrombus dislodgment and subsequent reperfusion through an underlying tight coronary artery stenosis, hence limiting coronary reflow and resulting in a gentle reperfusion. Alternatively, as often seen after thrombus aspiration, many STEMI patients underwent acute thrombotic occlusion upon a moderate coronary stenosis: in these cases, no limitation of reflow may occur and account for gentle reperfusion. Overall, despite the fact that we cannot exclude the confounding role of a gentle reperfusion, we think that the average smaller size observed in the present study more likely reflects a shorter ischaemic insult. Yet, whether the assumption by Manninveldt et al.26 of a loss of

### Table 2  Infarct size and determinants

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 46)</th>
<th>Post-conditioning (n = 44)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ischaemia times</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest pain to first medical care (min)</td>
<td>122 ± 136</td>
<td>132 ± 186</td>
<td>0.90</td>
</tr>
<tr>
<td>First medical care to hospital admission (min)</td>
<td>80 ± 64</td>
<td>81 ± 60</td>
<td>0.96</td>
</tr>
<tr>
<td>Hospital admission to intervention (min)</td>
<td>50 ± 34</td>
<td>63 ± 54</td>
<td>0.36</td>
</tr>
<tr>
<td>Chest pain to intervention (min)</td>
<td>249 ± 148</td>
<td>263 ± 209</td>
<td>0.93</td>
</tr>
<tr>
<td><strong>Coronary angiography</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>53 ± 8</td>
<td>53 ± 9</td>
<td>0.86</td>
</tr>
<tr>
<td>Area at risk [ACS (%)]</td>
<td>38 ± 12</td>
<td>38 ± 13</td>
<td>0.89</td>
</tr>
<tr>
<td>BARI score (%)</td>
<td>31 ± 8</td>
<td>32 ± 8</td>
<td>0.79</td>
</tr>
<tr>
<td>Culprit artery (RCA/LAD) (%/%)</td>
<td>42/48</td>
<td>49/51</td>
<td>0.54</td>
</tr>
<tr>
<td>Final TIMI flow grade &gt;2 (%)</td>
<td>95</td>
<td>100</td>
<td>0.49</td>
</tr>
<tr>
<td>Thrombus aspiration (%)</td>
<td>32</td>
<td>31</td>
<td>1.00</td>
</tr>
<tr>
<td>Distal protection (%)</td>
<td>0</td>
<td>5</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>Infarct size</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI LV mass (g)</td>
<td>137 ± 35</td>
<td>143 ± 38</td>
<td>0.76</td>
</tr>
<tr>
<td>MRI infarct mass (g)</td>
<td>23 ± 17</td>
<td>21 ± 18</td>
<td>0.64</td>
</tr>
<tr>
<td>MRI MVO mass (g)</td>
<td>2.4 ± 5.2</td>
<td>2.5 ± 5.8</td>
<td>0.51</td>
</tr>
<tr>
<td>Creatine kinase (AUC: AU)</td>
<td>47 424 ± 36 246</td>
<td>42 901 ± 34 463</td>
<td>0.49</td>
</tr>
<tr>
<td>Creatine kinase (peak: IU/L)</td>
<td>1755 ± 1360</td>
<td>1580 ± 1491</td>
<td>0.41</td>
</tr>
<tr>
<td>Troponin I (AUC: AU)</td>
<td>1941 ± 1637</td>
<td>1988 ± 2296</td>
<td>0.52</td>
</tr>
<tr>
<td>Troponin I (peak: µg/L)</td>
<td>70 ± 63</td>
<td>87 ± 140</td>
<td>0.45</td>
</tr>
</tbody>
</table>

Data for ischaemia times, coronary angiography, and infarct size are presented. There was no significant difference between the two groups.
protective effect when the index ischaemia is short holds true in the human heart remains to be demonstrated. Additional confounding factors might play a role in the absence of protective effect of post-conditioning in the present STEMI population, especially as regards the treatments received, mainly the antiplatelet agent clopidogrel.\textsuperscript{29} Our group demonstrated recently that clopidogrel itself exerts significant protection\textsuperscript{30} and experimental data in a monkey model corroborated this finding.\textsuperscript{31} As most of our patients (71–85\%) received clopidogrel, this could participate to the relatively small infarct size and could then limit the power of post-conditioning, although this retrospective analysis showed that post-conditioning was able to reduce infarct size on top of clopidogrel even in patients with small infarcts.\textsuperscript{30} Several options during the PCI could also contribute to abrogate the beneficial effect of post-conditioning. Inadvertent thrombus embolization secondary to repeated inflations–deflations of the angioplasty balloon may aggravate lethal myocardial damage. Whether mechanical post-conditioning by itself induces micro-embolization remains under debate\textsuperscript{32} although we have no evidence to support this in our previous clinical and basic works. Besides, the protective effect of post-conditioning has recently been shown to remain efficient despite the induction of micro-embolization in an experimental model.\textsuperscript{33} We recently reported that mechanical post-conditioning was able to reduce microvascular obstruction (or ‘no reflow’) in 0–1 TIMI flow grade STEMI patients, suggesting that it is likely not associated with major micro-embolization, provided the repeated inflations–deflations of the angioplasty balloon are not applied at the site of the coronary artery occlusion (but upstream the culprit lesion).\textsuperscript{34} Thrombus aspiration could be a significant confounding factor. However, recent works did not confirm the efficacy of thrombus aspiration to reduce major cardiovascular adverse events at 30 days.\textsuperscript{35} Distal protection was not used in this study and is not recommended in the ESC guidelines.\textsuperscript{7} Additional treatments remain also controversial, including the use of adenosine, which was allowed in this study at the PCI operator’s discretion.

\begin{figure}
\centering
\includegraphics[width=\columnwidth]{figure3.png}
\caption{Infarct size as assessed by cardiac magnetic resonance scan and cardiac enzymes release. Left: mean cardiac magnetic resonance infarct size was comparable between the two groups, averaging 23 ± 17 and 21 ± 18 g in the control and PostC groups, respectively (\(P = 0.64\)). Right: assessment of the infarct size by using the enzymatic release method through the area under the curve of creatine kinase revealed no significant difference between groups (47 424 ± 36 246 vs. 42 901 ± 34 463 in the control and PostC groups, respectively, \(P = 0.49\)).}
\end{figure}

Table 3  Treatments before percutaneous coronary intervention and at discharge
\begin{tabular}{|l|c|c|c|}
\hline
 & Control & Post-conditioning & \(P\)-value \\
 & \(n = 46\) & \(n = 44\) & \\
\hline
Before reperfusion & & & \\
Thrombolysis (%) & 30 & 19 & 0.32 \\
Aspirin (%) & 93 & 98 & 0.62 \\
Clopidogrel (%) & 85 & 71 & 0.19 \\
Prasugrel (%) & 20 & 34 & 0.15 \\
LMW heparin (%) & 43 & 38 & 0.67 \\
Anti-GPla\textsubscript{IIb}, (%) & 28 & 29 & 1.00 \\
Nitrates (%) & 65 & 71 & 0.65 \\
Morphine (%) & 46 & 48 & 1.00 \\
\(\beta\)-Blockers (%) & 9 & 14 & 0.51 \\
ACEI (%) & 7 & 7 & 1.00 \\
Adenosine (%) & 11 & 2 & 0.21 \\
\hline
At discharge & & & \\
Aspirin (%) & 96 & 98 & 0.62 \\
\(\beta\)-Blockers (%) & 100 & 95 & 0.23 \\
Statins (%) & 100 & 98 & 0.48 \\
Clopidogrel (%) & 61 & 58 & 0.82 \\
Prasugrel (%) & 39 & 43 & 0.82 \\
ACEI (%) & 98 & 95 & 0.61 \\
ARB (%) & 2 & 5 & 0.61 \\
Nitrates (%) & 23 & 20 & 0.79 \\
Diuretics (%) & 9 & 15 & 0.51 \\
\hline
\end{tabular}

Treatments before hospital admission and before percutaneous coronary intervention are presented, as well as treatments at discharge. There was no significant difference among groups. LMW, low molecular weight; ACEI, angiotensin-converting enzyme inhibitor.
NCT00781404) did not find any significant effect of adenosine to reduce infarct size in STEMI patient.

Altogether, we think that the absence of beneficial effect of ischaemic post-conditioning in 2–3 TIMI flow grade STEMI patients is not due to one of the abovementioned confounding effects. Rather, we believe that it is related to a delayed application of the post-conditioning algorithm.

Delayed ischaemic post-conditioning in STEMI patients

As mentioned earlier, the observation of an opened coronary artery at admission coronary angiography in STEMI patients means that spontaneous reflow had occurred in the time period between the first medical care and the coronary angiography. The factors that induce earlier reperfusion are unknown. In the present study, <30% of patients received a thrombolytic treatment (with no significant difference between both groups). In some patients, reperfusion might have been facilitated by antiplatelet agents including aspirin, thienopyridines, and anti-GPIIbIIIa agents.

Recent evidence indicates that lethal reperfusion injury exists in the human heart, that it represents a significant amount of tissue, and that it may be alleviated by the timely application of a protective intervention, including ischaemic PostC or cyclosporine.9–11,22,36 Our explanation for the lack of protection by ischaemic PostC in the present trial is that the protective intervention was applied too late, i.e. after lethal reperfusion injury had occurred and already induced irreversible damage to the myocardium. How long after reflow was ischaemic PostC applied here cannot be precisely determined. One may consider that this delay was within 2 h, since it corresponds to the delay between the first medical care (when ST segment shift and pain were still present) and the coronary angiography (when it was seen that the culprit coronary artery was opened). In other words, this would indicate that the infarct size reduction afforded by ischaemic PostC is gone when its application is delayed by only 2 h. This is in keeping with the initial study by Kin et al.16 who demonstrated in the dog heart that delaying the application of ischaemic PostC after reflow resulted in a loss of protection. This is however in contradiction with the recent proposal that delayed ischaemic PostC was still efficient in the mouse model.17

How wide exactly is the time window for protection by ischaemic PostC in STEMI patients remains to be determined. Whether this observation is true for pharmacological or remote PostC has to be demonstrated. With respect to pharmacological interventions, the present observation may help to put into perspective previous negative infarct size studies in which the therapeutic intervention was started after reperfusion.37–39 But unlike ischaemic PostC, both remote and pharmacological conditioning can be initiated before coronary angiography, as early as at the time of first medical care or during the ambulance transfer to the hospital. This is a major advantage that also opens the opportunity to treat 2–3 TIMI flow patients and have them benefit from protective interventions against lethal reperfusion injury. This however remains to be demonstrated. Early application of either remote or pharmacological PostC further opens the opportunity to propose this protection to patients whose reperfusion therapy is based on fibrinolysis instead of primary PCI, which remains the case in many countries worldwide.

Limitations

Our study presents several limitations. Beyond the relatively small number of patients, the main point is that the time lag of this ‘delayed’ post-conditioning appears difficult to determine precisely. Indeed, the very onset of the spontaneous reperfusion is difficult to assert, whereas time precision is critical here. Open label is another limitation, although unavoidable in this kind of post-conditioning protocol. As evaluations of primary and secondary endpoints were blinded to the group, we assume this is a mild limitation.

Finally, we cannot exclude a mild impact of the post-conditioning intervention on the infarct size, in other words our study could have been underpowered from the start yielding not-conclusive results. Indeed, the difference of 23–21 g was approximately a 10% difference instead of the hypothesized 30% difference, suggesting at best limited clinical benefit. The heterogeneity of reperfusion times before intervention could at least partly explain this lack of efficacy. Nevertheless, in comparison with our previous studies and publications by other groups, the effect is by far reduced if even relevant. In conclusion, the present study demonstrates that patients with an opened culprit coronary artery at hospital admission do not benefit from ischaemic PostC. This indirectly suggests that the time
window for protection by PostC is limited and that protective interventions must be applied as soon as possible, in any case before reflow.

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References


