Mechanical post-conditioning in STEMI patients undergoing primary percutaneous coronary intervention

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Although early myocardial reperfusion via primary percutaneous coronary intervention (PCI) allows the preservation of left ventricular function and improves outcome, the acute restoration of blood flow may contribute to the pathophysiology of infarction, a complex phenomenon called reperfusion injury. First described in animal models of coronary obstruction, mechanical post-conditioning, a sequence of repetitive interruption of coronary blood flow applied immediately after reopening of the occluded vessel, was able to reduce the infarct size. However, evidence of its real benefit remains controversial. This review describes the mechanisms of post-conditioning action and the different protocols employed focusing on its impact on primary PCI outcome.

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Introduction

For patients with ST-segment elevation myocardial infarction (STEMI), “time is myocardium”. Infarct size can be limited by early myocardial reperfusion via primary percutaneous coronary intervention (PCI), thus allowing the preservation of left ventricular function and improving clinical outcome [1,2]. However, the acute restoration of blood flow may contribute to the pathophysiology of infarction, a complex phenomenon called reperfusion injury [3,4]. Indeed, lethal reperfusion injury accounts for up to 50% of the final size of a myocardial infarct [4]. In 2003, Zhao et al. [5] were the first to describe a phenomenon known as “post-conditioning” in which a sequence of repetitive interruption of coronary blood flow was applied immediately after reopening of the occluded vessel. This adjunct treatment attenuated reperfusion injury, reduced infarct size and preserved vascular endothelial function comparable to ischemic preconditioning in a canine model of coronary obstruction [5]. Since the first report in a human heart by Staat et al. [6] in 2005, the interest in post-conditioning has increased. Although various parameters have been employed to assess its benefits, the real impact of post-conditioning in PCI remains controversial. The current review describes the mechanisms of post-conditioning action and the different protocols employed, focusing on its real impact on primary PCI outcome.

Mechanisms of post-conditioning action

In experimental models, the effect of post-conditioning on decreasing final infarct size is mediated through different pathways [5–8]. The molecular basis of post-conditioning action can be subdivided into the following three headings: triggers, mediators and end-effectors [7,8] (Fig. 1). Several activators of the signaling cascades (triggers) have been identified: adenosine, opioids, bradykinin, erythropoietin, endogenous nitric-oxide (eNO), acetylcholine, pro-inflammatory cytokines (particularly TNF-a and IL-6) and reactive oxygen species (ROS) [7]. The trigger phase is characterized by extracellular receptor/ligand interactions with autacoid, endocrine or paracrine signaling molecules [8]. The mediators of post-conditioning action can be subdivided into two pathways: the first is represented by reperfusion injury salvage kinase pathway, which includes phosphoinositide-3-kinases and extracellular regulated kinase-mitogen activated protein kinase, while the second consists of the reduction of intracellular calcium overload [7,8]. The mitochondrial permeability transition pore (mPTP) and mitochondrial potassium ATP (mKATP) channel [7] are currently considered as the most important end-effectors. The opening of mPTP, which is a voltage-dependent pore localized in the inner mitochondrial membrane, has been reported to occur within the first minutes of reperfusion. Such a phenomenon allows the transfer of small molecules into the matrix by osmosis, which is responsible for the swelling and rupturing of outer mitochondrial membrane with subsequent accumulation of calcium and other oxidants, eventually leading to alkalization of the intracellular matrix, and thus to apoptosis [7,8]. In the rabbit heart model, Argaud et al. [9] demonstrated that the magnitude of the protective effect of post-conditioning was similar to that obtained with NIM811, which specifically inhibited mPTP opening at the time of reperfusion. TRO40303 also inhibits mPTP opening, and has been shown to reduce infarct size in animal models of myocardial infarction [10,11]. However, in the MITOCARE study randomizing patients with STEMI requiring primary PCI to TRO40303 (n = 83) or placebo (n = 80) prior to balloon inflation, no significant
differences were observed between groups regarding infarct size assessed by necrosis biomarkers and cardiac magnetic resonance imaging (MRI) [12].

On the other hand, the use of glibenclamide and 5-OH decanoate, which are inhibitors of mKATP channel, has been shown to reverse the protective effects of post-conditioning [13]. It has also been reported that intermittent targeting of the mKATP channel in the early minutes of reperfusion triggers post-conditioning protection through reactive oxygen species generation [14].

Otherwise, post-conditioning may also have a passive impact on endothelial dysfunction, oxidant release, hypercontracture, cytokine levels, inflammation and apoptosis [7,8].

The majority of cellular signaling elements involved in such a process might be affected by
confounders, co-morbidities or co-medication, as these conditions are associated with fundamental molecular alterations, potentially explaining the variability of responses to post-conditioning between individuals [3].

Mechanical post-conditioning protocols and modalities

Accumulating evidence has suggested that several technical issues may improve cardioprotection by post-conditioning, such as the balloon position, the conditioning delay to first inflation, and even the stenting technique. Thuny et al. [15] suggested that the post-conditioning protocol should be performed upstream of the site of the culprit lesion in order to reduce microembolisms. On the other hand, the delay to first inflation has been recognized as an important determinant of reduction in infarct size [16]. In fact, delay prolongation from 10 to 30 to 60 s [17,18] or 10 min [19] has been shown to result in cardioprotection failure in animal models.

In currently available trials, the post-conditioning protocols consisted of two to four cycles of ischemia and reperfusion (produced by inflations/deflations of angioplasty balloon) after direct stenting [20–22]. Taking into account an average of three cycles plus one balloon inflation for direct stenting, the cut-off of four inflations would mimic post-conditioning in a real-life practice. After PCI of the presumed culprit lesion, the stent balloon is commonly used to perform alternating inflations and deflations. In the majority of studies, post-conditioning was performed by four 30–60-s cycles of low pressure balloon inflations (4–6 atm) at the site of previous occlusion, each separated by 30–60 s of reflow [20–23]. Table 1 summarizes the various post-conditioning protocols employed in different studies.

| Study             | Year | Protocol of POC | N POC/controls |
|-------------------|------|-----------------|----------------|
| Staat et al. [6]  | 2005 | 60 s x 4        | 14/16          |
| Ma et al. [34]    | 2006 | 30 s x 3        | 47/47          |
| Yang et al. [26]  | 2007 | 30 s x 3        | 23/18          |
| Thibault et al. [25] | 2008 | 60 s x 4        | 17/21          |
| Sorensso et al. [27] | 2010 | 60 s x 4        | 38/38          |
| Freixa et al. [28] | 2012 | 60 s x 4        | 39/40          |
| Tarantini et al. [29] | 2012 | 60 s x 4        | 39/39          |
| Zhao et al. [38]  | 2012 | 60 s x 4        | 32/30          |
| Hahn et al. [20]  | 2013 | 60 s x 4        | 350/350        |
| Dwyer et al. [41] | 2013 | 30 s x 4        | 50/52          |
| Limalanathan et al. [23] | 2014 | 60 s x 4        | 136/136        |

Abbreviations: PCI = percutaneous coronary intervention and POC = post-conditioning.

Post-conditioning effects

Post-conditioning and injury biomarkers

Serum creatine-kinase (CK) release was the most widely used study endpoint, and peak CK values strongly correlate with infarct size and predict cardiac outcomes in STEMI patients treated with primary PCI [24].

Yetgin et al. [21] found a lower CK peak in post-conditioning group compared with controls, corresponding to 21% reduction of enzymatic infarct size. This finding was similar to those reported by previous randomized studies, in which post-conditioning resulted in CK release reduction ranging from 27% to 40% [6,15,25,26]. However, Hahn et al. [20] failed to demonstrate any advantage of post-conditioning in terms of reperfusion markers as assessed by complete ST-segment resolution (≥70%), 30 min post-PCI and post-procedural TIMI flow or myocardial blush grade in a large randomized trial involving 700 STEMI patients.

Other results from recent studies assessed with troponin I (TnI) or TnT [27–30], were also controversial with earlier observations. When TnI or TnT were used as endpoints, there was no significant difference between post-conditioning group and controls (\(p = 0.74\)) [30]. In a multi-center randomized controlled study, Roubille et al. [31] failed to show any significant decrease in CK and TnI release, even after adjustment for the size of the area at risk. More recently, Limalanathan et al. [23] showed no significant difference in TnT peak between controls and post-conditioning group (\(p = 0.63\)).

On the other hand, some factors may have an influence on the impact of post-conditioning on injury markers. According to Yetgin et al. [21], the decrease in CK peak was more pronounced in women, patients without diabetes or hypercholesterolemia, patients presenting within 3–6 h or
with delay of first balloon re-occlusion ≤ 1 min. In a meta-analysis of 13 studies, Wang et al. [30] found that myocardial injury biomarkers were significantly reduced in cases of non-use of Gp IIb/IIIa inhibitors. A possible explanation is that Gp IIb/IIIa inhibitors and post-conditioning procedure may act via similar pathways, thus achieving balance on protection, particularly against no-reflow phenomenon.

**Post-conditioning and no-reflow**

Despite the continuous improvement in PCI equipment and techniques, 60–70% of patients with optimal angiographic reperfusion still display microvascular obstruction (the so-called no-reflow phenomenon) detected by cardiac MRI studies after reperfusion [32]. After prolonged ischemia reperfusion, endothelium destruction or swelling, vasospasm, plugging of leukocytes or red blood cells and micro-thrombi may lead to the microcirculation perfusion deficit. Myocardial edema and hemorrhage may contribute by extrinsic compression causing microvascular obstruction. Using contrast-enhanced cardiac-MRI within 3 days after reperfusion, Mewton et al. [32] showed that post-conditioning was associated with smaller, early and late microvascular obstruction size (p = 0.01). Furthermore, such a significant reduction was persistent after adjustment for thrombus aspiration [32].

Dong and colleagues [33] assessed the impact of post-conditioning on various reflow determinants. Compared with controls, patients who underwent post-conditioning showed better rates of ST-segment resolution (93.8% versus 73.3%, p = 0.029), final TIMI grade-3 flow (81.3% versus 56.7%, p = 0.036), and final myocardial blush grade 3 (23% versus 14%, p = 0.043).

Although the number of patients in these two studies was relatively limited (50 and 62 respectively), post-conditioning could improve myocardial reperfusion in patients with STEMI patients undergoing PCI by reducing no-reflow [32,33].

In order to evaluate the impact of post-conditioning on coronary blood flow velocity, Ma et al. [34] reported that patients with post-conditioning had much faster corrected TIMI frame count 8 weeks after the primary PCI. Moreover, the peak of malondialdehyde, an oxidative agent which is actively implicated in coronary endothelial cytotoxicity, was significantly lower after post-conditioning compared with controls [34]. This latter finding revealed the probable impact of post-conditioning in improving cardiac vascular endothelial function after myocardial infarction.

Conversely, Hahn et al. [20] did not find significant differences neither in 30 min ST-segment resolution (p = 0.79) nor in blush flow grade 30 days later (p = 0.20).

**Post-conditioning and left ventricular function**

Comparing 32 patients who underwent post-conditioning to 30 controls treated by PCI for acute myocardial infarction, Dong et al. [33] found a better echocardiographic left ventricular ejection fraction (LVEF) in a post-conditioned group (55.1 ± 9.8% versus 42.9 ± 10.7%, p = 0.042), 7 days after the procedure. Two meta-analyses [30,35] reported the same findings with an improvement of LVEF after post-conditioning of 4.2% and 3.55%, respectively. However, it is usually recognized that only an increase of LVEF > 5% is considered significant improvement in patients with abnormal LVEF.

In canine models, Zhao et al. [5] reported that ischemic post-conditioning did not improve myocardial segment contractile function in the first 3 h after reperfusion. Moreover, Vinten-Johansen et al. [36] and Couvreur et al. [37] revealed that ischemic post-conditioning was not able to protect against myocardial stunning in dogs and rabbits. Such findings may explain the fact that at short-term follow up, Zhao et al. [38] found similar contractile function in post-conditioned and control groups. However, at 6-month follow-up, the authors demonstrated an increased LVEF and reduced wall motion score index in the post-conditioned group compared with controls [38].

Thibault et al. [25] also observed a persistent infarct size reduction at 6 months assessed by myocardial scintigraphy, and an improved recovery of myocardial contractile function at 1-year control echocardiography. Conversely, Wang et al. [30] found LVEF reduction during medium and long-term follow-up, which could be due to left ventricular remodeling.

Furthermore, studies using cardiac MRI have emerged revealing modest reductions [15,39–41], no impact [30,22], and perhaps even potential increase in infarct size without improvement [28,29]. By studying myocardial salvage after 3 months as judged by delayed enhancement cardiac MRI, Lonborg et al. [41] found a 19% relative reduction of infarct size in the post-conditioning group (51 ± 16% of total area at risk versus 63 ± 17%, p < 0.01), corresponding to a 31% increase in salvage ratio. Conversely, Dwyer et al. [22] showed that post-conditioning neither significantly increases myocardial salvage (p = 0.08) nor reduces infarct size (p = 0.18).
assessed by cardiac MRI in patients with STEMI undergoing primary PCI. The same finding was reported by Roubille et al. [31] Moreover, Freixa et al. [28] found that post-conditioning was associated with lower myocardial salvage (4.1 ± 7.2 versus 9.1 ± 5.8% in controls; \( p = 0.004 \)) and lower myocardial salvage index (18.9 ± 27.4 versus 30.9 ± 20.5% in controls; \( p = 0.038 \)) with no significant differences in infarct size; and LVEF was found among the groups at 1 week and 6 months. More recently, in the POSTEMI trial, 272 patients were randomized to post-conditioning group (\( n = 136 \)) and control group (\( n = 136 \)); primary endpoint was infarct size measured by cardiac MRI [23]. After 4 months, no difference was observed between control group and post-conditioning group in percentage of left ventricular mass measured by cardiac MRI (14.4% versus 13.5%, respectively; \( p = 0.18 \)) and LVEF after 4 months (55% versus 56.5%, respectively; \( p = 0.19 \)) [23].

Post-conditioning and clinical outcome

Data regarding mid-term clinical follow-up are limited. In a cohort of 225 patients, Deftereos et al. [42] showed a lower 30-day rate of death or re-hospitalization for any cause in post-conditioned group compared with the control group (12.4% versus 22.3%; \( p = 0.05 \)). Conversely, in a multicenter randomized trial including 700 patients, Hahn et al. [20] assessed clinical outcomes at 1 month from procedures. No differences were observed between post-conditioned patients and controls regarding death (3.7% versus 2.7%; \( p = 0.53 \)) and major adverse cardiac events (MACE) (4.3% versus 3.7%; \( p = 0.70 \)). At 4 months, Limalanathan et al. [23] reported no significant difference between post-conditioned patients and controls regarding re-hospitalization for acute coronary syndromes or heart failure.

In another report, Tarantini et al. [29] showed even higher rates of major adverse events at 6-month follow-up in post-conditioned group compared with control group (16.7% versus 2.6%; \( p = 0.08 \)).

In a meta-analysis of 15 randomized trials including 1545 patients with a mean follow-up of 4.7 months, Khalili et al. [43] did not note any impact of mechanical post-conditioning on mortality (OR = 1.52; 95% CI 0.77–2.99; \( p = 0.23 \)), recurrent myocardial infarction (OR = 3.04; 95% CI 0.74–12.54; \( p = 0.12 \)), stent thrombosis (OR = 1.24, 95% CI 0.51–3.04; \( p = 0.83 \)), or the composite MACE outcome (OR = 1.53; 95% CI 0.89–2.63; \( p = 0.13 \)).

Pharmacological post-conditioning alternative

As an alternative to intra-coronary balloon inflations, several pharmacological agents designed to prevent lethal myocardial reperfusion injury by targeting its components have been evaluated in STEMI patients undergoing primary PCI. The most investigated of these pharmacological adjuncts were natriuretic peptide [44], cyclosporine A [45], and adenosine [46]. Kitakaze et al. [44] randomly assigned 277 patients to receive intravenous atrial natriuretic peptide for 3 days and 292 patients to receive the same dose of placebo. Patients with acute myocardial infarction and who were given atrial natriuretic peptide had lower infarct size of 14.7% (95% CI 3.0–24.9%), and better LVEF at 6–12 months (ratio 1.05, 95% CI 1.01–1.10, \( p = 0.024 \)) [44]. Piot et al. [45] randomly assigned 58 patients receiving either an intravenous bolus of cyclosporine A or normal saline (control group) immediately before undergoing primary PCI. The release of CK was significantly reduced in the cyclosporine group as compared with the control group (\( p = 0.04 \)), while the release of troponin I was not significantly reduced (\( p = 0.15 \)) [45]. On the fifth day, the absolute mass of the area of hyper-enhancement on MRI was significantly reduced in the cyclosporine group as compared with the control group, with a median of 37 g (interquartile range, 21–51) versus 46 g (interquartile range, 20–65; \( p = 0.04 \)). No adverse effects of cyclosporine administration were detected [45]. More recently, in placebo-controlled, randomized multicenter trial including 240 STEMI patients, Niccoli et al. [46] showed that the use of adenosine results not only in significant improvement of microvascular obstruction assessed by ST-segment resolution but also in MACE occurrence at 30 days. Although these are promising results, further studies are required to confirm the efficacy of these therapeutic agents and to determine whether they can improve clinical outcomes, especially if combined with intra-coronary balloon inflations.

Remote ischemic conditioning alternative

Remote ischemic conditioning is based on the fact that transient non-injurious ischemia of one organ or tissue can protect a distant organ or tissue from ischemic injury. Gho et al. [47] reported that brief ischemia of the kidney or small intestine was able to protect the myocardium against prolonged ischemia. Birnbaum et al. [48] demonstrated that rabbit hindlimb ischemia protected...
the heart against later ischemia. In 2005, Kerendi et al. [49] moved the remote ischemic stimulus in time, from before ischemia to later during the period of organ ischemia, and showed that renal ischemia was cardioprotective.

To understand the mechanisms involved, three theories have been advanced: (1) humoral factors acting via the systemic circulation, particularly eNO, ROS, adenosine, kinogens and opioids; (2) neurogenic transmission with involvement of muscle afferents and the autonomic nervous system; and (3) effects on immune cells with reduction of neutrophil activation and adherence to endothelium, and inflammatory gene expression [50]. The final common pathway of protection in the target organ involves activation of the reperfusion injury salvage kinases or survival-activating factor enhancement pathways that ultimately converge on the mitochondria to open mKATP channels, thereby preventing the opening of the mPTP [7,8].

In a meta-analysis of 23 randomized clinical trials of remote conditioning, most involving patients undergoing cardiac surgery, limb conditioning did not reduce mortality or major adverse cardiovascular events compared with no conditioning but did reduce the incidence of myocardial infarction and troponin release [51]. Botker and colleagues [52] reported the use of blood pressure cuff inflation/deflation for four cycles of 5-min occlusion in patients with STEMI before primary PCI. The intervention group (n = 73) had higher mean and median salvage indices at 30 days, estimated by gated single photon emission computed tomography, than the control group (n = 69). The benefit was greatest in the subset of patients with coronary vessel occlusion on admission angiography. More recently, Crimi et al. [53] showed that in patients with anterior STEMI, remote ischemic conditioning of the lower limb at the time of primary PCI reduced enzymatic infarct size and was also associated with ST-segment resolution and improvement of T2-weighted edema volume in cardiac MRI.

Conclusion

Although the majority of the studies demonstrate that post-conditioning might reduce injury biomarkers, the other benefits of post-conditioning remain controversial, and data on long-term outcomes are limited. Several confounders such as co-morbidities, co-medication and the difference in post-conditioning protocols might be responsible for the huge disparity observed between the various studies. Moreover, the limited number of randomized trials, including large cohorts, and the significant variations encountered in clinical events when the STEMI model is employed as a post conditioning model make it difficult to confirm the impact of post-conditioning. Further studies are therefore needed to better identify the best protocol to adopt, which patient might gain more benefit from such a procedure, and the overall possible benefits of associating post-conditioning with pharmacological and remote ischemic conditioning.

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