

Coronary No-reflow Phenomenon: A Review of Therapeutic Pharmacological Agents

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Abstract

Coronary no-reflow phenomenon (CNRP) is one of the leading catastrophic consequences of percutaneous coronary intervention (PCI). Although several preventive strategies have been advised, yet CNRP is not entirely controlled with pharmacological agents after diagnosis. This study is a review of therapeutic pharmacological agents used in various studies for post-PCI-CNRP. Several pharmacological agents have been introduced for reducing the burden of adverse outcome, before or during PCI. Although most of these agents have shown a remarkable effect on post-PCI CNRP incidence reduction, and it seems more powerful are still needed for a better validation of the results. It appears that intra lesion and distal intracoronary administrations would have a less systemic effect, and therefore may be safer than catheter injection. Moreover, adenosine, sodium nitroprusside, and calcium channel blockers are among the most routinely used methods. However, we believe that the best approach in treating or preventing no-reflow post-STMI might be combinational therapy. By the way, although there have been numerous studies on different agents capable of lessening the no-reflow phenomenon, yet there is no exact guideline for choosing the most appropriate drug. A systematic review and meta-analysis on all available or practiced combinational pharmacotherapies to prevent PCI-related no-reflow are needed to suggest the most appropriate therapy.

Keywords: Coronary no-reflow phenomenon, Pharmacotherapy, adenosine, nitroprusside, review

1. Introduction

Coronary no-reflow phenomenon (CNRP) occurs when, despite percutaneous coronary intervention (PCI) and opening up the occluded vessel, the myocardial reperfusion does not naturally happen [1]. This phenomenon may occur in more than 10% of the cases of primary PCI, worsening the survival rate of the patients [2]. Although the underlying pathogenic mechanism is not yet completely known, it is evident that thrombus in the human artery after PCI or stent placing may result in small distal emboli, thereby reducing coronary flow and no-reflow [3,4]. In addition, some clinicians believe that CNRP may be secondary to microvascular arteriolar spasm and abrupt flow stop after myocardial infarction, thrombolysis in myocardial infarction (TIMI) zero flow [5].

The CNRP may have long-term consequences,

including myocardial necrosis lesion, which traps blood flow and results in a lack of normal existence of macrophages and hormones needed for removal of the debris and healing of the infarcted area. Moreover, CNRP may cause adverse left ventricle remodeling, resulting in heart failure and mortality [6]. Although several preventive strategies, such as thrombus aspiration before PCI or avoiding stent deployment at very high pressure, have been advised, CNRP is out of individual control and pharmacological treatment after diagnosis [5]. In recent years, several pharmacological agents have been identified as effective in the prevention and treatment of CNRP after PCI. Some of these pharmacological agents are now routinely administered and some are not. These agents can be either intracoronarily or intravenously administered. With this background in mind, the current study aimed to review all routinely and nonroutinely administered

pharmacological therapeutic agents and their efficacy in CNRP.

2. Pharmacologic therapy

2.1. Adenosine

Adenosine is an endogenous nucleoside that is usually produced by the degradation of adenosine triphosphate (ATP) and made by occluded coronary vessels after the flow stoppage. It acts on smooth muscles of cardiac vessels through its vasodilator effect, improving coronary blood flow. Moreover, it antagonizes neutrophils as well as platelets and prevents calcium overload. In addition, it activates the one-way movement of potassium into cardiomyocytes [7, 8]. Therefore, hyperpolarization occurs and calcium-channel dependent action potentials become suppressed [9, 10]. Despite all adenosine known actions, the exact mechanism by which it affects no-reflow after PCI is yet not clear [11]. In a randomized controlled trial, Xiaowei et al. observed that intracoronary adenosine after PCI administration increased the coronary flow and reperfusion without adverse effects on cardiovascular outcomes [12]. Two previous randomized trials (i.e., AMISTAD [13] and AMISTAD II [14]) reported that intravenous adenosine infusion downturns infarct size. However, it was not effective in reducing the incidence of mortality and congestive heart failure in patients with acute myocardial infarction (AMI).

2.2. Calcium channel blockers

Calcium channel blockers (CCBs) are well tolerated far-reaching antihypertensive drugs [15], with beneficial cardiovascular effects on patients at high risk of cardiovascular diseases [16]. They are also used for the treatment of no-reflow following an AMI [12]. Impaired myocardial perfusion after blood flow obstruction is associated with vaster infarct size [17], worsened clinical outcomes, adverse remodeling of the left ventricle, and reduced left ventricular ejection fraction (LVEF) [18]. Vasodilator therapy with CCBs is a currently available treatment to avoid these consequences [19]. In a randomized controlled trial, Zhao JL et al. examined the efficacy of CCBs with adenosine in PCI-related no-reflow. They suggested that both could significantly lessen the size of the no-reflow area. However, in comparison to CCB, adenosine also positively affected the necrosis area [20]. That is why it is said that adenosine both structurally and functionally improves the no-reflow phenomenon [21, 20].

2.3. Sodium nitroprusside

Sodium nitroprusside (SNP) is considered a potent vasodilator in arterioles and venues. The SNP has to

break down into circulation to release nitric oxide (NO) [22]. NO has a variety of activities, including antiplatelet as well as anti-inflammatory activities [23, 24]. It is assumed that SNP leads to the increase of reperfusion in PCI-related no-reflow as a result of vascular smooth muscle relaxation and hyperemia, due to the NO-releasing capacity of nitroprusside [25-27]. The results of another study showed that patients receiving nitroprusside had a better angiographic blood flow ($P>0.01$) and improved TIMI flow in 82% of cases [28, 29]. The combined therapy of adenosine and nitroprusside improved TIMI flow more than adenosine therapy (1.5 ± 1 vs. 0.8 ± 0.6 ; $P<0.005$) [28]. Moreover, although the systemic effect of distally-injected intracoronary nitroprusside is minor, it significantly improves blood flow [5].

Zhao et al. studied nitroprusside efficacy from the aspect of the improvement of ST-segment elevation resolution (STR), LVEF, TIMI flow grade, and adverse cardiac events in two groups, including tirofiban alone and tirofiban plus nitroprusside group, indicating an improvement with nitroprusside group [5]. Considering the fact that TIMI flow in the two groups was similar, it was concluded that myocardial blush grade is a more reliable strategy to define pharmacotherapy efficacy in reperfusion injury [5]. Statistically significant effect of SNP on the treatment of PCI-related reperfusion injury regarding TIMI frame count was also proven in comparison to that reported for nicorandil [30]. In another study, Parham et al. demonstrated that both adenosine and nitroprusside had a similar effect on hyperemia (and maybe no-reflow) although the improved results for blood flow development favored SNP [31].

In another study, the effect of prophylactic intracoronary injection of sole adenosine and adenosine plus SNP before PCI was investigated during a 6 months follow-up [32]. Thrombolysis in myocardial infarction flow grade (TFG) was higher in the control group (i.e., sole adenosine administration) than that reported for the nitroprusside plus anisodamine group (odds ratio [OR]: 1.85; 95% CI: 1.23-2.86). Furthermore, STR significantly reduced in comparison to that reported for anisodamine (OR: 0.36; 95% CI: 0.17-0.82) and nicorandil (OR: 0.37; 95% CI: 0.14-1.00). The LVEF in the control group was significantly lower than that of the nitroprusside group (95% CI: 6.18-0.27). Moreover, major adverse cardiac events (MACE) were less frequent in the nitroprusside group than those reported for the control group (OR: 1.23; 95% CI: 0.69-2.19) [32].

2.4. Glycoprotein IIb/IIIa inhibitors (i.e., eptifibatide, abciximab, and tirofiban)

The use of glycoprotein IIb/IIIa inhibitors is common

during PCI. These drugs are classified as antiplatelet and antithrombus formation glycoprotein IIb/IIIa antagonizes platelet aggregation by the inhibition of the glycoprotein IIb/IIIa receptor on the surface of the platelet [33]. One of the suggested mechanisms of post-PCI CNRP is platelet aggregation. These drugs inhibit the final pathway of platelet formation. Glycoprotein IIb/IIIa inhibitors could have potential benefits during PCI for the prevention of CNRP after acute coronary syndrome intervention [34]. A meta-analysis carried out by Tao Qin et al. evaluated the efficacy and safety of intracoronary tirofiban during PCI in the improvement of TIMI flow and MACE. The results of the aforementioned study showed that tirofiban significantly improved TIMI flow (OR: 0.24; 95% CI: 0.15-0.37; $P < 0.00001$), compared to conventional pharmacological agents for NR [35]. Koon-Hou Mak et al. proved the association of 87% reduction in distal embolization with abciximab during percutaneous treatment in vein graft disease. They believed that it points to the fact that the most suggestive mechanism of distal emboli is platelet aggregation [36]. Benjie Sun et al. in a meta-analysis included six randomized controlled trials indicating that the intralesional administration of glycoprotein IIb/IIIa inhibitors gained better results in TIMI grade 3 flow (OR: 2.29; 95% CI: ; STR [OR: 1.55; 95% CI: 1.12-2.14; $P = 0.008$] [37].

2.5. Nitroglycerin

Nitroglycerin has been medically used as a potent vasodilator as it converts to nitric oxide (i.e., a potent vasodilator). Ischemia originates either from focal epicardial spasm or distal plaque embolization showing that nitroglycerin may be effective in epicardial-spasm ischemia [38]. A study carried out by Piana et al. investigated the patients undergoing PCI and intracoronary nitroglycerin administration just before PCI, followed by verapamil, and indicated that most of the patients did not respond to nitroglycerin. Two of the patients were treated with nitroglycerin alone plus balloon inflation, in which the partial improvement of TIMI flow was observed [37]. In another retrospective study, Sitaram et al. compared intracoronary administration of nitroprusside and nitroglycerin in STEMI patients undergoing PCI from the aspect of no-reflow incidence and TIMI flow. The incidence of no-reflow in the nitroprusside group was lower than that reported for the nitroglycerin group (19% vs. 36%; $P = 0.0442$) and almost the same TIMI flow grade (III: II:I: 31:2:1:0 vs. 29:4:2:0; $P = 0.5524$) and improved blush grade for the nitroprusside group [39].

2.6. Epinephrine

Epinephrine is a beta-2-agonist, with potent coronary

vasodilatory effect and chronotropic and inotropic effect on the heart [40]. Aksu et al., in their retrospective study, suggested the use of intracoronary epinephrine as an alternative treatment for no-reflow post-primary PCI. The results of the aforementioned study showed that in 75% of patients treated with epinephrine, normal perfusion successfully returned. In addition, epinephrine did not have major adverse effects and was well tolerated [39].

2.7. Nicorandil

Nicorandil, as an anti-angina medication, has proven to have dual properties of nitrate and potassium (K^+) ATP channel agonist. It affects K^+ channels, promoting K^+ efflux as well as the ensuing hyperpolarization, and inhibits voltage-gated calcium channels, which leads to smooth muscle relaxation and vasodilation of the coronary arteries [41]. Nicorandil probably prevents reperfusion injury by blocking mitochondrial permeability transition pore (MPTP) [42]. Moreover, it seems that the effect of nicorandil on CNRP is due to its K^+ ATP channel agonist action causing pharmacological preconditioning and providing cardioprotective effects against ischemia [43]. In another study, it is declared that intravenous nicorandil just before PCI was related to a lower incidence of CNRP, better ventricular function, and improved clinical outcomes [44].

Another clinical study investigated a combinational therapy of adenosine plus nicorandil resulting in the reduction of CNRP incidence and improved clinical outcome of AMI than sole adenosine administration [45]. Another study carried out by Tsuneo Mizumura et al. demonstrated a relationship between the reduction of nicorandil infarct size and its KATP channel mechanism (not nitrate-like property) [46]. Another study assessed the efficacy and safety of nicorandil in comparison to verapamil indicating that nicorandil is both safer and more effective than verapamil in CNRP prevention [47]. Another study compared the use of nitroprusside and nicorandil for the treatment of CNRP and concluded a better TIMI flow grade for nitroprusside and almost the same efficacy in the improvement of blood flow for both agents [30].

2.8. Cyclosporine A

As a potential cardioprotective, cyclosporine A is an immunosuppressive agent blocking MPTP. Due to the aforementioned mechanism, Piot C et al. assessed intravenous cyclosporine administration during PCI and regarded it as an efficient agent in the improvement of no-reflow [48]. A study carried out by Kucukcelebi et al. also examined the efficacy of cyclosporine A in the improvement of reperfusion injury in rat skin island flaps. According to the results of the aforementioned

study, this agent is considered statistically beneficial in the improvement of survival rate due to the treatment or prevention of the no-reflow phenomenon [49].

2.9. Anticoagulants (dabigatran)

Dabigatran is an anticoagulant agent belonging to the category of direct thrombin inhibitors (DTIs) or novel DTIs functioning by directly inhibiting both free and fibrin-bound thrombin [50]. Spangle et al. in their study examined the blood samples of PCI candidates for ST-elevation myocardial infarction (STEMI) just before and at the end of PCI in addition to 2, 6, and 12 h after angiography. A rapid increase of thrombin occurred during PCI in 69% of patients, which is suggestive of the potential benefits of antithrombin agents for CNRP [51]. However, Hale SL et al. evaluated the efficacy of dabigatran in the no-reflow model and declared that dabigatran did not affect the improvement of blood flow to the infarct area [52].

2.10. Liraglutide

Liraglutide is a derivative of human incretin (i.e., metabolic hormone) glucagon-like peptide-1 (GLP-1) that is used as a long-acting GLP-1 receptor agonist. This agent binds to the same receptors, as does the endogenous metabolic hormone GLP-1, stimulating insulin secretion [53]. Based on the results of their clinical study, Wei Ren Chen et al. suggested that liraglutide is associated with lower incidence of CNRP in patients undergoing PCI for STEMI in comparison to that reported for the control group (5% vs. 15%; $P=0.01$). Wei Ren Chen et al. also confirmed the efficacy of liraglutide in the reduction of myocardial injury and improvement of reperfusion [54].

2.11. Anisodamine

Anisodamine, an anticholinergic and alpha-1 adrenergic receptor antagonist, is a tropane alkaloid observed in some plants of the Solanaceae family. Many fundamental studies have proven the efficacy of anisodamine in the improvement of microvascular flow [55]. In a meta-analysis carried out by Niu et al., it was demonstrated that the intracoronary administration of anisodamine would help to improve myocardial reperfusion, clinical outcomes, cardiac function, and TFG with no MACE [56]. A clinical study conducted by Fu XH et al. studied a group of nitroglycerin intracoronary administration and a group treated by intracoronary anisodamine after nitroglycerin. The results of the aforementioned study showed that anisodamine might have a significant effect on relieving microvascular spasm in addition to the MACE effect [57].

2.12. Melatonin

Melatonin is a hormone produced by the pineal gland

which is involved in the circadian rhythm as well as being a potent free radical scavenger and electron donor [58]. Due to the anti-inflammatory, antioxidant, and lipid regulatory actions of melatonin, it is imaginable to regard it as an effective agent in post-PCI coronary flow improvement [59]. RJ Reiter declared that melatonin could prevent ROS and therefore might have a potential role in overcoming cardiovascular diseases and reperfusion injury [60].

2.13. Atorvastatin

Atorvastatin is a lipid-lowering agent of the statin drug class which is routinely prescribed for the prevention of cardiovascular diseases [61]. As most of the no-reflow cases present a high serum lipoprotein, there might be an association between hyperlipidemia and reperfusion injury. A previous trial showed that high-dose statin therapy before PCI promoted prognosis and decreased CNRP incidence [62]. In another study, high doses of atorvastatin at least days before elective PCI was related to lower incidence of myocardial infarction (the incidence of myocardial infarction in the atorvastatin group reported as 9.5% and in the control group without prophylactic atorvastatin reported as 15.8%; OR: 0.56; 95% CI: 0.35-0.89; $P=0.014$) [63].

2.14. N-acetyl cysteine

N-acetyl cysteine (NAC) is a prodrug of L-cysteine, which in addition to other properties, provides antioxidative effects. Younes Nozari et al. assessed the potential role of NAC (due to its anti-oxidant action) and observed remarkable improvement of myocardial reperfusion [64]. Another study carried out by Neil P Andrews et al. evaluated the effect of NAC on blood flow change and compared the differences in two postmyocardial infarction reperfusion groups. Firstly, when patients received adenosine and secondly when they received NAC following adenosine. The vasodilation effect pattern of adenosine neither increased nor decreased after NAC administration; however, NAC could improve coronary and vascular function [65]. In another study, the improvement of lung blood flow injury after other organ's transplantati.

3. Conclusion

The CNRP is an essential consequence of PCI for reperfusion, leading to impaired blood flow, increasing infarct size, reducing LVEF, and increasing the mortality rate. Several pharmacological agents have been introduced for reducing the burden of this adverse outcome before or during PCI. Although most of these agents have shown a remarkable effect on the reduction of post-PCI CNRP incidence, it seems more powerful are still required for a

better validation of the results. It appears that intralesional and distal intracoronary administrations would have a less systemic effect and therefore may be safer than catheter injection. Moreover, adenosine, SNP, and CCBs are among the most routinely used agents. However, it is believed that the best approach in the treatment or prevention of no-reflow post-STMI might be combinational therapy. In addition, although there have been numerous studies carried out on different agents capable of lessening the no-reflow phenomenon, there is no exact guideline for the selection of the most appropriate drug. It is required to carry out a systematic review and meta-analysis on all available or practiced combinational pharmacotherapies for the prevention of PCI-related no-reflow to suggest the most appropriate therapy.

References

1. Danesh Sani SH, Eshraghi A, Shahri B, Vojdanparast M. No-reflow phenomenon in patients with STElevation acute myocardial infarction, treated with primary percutaneous coronary intervention: a study of predictive factors. **Journal of Cardio-Thoracic Medicine**. 2014; 2 (4):221-226
2. Assali AR, Sdringola S, Ghani M, Denkats AE, Yepes A, Hanna GP, Schroth G, Fujise K, Anderson HV, Smalling RW. Intracoronary adenosine administered during percutaneous intervention in acute myocardial infarction and reduction in the incidence of "no reflow" phenomenon. **Catheterization and Cardiovascular interventions**. 2000; 51 (1):27-31
3. Bouleti C, Mewton N, Germain S. The no-reflow phenomenon: state of the art. **Archives of cardiovascular diseases**. 2015; 108 (12):661-674
4. Kloner RA. No-reflow phenomenon: maintaining vascular integrity. **Journal of Cardiovascular Pharmacology and Therapeutics**. 2011; 16 (3-4):244-250.
5. Rezkalla SH, Stankowski RV, Hanna J, Kloner RA. Management of no-reflow phenomenon in the catheterization laboratory. **JACC: Cardiovascular Interventions**. 2017; 10 (3):215-223.
6. Brosh D, Assali AR, Mager A, Porter A, Hasdai D, Teplitsky I, Rechavia E, Fuchs S, Battler A, Kornowski R. Effect of no-reflow during primary percutaneous coronary intervention for acute myocardial infarction on six-month mortality. **American Journal of Cardiology**. 2007; 99 (4):442-445
7. Born GVR. Aggregation of blood platelets by adenosine diphosphate and its reversal. **Nature**. 1962; 194 (4832):927-929
8. Dhalla N, Pierce G, Panagia V, Singal P, Beamish R. Calcium movements in relation to heart function. Springer, 1982.
9. Post R, Merritt C, Kinsolving C, Albright C. Membrane adenosine triphosphatase as a participant in the active transport of sodium and potassium in the human erythrocyte. **J biol chem**. 1960; 235:1796-1802
10. Paller MS, Hoidal J, Ferris TF. Oxygen free radicals in ischemic acute renal failure in the rat. **The Journal of clinical investigation**. 1984; 74 (4):1156-1164
11. Barcin C, Denktas AE, Lennon RJ, Hammes L, Higano ST, Holmes DR, Garratt KN, Lerman A. Comparison of combination therapy of adenosine and nitroprusside with adenosine alone in the treatment of angiographic no-reflow phenomenon. **Catheterization and cardiovascular interventions**. 2004; 61 (4):484-491
12. Galiuto L. Optimal therapeutic strategies in the setting of post-infarct no reflow: the need for a pathogenetic classification. **Heart**. 2004 Feb; 90(2): 123-125.
13. Mahaffey KW, Puma JA, Barbagelata NA, DiCarli MF, Leesar MA, Browne KF, Eisenberg PR, Bolli R, Casas AC, Molina-Viamonte V. Adenosine as an adjunct to thrombolytic therapy for acute myocardial infarction: results of a multicenter, randomized, placebo-controlled trial: the Acute Myocardial Infarction Study of Adenosine (AMISTAD) trial. **Journal of the American College of Cardiology**. 1999; 34 (6):1711-1720
14. Ross AM, Gibbons RJ, Stone GW, Kloner RA, Alexander RW, Investigators A-I. A randomized, double-blinded, placebo-controlled multicenter trial of adenosine as an adjunct to reperfusion in the treatment of acute myocardial infarction (AMISTAD-II). **Journal of the American College of Cardiology**. 2005; 45 (11):1775-1780
15. Braunwald E. Mechanism of action of calcium-channel-blocking agents. **New England Journal of Medicine**. 1982; 307 (26):1618-1627
16. Verdecchia P, Reboldi G, Angeli F, Gattobigio R, Bentivoglio M, Thijs L, Staessen JA, Porcellati C. Angiotensin-converting enzyme inhibitors and calcium channel blockers for coronary heart disease and stroke prevention. **Hypertension**. 2005; 46 (2):386-392
17. Reffellmann T, Hale SL, Li G, Kloner RA. Relationship between no reflow and infarct size as influenced by the duration of ischemia and reperfusion. **American Journal of Physiology-Heart and Circulatory Physiology**. 2002; 282 (2):H766-H772
18. Abbo KM, Dooris M, Glazier S, O'Neill WW, Byrd D, Grines CL, Safian RD. Features and outcome of no-reflow after percutaneous coronary intervention. **The American journal of cardiology**. 1995; 75 (12):778-782
19. Su Q, Li L, Liu Y. Short-term effect of verapamil on coronary no-reflow associated with percutaneous coronary intervention in patients with acute coronary syndrome: a systematic review and meta-analysis of randomized controlled trials. **Clinical cardiology**. 2013; 36 (8)
20. Zhao J-L, Yang Y-J, Cui C-J, You S-J, Wu Y-J, Gao R-L. Different effects of adenosine and calcium channel blockade on myocardial no-reflow after acute myocardial infarction and reperfusion. **Cardiovascular drugs and therapy**. 2006; 20 (3):167-175
21. Babbitt DG, Virmani R, Forman MB. Intracoronary adenosine administered after reperfusion limits vascular injury after prolonged ischemia in the canine model. **Circulation**. 1989; 80 (5):1388-1399
22. Grossi L, D'Angelo S. Sodium nitroprusside: mechanism of NO release mediated by sulfhydryl-containing molecules. **Journal of medicinal chemistry**. 2005; 48 (7):2622-2626
23. Salvemini D, Currie MG, Mollace V. Nitric oxide-mediated cyclooxygenase activation. A key event in the antiplatelet effects of nitrovasodilators. **The Journal of clinical investigation**. 1996; 97 (11):2562-2568
24. Massoudy P, Zahler S, Barankay A, Becker BF, Richter JA, Meisner H. Sodium nitroprusside during coronary artery bypass grafting: evidence for an antiinflammatory action. **The Annals of thoracic surgery**. 1999; 67 (4):1059-1064
25. Ignarro LJ, Lippton H, Edwards JC, Baricos WH, Hyman AL, Kadowitz PJ, Gruetter CA. Mechanism of vascular smooth muscle relaxation by organic nitrates, nitrites, nitroprusside and nitric oxide: evidence for the involvement of S-nitrosothiols as active intermediates. **Journal of Pharmacology and Experimental Therapeutics**. 1981; 218 (3):739-749
26. Leone AM, Porto I, De Caterina AR, Basile E, Aurelio A, Gardi A, Russo D, Laezza D, Niccoli G, Burzotta F. Maximal hyperemia in the assessment of fractional flow reserve: intracoronary adenosine

- versus intracoronary sodium nitroprusside versus intravenous adenosine: the NASCI (Nitroprusside versus Adenosine nelle Stenosi Coronarie Intermedie) study. **JACC: Cardiovascular Interventions**. 2012; 5 (4):402-408
27. Benz S, Schnabel R, Weber H, Pfeffer F, Wiesner R, von Breitenbuch P, Nizze H, Schareck W, Hopt UT. THE NITRIC OXIDE DONOR SODIUM NITROPRUSSIDE IS PROTECTIVE IN ISCHEMIA/ REPERFUSION INJURY OF THE PANCREAS. **Transplantation**. 1998; 66 (8):994-999
 28. Berg R, Buhari C. Treating and preventing no reflow in the cardiac catheterization laboratory. **Current cardiology reviews**. 2012; 8 (3):209-214
 29. Wang HJ, Lo PH, Lin JJ, Lee H, Hung JS. Treatment of slow/no-reflow phenomenon with intracoronary nitroprusside injection in primary coronary intervention for acute myocardial infarction. **Catheterization and cardiovascular interventions**. 2004; 63 (2):171-176
 30. Kobatake R, Sato T, Fujiwara Y, Sunami H, Yoshioka R, Ikeda T, Saito H, Ujihira T. Comparison of the effects of nitroprusside versus nicorandil on the slow/no-reflow phenomenon during coronary interventions for acute myocardial infarction. **Heart and vessels**. 2011; 26 (4):379-384
 31. Parham WA, Bouhasin A, Ciaramita JP, Khoukz S, Herrmann SC, Kern MJ. Coronary hyperemic dose responses of intracoronary sodium nitroprusside. **Circulation**. 2004; 109 (10):1236-1243
 32. Parikh KH, Chag MC, Shah KI, Shah UG, Baxi HA, Chandarana AH, Naik AM, Shah JN, Shah HD, Goyal RK. Intracoronary boluses of adenosine and sodium nitroprusside in combination reverses slow/no-reflow during angioplasty: a clinical scenario of ischemic preconditioning. **Canadian journal of physiology and pharmacology**. 2007; 85 (3-4):476-482
 33. Collier BS. Platelet GPIIb/IIIa antagonists: the first anti-integrin receptor therapeutics. **The Journal of clinical investigation**. 1997; 99 (7):1467-1471
 34. Eeckhout E, Kern M. The coronary no-reflow phenomenon: a review of mechanisms and therapies. **European heart journal**. 2001; 22 (9):729-739
 35. Qin T, Xie L, Chen M-H. Meta-analysis of randomized controlled trials on the efficacy and safety of intracoronary administration of tirofiban for no-reflow phenomenon. **BMC cardiovascular disorders**. 2013; 13 (1):68 .
 36. Mak K-H . Recovery of coronary flow and left ventricular function after abciximab. **Circulation**. 1999; 100 (22):e110-e110
 37. Sun B, Liu Z, Yin H, Wang T, Chen T, Yang S, Jiang Z. Intracoronary versus intracoronary administration of glycoprotein IIb/IIIa inhibitors during percutaneous coronary intervention in patients with acute coronary syndromes: A meta-analysis of randomized controlled trials. **Medicine** 2017; 96 (40).
 38. Chiariello M, Gold HK, Leinbach RC, Davis MA, Maroko PR. Comparison between the effects of nitroprusside and nitroglycerin on ischemic injury during acute myocardial infarction. **Circulation**. 1976; 54 (5):766-773
 39. Sai S, Louie F, Sitaram S, Arunachalam V. Impact of intracoronary administration of nitroprusside vs. nitroglycerine before balloon dilatation on slow reflow during percutaneous coronary intervention in patients with acute ST elevation myocardial infarction. **Cardiovascular Revascularization Medicine**. 2011; 12 (3):e15-e16
 40. Kaumann A, Lemoine H. β 2-Adrenoceptor-mediated positive inotropic effect of adrenaline in human ventricular myocardium. **Naunyn-Schmiedeberg's archives of pharmacology**. 1987; 335 (4):403-411.
 41. Sato T, Sasaki N, O'Rourke B, Marbán E. Nicorandil, a potent cardioprotective agent, acts by opening mitochondrial ATP-dependent potassium channels. **Journal of the American College of Cardiology**. 2000; 35 (2):514- 518
 42. Cahoon NJ. Efficacy and mechanism of nicorandil in perioperative protection of skeletal muscle from ischaemia and reperfusion injury in a porcine model. University of Glasgow. 2012. In available: <https://eleanor.lib.gla.ac.uk/record=b2979529>
 43. Ito H, Taniyama Y, Iwakura K, Nishikawa N, Masuyama T, Kuzuya T, Hori M, Higashino Y, Fujii K, Minamino T. Intravenous nicorandil can preserve microvascular integrity and myocardial viability in patients with reperfused anterior wall myocardial infarction. **Journal of the American College of Cardiology**. 1999; 33 (3):654-660
 44. Ishii H, Ichimiya S, Kanashiro M, Amano T, Imai K, Murohara T, Matsubara T. Impact of a Single Intravenous Administration of Nicorandil Before Reperfusion in Patients With ST-Segment-Elevation Myocardial Infarction. **Circulation**. 2005; 112 (9):1284-1288
 45. Lim SY, Bae EH, Jeong MH, Kang DG, Lee YS, Kim KH, Lee SH, Yoon KH, Hong SN, Park HW. Effect of combined intracoronary adenosine and nicorandil on no-reflow phenomenon during percutaneous coronary intervention. **Circulation Journal**. 2004; 68 (10):928-932
 46. Mizumura T, Nithipatikom K, Gross GJ. Infarct size-reducing effect of nicorandil is mediated by the KATP channel but not by its nitrate-like properties in dogs. **Cardiovascular research**. 1996; 32 (2):274-285
 47. Tsubokawa A, Ueda K, Sakamoto H, Iwase T, Tamaki S-i. Effect of intracoronary nicorandil administration on preventing no-reflow/slow flow phenomenon during rotational atherectomy. **Circulation journal**. 2002; 66 (12):1119-1123
 48. Piot C, Croisille P, Staat P, Thibault H, Rioufol G, Mewton N, Elbelghiti R, Cung TT, Bonnefoy E, Angoulvant D. Effect of cyclosporine on reperfusion injury in acute myocardial infarction. **New England Journal of Medicine**. 2008; 359 (5):473-481
 49. Kucukcelebi A, Ozcan M. The beneficial effect of cyclosporin-A on the no-reflow phenomenon in rat skin island flaps. **British journal of plastic surgery**. 1992; 45 (7):512-514
 50. Stangier J, Rathgen K, Stähle H, Gansser D, Roth W. The pharmacokinetics, pharmacodynamics and tolerability of dabigatran etexilate, a new oral direct thrombin inhibitor, in healthy male subjects. **British journal of clinical pharmacology**. 2007; 64 (3):292-303
 51. Spagnoli V, Klein E, Sideris G, Magkoutis N, Brumpt C, Bal Dit Sollier C, Henry P, Drouet L. Correlation between burst of thrombin and microvascular obstruction (no reflow) during ST Elevation Myocardial Infarction treated by primary percutaneous coronary Intervention. **European Heart Journal**. 2013; 34 (suppl_1):1608
 52. Hale SL, Kloner RA. Dabigatran treatment: effects on infarct size and the no-reflow phenomenon in a model of acute myocardial ischemia/ reperfusion. **Journal of thrombosis and thrombolysis**. 2015; 39 (1):50-54
 53. Nauck MA, Meier JJ. Glucagon-like peptide 1 and its derivatives in the treatment of diabetes. **Regulatory peptides**. 2005; 128 (2):135-148
 54. Chen WR, Tian F, Dai Chen Y, Wang J, Yang JJ, Wang ZF, Da Wang J, Ning QX. Effects of liraglutide on no-reflow in patients with acute ST-segment elevation myocardial infarction. **International journal of cardiology**. 2016; 208:109-114
 55. Poupko JM, Baskin SI, Moore E. The pharmacological properties of

- anisodamine. **Journal of Applied Toxicology**. 2007; 27 (2):116-121
56. Niu X, Zhang J, Bai M, Peng Y, Sun S, Zhang Z. Effect of intracoronary agents on the no-reflow phenomenon during primary percutaneous coronary intervention in patients with ST-elevation myocardial infarction: a network meta-analysis. **BMC cardiovascular disorders**. 2018; 18 (1):3
 57. Jun W, FAN G, Yunfa WJ. Effect of intracoronary administration of anisodamine on slow reflow phenomenon following primary percutaneous coronary intervention in patients with acute myocardial infarction [J]. **Journal of Clinical Cardiology**. 2006; 1:008
 58. Poeggeler B, Saarela S, Reiter RJ, TAN DX, CHEN LD, Manchester LC, BARLOW- WALDEN LR. Melatonin—a highly potent endogenous radical scavenger and electron donor: new aspects of the oxidation chemistry of this indole accessed in vitro. **Annals of the New York Academy of Sciences**. 1994; 738 (1):419-420
 59. Zhou H, Ma Q, Zhu P, Ren J, Reiter RJ, Chen Y . Protective role of melatonin in cardiac ischemia- reperfusion injury: from pathogenesis to targeted therapy. **Journal of pineal research**. 2018; 64(3).
 60. Reiter RJ, Tan D-X. Melatonin: a novel protective agent against oxidative injury of the ischemic/reperfused heart. **Cardiovascular research**. 2003; 58 (1):10-19
 61. Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial— Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. **The Lancet**. 2003; 361 (9364):1149- 1158
 62. Liu W, Zou Z, Jiang H, Li Q, Guo F, Wang Z, Zhu H. Clinical effect of preoperative high-dose atorvastatin against no-reflow after PCI. **Experimental and therapeutic medicine**. 2017; 13 (1):97-102
 63. Briguori C, Visconti G, Focaccio A, Golia B, Chieffo A, Casteli A, et al. Novel approaches for preventing or limiting events (Naples) II trial: impact of a single high loading dose of atorvastatin on periprocedural myocardial infarction. **J Am Coll Cardiol**. 2009 Dec 1;54(23):2157-63.
 64. Eshraghi A, Talasaz AH, Salamzadeh J, Salarifar M, Pourhosseini H, Nozari Y, Bahremand M, Jalali A, Boroumand MA . Evaluating the effect of intracoronary N-acetylcysteine on platelet activation markers after primary percutaneous coronary intervention in patients with ST-elevation myocardial infarction. **American journal of therapeutics**. 2016; 23 (1):e44-e51
 65. Andrews NP, Prasad A, Quyyumi AA. N-acetylcysteine improves coronary and peripheral vascular function. **Journal of the American College of Cardiology**. 2001; 37 (1):117-123
 66. Weinbroum AA, Kluger Y, Abraham RB, Shapira I, Karchevski E, Rudick V. LUNG PRECONDITIONING WITH N-ACETYL-L-CYSTEINE PREVENTS REPERFUSION INJURY AFTER LIVER NO FLOW-REFLOW: A DOSE-RESPONSE STUDY1. **Transplantation** 2001; 71 (2):300-306