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

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Source of support: This work was supported by a grant from the Chinese Medical Doctor Association (grant no. DFCMDA201303), the Qingdao Benefit the People’s Special Project (15-9-2-70-nsh), and the National Natural Science Foundation of China (grant no. 81300695)

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

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/923129

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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 preconditioning (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 preconditioning (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 myocardial 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 Ca²⁺ overload and oxidative stress can cause mPTP opening,
which can result necrotic cell death. Other common causes of lethal reperfusion injury include inflammation, hypercontraction, 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-e [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 glycolgen syntheses kinase-3) [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 bio-activation 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 1-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 over-activation 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 thrombolyis 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 inhospital 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 GRADE 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
nitrates. 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 completely 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.

References:

1. O’Gara PT, Kushner FG, Ascheim DD et al: 2013 ACCF/AHA guideline for the management of ST elevation myocardial infarction: Executive summary: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol, 2013; 61: 485–510
2. Ibáñez B, Heusch G, Ozize M, Van de Werf F: Evolving therapies for myocardial ischemia/reperfusion injury. Am Coll Cardiol, 2015; 65(14): 1454–71
3. Murray CE, Jennings RB, Reimer KA: Preconditioning with ischemia: A delay of lethal cell injury in ischemic myocardium. Circulation, 1986; 74: 1124–36
4. Hausenloy DJ, Barrabes JA, Bøtker HE et al: Ischaemic conditioning and targeting reperfusion injury: A 30-year voyage of discovery. Basic Res Cardiol, 2016; 111(6): 70
5. Zhao ZQ, Contera JS, Halkos ME et al: Inhibition of myocardial injury by ischemic preconditioning during reperfusion: Comparison with ischemic preconditioning. Am J Physiol Heart Circ Physiol, 2003; 285(2): H579–88
6. Caricati-Neto A, Errante PR, Menezes-Rodrigues FS: Recent advances in pharmacological and non-pharmacological strategies of cardioprotection. Int J Mol Sci, 2019; 20(16): 4002
7. Förstermann U, Xia N, Li HG: Roles of vascular oxidative stress and Nitric Oxide in the pathogenesis of atherosclerosis. Circ Res, 2017; 120(4): 355–67
8. Braunwald E, Kloner RA: Myocardial reperfusion: A double-edged sword? J Clin Invest, 1985; 76(3): 1713–19
9. Jennings RB, Sommers HM, Smyth G et al: Myocardial necrosis induced by temporary occlusion of a coronary artery in the dog. Arch Pathol, 1960; 70: 68–78
10. Guarini G, Huqi A, Capozza P et al: Therapy against ischemic injury. Cur Pharm Des, 2013; 19(25): 4597–621
11. Frommeyer M, Puckhaber D, Ellermann C et al: Interactions of digitalis and class-III antiarrhythmic drugs: Amiodarone versus dronedarone. Int J Cardiol, 2017; 228: 74–79
12. Hausenloy DJ, Chillian W, Crea F et al: The coronary circulation in acute myocardial ischaemia/reperfusion injury – a target for cardioprotection. Cardiovas Res, 2018; 115(7): 1143–55
13. Bernier M, Hears D, Manning AS: Reperfusion-induced arrhythmias and oxygen-derived free radicals. Studies with “anti-free radical” interventions and a free-radical-generating system in the isolated perfused rat heart. Circ Res, 1986; 58(3): 311–40
14. Shekarforoush S, Safari F: Lactation protects against myocardial ischemia-reperfusion injury in rats. Acta Physio Hung, 2015; 102(4): 372–79
15. Hirche H, Franz C, Bos L et al: Myocardial extracellular K+ and H+ increase and noradrenaline release as possible cause of early arrhythmias following acute coronary artery occlusion in pigs. J Mol Cell Cardiol, 1980; 12(6): 579–93
16. Lekl I, Haines DD, Balla G, Tosaki A: Autophagy: An adaptive physiological countermeasure to cellular senescence and ischaemia/reperfusion-associated cardiac arrhythmias. J Cell Mol Med, 2017; 21(6): 1058–72
17. Touchstone DA, Beller GA, Nygaard TW et al: Effects of successful intravenous reperfusion therapy on regional myocardial function and geometry in humans: A tomographic assessment using two-dimensional echocardiography. J Am Coll Cardiol, 1989; 13: 1506–13
18. McCormick LM, Hoole SP, White PA et al: Pre-treatment with glucagon-like Peptide-1 protects against ischemic left ventricular dysfunction and stunning without a detected difference in myocardial substrate utilization. JACC Cardiovasc Interv, 2015; 8: 292–301
19. Kloner RA: Stunned and hibernating myocardium: Where are we nearly 4 decades later? J Am Heart Assoc, 2020; 9(3): e015502
20. PI SF, Liu YW, Li T et al: Effect of sequential nicorandil on myocardial microcirculation and short-term prognosis in acute myocardial infarction patients undergoing coronary intervention. J Thorac Dis, 2019; 11(3): 744–52
21. Guaracchi AI, Bulzis G, Pontone G et al: Current interpretation of myocardial stunning. Trends Cardiovasc Med, 2018; 28(4): 263–71
22. Jaffe R, Dick A, Strauss BH: Prevention and treatment of microvascular obstruction-related myocardial injury and coronary no-reflow following percutaneous coronary intervention: A systematic approach. JACC Cardiovasc Interv, 2010; 3(7): 695–704
23. Hausenloy DJ, Chillian W, Crea F et al: The coronary circulation in acute myocardial ischaemia/reperfusion injury: A target for cardioprotection. Cardiovas Res, 2019; 115(7): 1143–55
24. Jennings RB: Historical perspective on the pathology of myocardial ischemia/reperfusion injury. Circ Res, 2013; 113(4): 428–38
25. Schwartz BG, Kloner RA: Coronary no reflow. J Mol Cell Cardiol, 2012; 52(4): 873–82
26. Yetgin T, Uitterdijk A, Te Lintel Hekkert M et al: Limitation of infarct size and no-reflow by intracoronary adenosine depends critically on dose and duration. JACC Cardiovasc Interv, 2015; 8(15): 1990–99
27. Garcia-Dorado D, Ruiz-Meana M, Piper HM: Lethal reperfusion injury in acute myocardial infarction: facts and unresolved issues. Cardiovasc Res, 2009; 83(2): 165–68
28. Frangogiannis NG, Smith CW, Entman ML: The inflammatory response in myocardial infarction. Cardiovasc Res, 2002; 53(1): 31–47
29. Vedder NB, Winn RK, Rice CL et al: Inhibition of leukocyte adherence by anti-CD18 monoclonal antibody attenuates reperfusion injury in the rabbit ear. Proc Natl Acad Sci USA, 1990; 87(7): 2643–46
30. Zhao QZ, Veiz DA, Wang NP et al: Progressively developed myocardial apoptotic cell death during late phase of reperfusion. Apoptosis, 2001; 6(4): 279–90
31. Kitakaze M, Asakura M, Kim J et al: Human atrial natriuretic peptide and nicorandil as adjuncts to reperfusion treatment for acute myocardial infarction (J-WIND): Two randomised trials. Lancet, 2007; 370(9597): 1483–93
32. Plot C, Croisille P, Staat P et al: Effect of cyclosporine on reperfusion injury in acute myocardial infarction. N Engl J Med, 2008; 359(5): 473–81
33. Rodriguez-Sinovas A, Abdallah Y, Piper HM et al: Reperfusion injury as a therapeutic challenge in patients with acute myocardial infarction. Heart Fail Rev, 2007; 12(3–4): 207–16
34. Zaugg M, Schaub MC: Signaling and cellular mechanisms in cardiac protection by ischemic and pharmacological preconditioning. J Muscle Res Cell Motil, 2003; 24(2–3): 219–49
35. Otani H: Ischemic preconditioning: From molecular mechanisms to therapy. Circulation, 2005; 112(21): 2270–82
36. Casós K, Pérez ML, Blasco-Lucas A et al: Ischemic preconditioning of the left coronary artery by balloon inflation during coronary artery bypass graft. Ann Thorac Cardiovasc Surg, 2010; 16(4): 246–50
37. Wagner R, Piler P, Bedanova H et al: Myocardial injury is decreased by late remote ischemic preconditioning and aggravated by tramadol in patients undergoing cardiac surgery: A randomized controlled trial. Interact Cardiovasc Thorac Surg, 2010; 11(6): 756–62
38. Jebeli N, Esmaili HR, Manegar MH et al: Evaluation of the effects of ischemic preconditioning with a short reperfusion phase on patients undergoing a coronary artery bypass graft. Ann Thorac Cardiovasc Surg, 2010; 16(4): 248–52
39. Mewarton N, Thibault H, Rouble F et al: Postconditioning attenuates no-reflow in STEMI patients. Basic Res Cardiol, 2013; 108(6): 383
40. Pong T, Scherrer-Crosbie M, Atochin DN et al: Phosphomimetic modulation of ENOS improves myocardial reperfusion and mimics cardiac preconditioning in mice. PLOS One, 2014; 9(1): e85946
41. Pong T, Scherrer-Crosbie M, Atochin DN et al: Phosphomimetic modulation of ENOS improves myocardial reperfusion and mimics cardiac preconditioning in mice. PLOS One, 2014; 9(1): e85946
42. Caccioppo A, Franchin L, Grosso A et al: Ischemia reperfusion injury: mechanisms of damage/protection and novel strategies for cardiac recovery/regeneration. Int J Mol Sci, 2019; 20(20): pii: E5024
43. Penna C, Rastaldo R, Mancardi D et al: Post-conditioning induced cardioprotection requires signaling through a redox-sensitive mechanism, mitochondrial ATP-sensitive K+ channel and protein kinase C activation. Basic Res Cardiol, 2006; 101(2): 180–89
44. Mykytenko I, Kerenid F, Reeves IG et al: Long-term inhibition of myocardial infarction by postconditioning during reperfusion. Basic Res Cardiol, 2007; 102(1): 90–100
45. Kim H, Zhao QZ, Sun HY et al: Postconditioning attenuates myocardial ischemia-reperfusion injury by inhibiting events in the early minutes of reperfusion. Cardiovasc Res, 2004; 62(1): 74–85
46. Penna C, Rastaldo R, Mancardi D et al: Post-conditioning induced cardioprotection requires signaling through a redox-sensitive mechanism, mitochondrial ATP-sensitive K+ channel and protein kinase C activation. Basic Res Cardiol, 2006; 101(2): 180–89
47. Tsutsumi YM, Yokoyama T, Hirakawa Y et al: Reactive oxygen species trigger ischemic and pharmacological postconditioning: In vivo and in vitro characterization. Life Sci, 2007; 81(13): 1223–27
48. Freixa X, Bellora N, Ortiz-Perez JT et al: Ischemic preconditioning revisited: Lack of effects on infarct size following primary percutaneous coronary intervention. Eur Heart J, 2012; 33(1): 103–12
49. Skyschaly A, Walter B, Heusch G: Coronary microembolization during early reperfusion: Infarct extension, but protection by ischemic postconditioning. Eur Heart J, 2013; 34(42): 3314–21
50. Heusch G: Treatment of myocardial ischemia/reperfusion injury by ischemic and pharmacological postconditioning. Compr Physiol, 2015; 5(3): 1123–45
51. Marzilli M, Orsini E, Marraccini P et al: Beneficial effects of intracoronary adenosine as an adjunct to primary angioplasty in acute myocardial infarction. Circulation, 2000; 102(18): 2154–59
52. Ferrario M, Arbustini E, Massa M et al: High-dose erythropoietin in patients with acute myocardial infarction: A pilot, randomized, placebo-controlled study. Int J Cardiol, 2011; 147(1): 124–31
53. Argaud L, Gateau-Roesch O, Muntean D et al: Specific inhibition of the mitochondrial permeability transition pore during reperfusion. Cardiovasc Diabetol, 2011; 10(1): 18
54. Argaud L, Gateau-Roesch O, Raisky O et al: Postconditioning inhibits mitochondrial permeability transition. Circulation, 2005; 111(2): 194–97
55. Sasso FC, Pafundi PC, Marfella R et al: Adjunction of nicardipine and insulin resistance are related to restenosis and overall new PCI in subjects with normal glucose tolerance: The prospective AIRE Study. Cardiovasc Diabetol, 2019; 18(1): 24
56. Lonborg I, Velistrup N, Kelbæk H et al: Exenatide reduces reperfusion injury in patients with ST-segment elevation myocardial infarction. Eur Heart J, 2012; 33(12): 1491–99
57. Ndrepepa G, Kastrati A: Intravenous beta-blockers in primary percutaneous coronary intervention: New hope for an old therapy. Circulation, 2013; 128(14): 1487–89
58. Marfella R, Sardu C, Calabro P et al: Non-ST-elevation myocardial infarction outcomes in patients with type 2 diabetes with non-obstructive coronary artery stenosis: Effects of inrect treatment. Diabetes Obes Metab, 2018; 20(3): 723–29
59. Wang G, Liem DA, Vondriska TM et al: Nitric oxide donors protect murine myocardium against infarction via modulation of mitochondrial permeability transition. Am J Physio Heart Circ Physiol, 2005; 288(3): H1290–95
60. Bolli R: Cardioprotective function of inducible nitric oxide synthase and role of nitric oxide in myocardial ischemia and preconditioning: An overview of a decade of research. J Mol Cell Cardiol, 2001; 33(11): 1897–918
71. Divakaran S, Loscalzo J: The role of nitroglycerin and other nitrogen oxides in cardiovascular therapeutics. J Am Coll Cardiol, 2017; 70(19): 2393–410
72. Murrell W: Nitroglycerine as a remedy for angina pectoris. Lancet, 1879; 80: 80–81
73. Leesar MA, Stoddard MF, Dawn B et al: Delayed preconditioning-mimetic action of nitroglycerin in patients undergoing coronary angioplasty. Circulation, 2001; 103(24): 2935–41
74. European Study of Prevention of Infarct with Molsidomine (ESPRIM) Group: The ESPRIM trial: short-term treatment of acute myocardial infarction with molsidomine. Lancet, 1994; 344(8915): 91–97
75. Jugdutt BI: Effect of nitrates on myocardial remodeling after acute myocardial infarction. Am J Cardiol, 1996; 77(13): 17C–23C
76. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group: ISIS-4: A randomized factorial trial assessing early oral captopril, oral mononitrates, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. Lancet, 1995; 345(8915): 669–85
77. Sellers SL, Tran AE, Bernatchez PN: Caveolin as a potential drug target for cardiovascular protection. Front Physiol, 2012; 3: 280
78. Morris JL, Zaman AG, Smyllie JH et al: Nitrates in myocardial infarction: Influence on infarct size, reperfusion, and ventricular remodelling. Br Heart J, 1995; 73(4): 310–19
79. Pipilis A, Flather M, Collins R et al: Hemodynamic effects of captopril and isosorbide mononitrate started early in acute myocardial infarction: A randomized placebo-controlled study. J Am Coll Cardiol, 1993; 22(1): 73–79
80. Shao Q, Casin KM, Mackowski N et al: Adenosine A1 receptor activation increases myocardial protein S-nitrosothiols and elicits protection from ischemia-reperfusion injury in male and female hearts. PLoS One, 2017; 12(5): e0177315
81. Hackett D, Davies G, Chierchia S et al: Intermittent coronary occlusion in acute myocardial infarction. Value of combined thrombolytic and vasodilator therapy. N Engl J Med, 1987; 317(17): 1055–59
82. Zhao X, Wang M, Li M et al: Cardioprotective effect of isosorbide dinitrate postconditioning against rat myocardial ischemia-reperfusion injury in vivo. Med Sci Monit, 2019; 25(2): 1629–36
83. Wei K, Serpooshan V, Hurtado C et al: Epicardial FSTL1 reconstitution renews the adult mammalian heart. Nature, 2015; 525(7570): 479–85
84. Wang X, Morelli MB, Matrese A et al: Cardiomyocyte-derived exosomal microRNA-92a mediates post-ischemic myocardial infarction activation both in vitro and ex vivo. ESC Heart Fail, 2020; 7(1): 284–88
85. Morelli MB, Shu J, Sardu C et al: Cardiosomal microRNAs are essential in post-infarction myocardial fibroblast phenconversion. Int J Mol Sci, 2019; 21(1): pii: E201