REVIEW ARTICLE

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

Marouane Boukhris [a,b,*], Radhouane Bousselmi [b], Salvatore Davide Tomasello [a], Zied Ibn Elhadj [b], Salvatore Azzarelli [a], Francesco Marzà [a], Alfredo R. Galassi [a]

[a] Department of Medical Sciences and Pediatrics, Catheterization Laboratory and Cardiovascular Interventional Unit, Cannizzaro Hospital, University of Catania, Catania
[b] Faculty of Medicine of Tunis, University of Tunis El Manar

[a] Italy
[b] Tunisia

**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.**



*Keywords:* Post-conditioning, Balloon inflation, Primary PCI, Reperfusion injury

**Contents**



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* Corresponding author at: Catheterization Laboratory and Cardiovascular Interventional, Cannizzaro Hospital, University of Catania, 95100 Catania, Italy.
E-mail address: mar1bou@hotmail.com (M. Boukhris).

P.O. Box 2925 Riyadh – 11461KSA
Tel: +966 1 2520088 ext 40151
Fax: +966 1 2520718
Email: sha@sha.org.sa
URL: www.sha.org.sa



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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.

**Abbreviations**

| | |
|---|---|
| CK | creatine-kinase |
| eNO | endogenous nitric-oxide |
| LVEF | left ventricular ejection fraction |
| MACE | major adverse cardiac events |
| mKATP | mitochondrial potassium ATP |
| mPTP | mitochondrial permeability transition pore |
| MRI | magnetic resonance imaging |
| PCI | percutaneous coronary intervention |
| ROS | reactive oxygen species |
| STEMI | ST-segment elevation myocardial infarction |
| Tn | troponin |

## 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