Postconditioning with Nitrates Protects Against Myocardial Reperfusion Injury: A New Use for an Old Pharmacological Agent

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Early reperfusion remains the key therapy to salvage viable myocardium and must be applied as soon as possible following an acute myocardial infarction (AMI) to attenuate the ischemic insult. However, reperfusion injury may develop following reintroduction of blood and oxygen to vulnerable myocytes, which results in more severe cell death than in the preceding ischemic episode. Ischemic postconditioning (I-PostC) provides a cardioprotective effect in combination with pharmacological agents. Although nitrates have been tested in many experimental and clinical studies of acute AMI to evaluate the cardioprotective effect, few investigations have been focused on nitrates postconditioning in patients undergoing percutaneous coronary intervention (PCI). This review presents the manifestations of myocardial reperfusion injury (RI) and potential mechanisms underlying it, and provides the mechanisms involved in the cardioprotection of I-PostC. We also present a new therapeutic approach to attenuate RI by use of an 'old' agent – nitrates – in AMI patients.

MeSH Keywords: Acute Coronary Syndrome • Ischemic Postconditioning • Nitrates • Reperfusion Injury

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Background

Acute myocardial infarction (AMI) is responsible for the death of millions of people worldwide each year and seriously worsens patient prognosis. Early reperfusion, either by percutaneous coronary intervention (PCI) or thrombolytic therapies, confers robust cardioprotection and enhance the survival of patient with AMI [1]. However, after the great success of therapies to reduce acute ischemic injury, the time has come to focus efforts on therapies to reduce myocardial "reperfusion injury" (RI) [2].

The seminal discovery of ischemic preconditioning (IPC) in 1986 [3], in which brief episodes of ischemia and reperfusion dramatically reduce myocardial infarct (MI) size, gave rise to the field of cardioprotection, and has resulted in over 10 000 publications in the research literature [4]. The cardioprotective strategy of ischemic postconditioning (I-PostC) was applied at the onset of reperfusion after sustained ischemia in 2003 [5], and is a powerful intervention that dramatically reduces RI. Over the past 2 decades, pharmacological postconditioning (PPostC) has been studied; it was given as a new pharmacological agent before or at the time of reperfusion, to mimic the protective effect of I-PostC [6].

Nitrate is an old anti-ischemic pharmacological agent and exogenous donor of NO with a more than 130-year history. It also has been suggested that mitochondria are a target of protective signaling to NO in cardiac myocytes, and the first event to take place during reperfusion without protection is the development of endothelial dysfunction due to loss of the ability of endothelial cells to release nitric oxide (NO) [7]. However, previous research failed to consider the efficacy of nitrate against RI in AMI patients receiving PCI administered before or after opening with culprit vessels. Following this review, we present possible new role for nitrate use as PPostC to protect RI in AMI and we also present some key concepts and discuss the advanced mechanisms.

Reperfusion Injury

Ischemic myocardium reperfusion was described as a 'double-edged sword' [8]. Myocardial reperfusion injury was first introduced by Jennings et al. [9], and this phenomenon occurs following PCI, coronary artery bypass grafting (CABG), or other cardio-thoracic surgery, in which both ischemia and reperfusion take place [10]. RI is traditionally classified into reversible damage (reperfusion arrhythmias, myocardial stunning) and irreversible injury (myocardial no-reflow, lethal reperfusion injury).

Reperfusion arrhythmias (RA)

Although myocardial ischemia and RI are both potent arrhythmogenic stimuli, the mechanisms involved in RA are unclear [11,12]. Oxygen-derived free radicals [13] and cytosolic calcium overload [14] are the 2 main factors of RA, and disturbance of potassium homeostasis is undoubtedly responsible for arrhythmogenesis [15]. In addition, autophagy is an adaptive physiological countermeasure to RA associated with cellular senescence and ischemia/reperfusion [16]. Recent studies tend to regard RA as an indicator of RI, so we observed the control of RA while studying the mechanism and treatment of RI.

Myocardial stunning

Myocardial stunning is a temporary post-ischemic cardiac mechanical dysfunction. The initial descriptions supporting the concept of stunned myocardium in humans occurring after reperfusion for acute MI came from the thrombolytic therapy literature [17]; it occurs after even brief inflations of an angioplasty balloon in the coronary artery of patients undergoing elective PCI [18]. The leading hypotheses are oxygen radical damage that occurs in the first few minutes of reperfusion and altered calcium flux with calcium overload that then desensitizes the myofilaments [19]. Free radical scavenger pretreatment before or immediately at the time of reperfusion can totally prevent stunning [20], and myocardial inflammation is a possible cause of myocardial stunning [21].

Myocardial no-reflow

Myocardial no-reflow is defined as an inadequate myocardial tissue perfusion without evidence of mechanical obstruction of the epicardial artery after a period of transient ischemia [22]. The no-reflow is still a serious complication of RI independent of infarct size [23].

The no-reflow phenomenon remains a difficult therapeutic target [24]. Potential therapies include vasodilators, statins, antiplatelet agents, thrombus aspiration, distal protection devices, IPC, remote ischemic preconditioning and postconditioning, pharmacologic preconditioning, and hypothermia [45]. In a porcine model of RI, infarct size and no-reflow was limited by intracoronary adenosine as an adjuvant therapy during early reperfusion [26].

Lethal reperfusion injury

The term 'lethal reperfusion injury' specifically refers to myocardial cell death caused by restoration of blood and accounts for a significant proportion (one-third or more) of cell death due to transient global or regional myocardial ischemia [27]. Cellular Ca^{2+} overload and oxidative stress can cause mPTP opening,

which can result necrotic cell death. Other common causes of lethal reperfusion injury include inflammation, hypercontracture, rapid restoration of physiological pH, and apoptotic cell death [28–30]. Many interventions have been tested in human trials after encouraging animal studies showed protection of the heart against ischemia/reperfusion-induced injury. These strategies include I-PostC, atrial natriuretic peptide (ANP), and cyclosporine A, which is an inhibitor of mPTP [3,132]. However, I-PostC is the most promising strategy because of its effectiveness, safety, commercial availability, feasibility, and costs.

Therapeutic Strategies Protecting Against Reperfusion Injury

Many cardioprotective interventions based on mechanical pathways of RI that have the potential to reduce infarct size have been translated from animal models to humans.

Mechanical therapeutic interventions for reducing myocardial reperfusion injury

Ischemic preconditioning (IPC) provides the strongest endogenous protection against cell death after transient coronary occlusion and against cell injury from reperfusion [33,34]. Clinical evidence suggests that this phenomenon may be greatly protective by attenuation of lethal reperfusion injury [35,36] and reduced release of biomarker in the surgical settings [37,38].

Ischemic postconditioning (I-PostC) as another promising strategy that targets the first minutes of restoration of blood flow; it reduces infarct size and all RI (e.g., RA, stunning, and no-reflow size) [39,40]. I-PostC decreases vascular dysfunction and inhibits cytokine release and apoptosis [41]. The good efficacy of I-PostC provides the most convincing evidence of the existence of lethal reperfusion injury.

The intermittent initial reperfusion associated with I-PostC leads to a delay of restoration of normal pH. As a result, the transient acidosis inhibits the formation of mPTP [42]. At the same time, intermittent reperfusion also causes the retention of triggering molecules (such as bradykinin [43], opioids [44], and adenosine [45,46]) within the myocardium, which then triggers their respective receptors to activate a protective signaling pathway(s). Based on various studies, diverse signaling mechanisms have been proposed. I-PostC activates G-protein-coupled receptor (GPCR) [44,46,47], stimulates survival kinases such as the p42/44 ERK MAPK, PI-3K-Akt, and protein kinase C-ε [46,48,49], reduces activity death kinases including JNK MAPK and p38 MAPKs, inhibits phosphorylation of inducible transcription factor (i.e., NF-κB) [50] and glycogen syntheses kinase-3β [51], and activates mitochondrial K^+_{ATP} channels [52,53]. Yang et al. [52] first demonstrated that

NO is involved in the protective signal transduction pathway of I-PostC through activation of protein kinase G. Compared to control hearts, I-PostC reduced free radical generation [54,55]. In contrast, administration of free radical scavengers either before or during the I-PostC intervention abrogates its cardioprotective effects, suggesting an important role in oxygen delivery of the I-PostC intervention [43,56,57]. However, negative results of I-PostC have been found in clinical practice and in experimental research [58,59]. Therefore, pharmacological postconditioning might provide cardioprotection as I-PostC, and avoid the additional damage resulting from mechanical intervention during I-PostC.

Pharmacological therapeutic agents to attenuate RI-PPostC

Several drugs that stimulate signaling steps of ischemic postconditioning can induce cardioprotection, even when the drug is only administered at reperfusion when there is also pharmacological postconditioning (PPostC) [60]. Clinical trials revealed the protective effects of adenosine [61], ANP and erythropoietin (EPO) [62], cyclosporine A\CsA\CsA-analogs [63,64], glucose-insulin-potassium [65], glucagons-like-peptide-1 [66], and beta-blockers [67]. Conversely, hypoglycemic drugs showed an anti-inflammatory/oxidative effect and could reduce and/or avoid the RI phenomena [68].

In addition, nitrate, which is a well-known nitric oxide donor, has long been used clinically. Studies also indicated that many nitric oxide donors protect murine myocardium against infarction via modulation of mitochondrial permeability transition [69]. NO has been shown to induce a powerful "late phase" of cardioprotection in rabbits 24 h after administration of the drug, and it increases tolerance of the heart to ischemia-reperfusion insult [70]. However, there are few studies assessing whether nitrate provides protection if used as a pharmacological postconditioning agent during PCI. Here, we review the potential mechanisms of cardioprotection against RI driven by nitrate and discuss a new therapeutic application of nitrate combined with PCI in AMI patients.

Nitrates

The use of nitrates in cardiovascular disease has a long history and continues to play a major role in clinical practice. The bioactivation of organic nitrates liberates NO, which causes vasodilation via its effect on vascular smooth muscle cells and impairs platelet activation [71]. Nitroglycerin was the first [72] and most frequently used nitrate for clinical treatment of angina pectoris. It causes vasodilatation of the capacitance veins and improves ventricular filling pressure, and also dilates the epicardial coronary arteries, improving coronary blood flow, particularly in ischemic zones.

In the PCI era, the use of nitrates is being reconsidered. Nitroglycerin is injected into the heart to relieve coronary spasm and to diagnose the cause of coronary artery stenosis during PCI. It improves prognosis of patients with heart failure and has beneficial effects on early and late left ventricle remodeling after myocardial infarction, as well reducing the incidence of silent ischemia. For more extensive recommendations of the use of nitrate in myocardial infarction, several unanswered questions need to be addressed. A few studies assessing the protective effect of nitrate reported positive results, but most of the clinical trials produced negative findings [73–76].

Mechanisms of nitrate in cardioprotection

Some studies found cardioprotective effects of nitrate in reduction of infarct size and improvement of clinical outcomes, but the mechanisms underlying the effect of nitrate against RI is currently unknown. It is well known that nitrate is the NO donor and NO has a cytoprotective effect via activation of its downstream pathways. Since ischemia-reperfusion is characterized as a NO deficit, replacement or restoration of physiological levels of NO is theoretically possible. Therefore, we can speculate that nitrate mediates cardioprotection against RI mainly through generation of NO. Interestingly, numerous studies have reported that NO affects mitochondrial function. In noncardiac cells, NO has been shown to attenuate apoptosis by inhibiting caspase activity while preventing mitochondrial membrane potential loss and the release of cytochrome c [77]. It has been suggested that, in the heart, mitochondria are a target of protective signaling by NO.

Nitrates can favorably influence myocardial infarction through several mechanisms [78]. They can reduce infarct size through hemodynamic effects and increased collateral flow [79,80]. Interacting with thrombolytic treatment, they accelerate or stabilize reperfusion [81]. Finally, they can prevent adverse remodeling in patients who fail in reperfusion. Zhao et al. investigated the cardioprotective effect of isosorbide dinitrate (ISDN) postconditioning against rat RI *in vivo*, and demonstrated that ISDN postconditioning induces a similar cardioprotective effect as I-PostC via improvement of myocardial antioxidant capacity [82]. Nitrate redistributes coronary flow to the ischemic regions of the heart, which was initially observed by measuring the oxygen saturation in large and small arteries of the coronary circulation *in vivo* [83].

Studies of AMI have clearly shown that the fibroblastic cells overactivation and the subsequent myocardial scar extension with cardiac pump depression are complex and multifactorial events. In this setting, a clear and central role is played by cardiomyocyte-derived exosomal microRNA-92a as a mediator of post-ischemic myofibroblast activation, both *in vitro* and *ex vivo* [84]. Indeed, cardiosomal microRNAs are essential in postinfarction myofibroblast phenoconversion [85]. However, both these pathways could explain the fibroblastic cells overactivation and the myocardial scar extension after myocardial infarction [84,85].

Clinical and experimental efficacy of nitrates in AMI

Predating the thrombolytic era, intravenous nitrate treatment has suggested beneficial effects on infarct size and ventricular functions, as well as statistically significant reduction in AMI mortality [86]. However, its applicability to patients undergoing thrombolysis and PCI remains uncertain. In a small clinical trial, 27 patients with AMI received isosorbide dinitrate (ISDN) to reduce infarct size; an 11% reduction of infarct size was found in the treatment group compared with the control group, but the result was not statistically significant. However, there were significantly less in-hospital complications in the treated group [87]. This result suggests that ISDN is candidate for improving clinical outcomes of AMI. GISSI-3 (Gruppo Italiano per lo studio Della sopravvivenza nell'infarto miocardico) [88] and ISIS-4 (the 4th International Study of Infarct Survival) [73] failed to demonstrate an overall benefit of nitrate in the acute and subacute phases of infarction in the setting of AMI with thrombolytic therapy. Publication of these 2 trials resulted in confusion among clinicians, who did not believe that nitrate is an effective drug for short-term and long-term use in AMI patients. However, the following 3 reasons may explain this negative result: (1) neither of these studies was double-blinded.; (2) patients with ischemic symptoms could not be in the placebo group forever. Some control group patients took nitrates later to prevent angina; and (3) nitrates resistance cannot be easily solved during the long-term clinical observation. Several studies indicated that nitrates also benefit other types of RI other than infarct size. NO donors were shown to suppress arrhythmias after myocardial infarction in a pig model [89]. Intravenous nitroglycerin infusion given in low dose before, during, and after coronary reperfusion (intracoronary streptokinase and/or angioplasty) to patients after anterior myocardial infarction was shown to recruit left ventricular function and accelerate recovery of left ventricular function, suggesting decreased myocardial 'stunning' [90,91].

In another double-blind placebo-controlled clinical trial, the possible benefits of intravenous ISDN were investigated in the acute phase of myocardial infarction and oral ISDN in subacute myocardial infarction. Overall, there was no benefit on either acute or subacute infarction. This was consistent with the GISSI-3 and ISIS-4 results [88]. A group of researchers studied GRACE data and found that 18% of long-term nitrate users were diagnosed with STEMI compared with 41% of nitrate-naive patients. Likewise, 82% of nitrate users presented with non-STEMI compared with 59% of patients who were

nitrate-naive. They also found that previous nitrate use was associated with lower CK-MB and troponin levels, regardless of acute coronary syndrome type [92]. Long-term oral nitrate therapy was associated with adverse cardiac events after 102 months of follow-up [93] and this result was the same in diabetic patients who underwent elective PCI [94]. The relationship between adverse outcome and long-term use of oral nitrate therapy, particularly in diabetic patients, is unclear. The major limitation may be nitrate tolerance characterized as decrease of hemodynamic and anti-ischemic effects. Increased ROS induced by long-term nitrate therapy may aggravate the harmful vascular effects and lead to increased adverse long-term clinical outcomes. These studies revealed that nitrates have disadvantages if used inappropriately.

In clinical practice, several related questions must be addressed. Will RI occur in most patients with unstable angina pectoris, when the coronary artery is not completed occluded, who receive stent implantation? In addition, nearly 20% of STEMI patients present TIMI flow of 2–3 at hospital presentation due to thrombus aspiration [95]. Thus, it is unknown whether these patients could benefit from postconditioning because I-PostC was applied in the catheter lab beyond the first minute after reflow threshold. For AMI patients, it is valuable to assess risk stratification in order to identify a group of patients who are more likely to develop RI and could get the maximum benefit from interventions. Unfortunately, there is no guideline on the standardized application of this intervention, and most cardiologists neglect this potential strategy due to the lack of intensive study of RI and I-PostC. Whether NO is safe remains to unclear because some findings suggested that low doses of NO donors are beneficial after ischemia-reperfusion, while high doses may be detrimental [95,96].

Conclusions

PPostC could be applied to almost all AMI patients to mimic the protective effects of I-PostC, without mechanical damage. Nitrate, among those potential agents, is a donor of NO, with endothelial-protective effects, and was found to reduce infarct size in several small clinical trials. To date, no clinical trial has assessed the use of nitrates for postconditioning during PCI. Postconditioning with nitrates may improve outcomes significantly, both in experimental models and large-scale trials, which would lead to an important new role for nitrates.

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