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Safety and Efficacy of Intracoronary Vasodilators in the Treatment of No-Reflow after Primary Percutaneous Intervention in Patients with Acute ST-Elevation Myocardial Infarction: A Literature Review

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ABSTRACT

Introduction: The investigation of no-reflow phenomenon after Percutaneous Coronary Intervention (PCI) in patients with acute ST-segment Elevation Myocardial Infarction (STEMI) has therapeutic implications. Several vasodilators were administered through intracoronary injection to treat this phenomenon. We aimed to elucidate the risk factors, predictors, and long-term effects of no-reflow phenomenon, and to compare the effects of various vasodilators on re-opening the obstructed vessels.

Materials and Methods: All the reviewed articles were retrieved from MEDLINE and Science Direct (up to October 2014). All no-reflow cases were determined through Thrombolysis in Myocardial Infarction grading (TIMI) system.

Results: Four articles were included, two of which mainly focused on risk factors, predictors, and long-term prognosis of no-reflow phenomenon, and its association with patient mortality and morbidity. The other two articles evaluated therapeutic interventions and compared their efficacy in treating no-reflow.

Conclusion: Development of no-reflow in patients with STEMI after primary PCI is associated with low myocardial salvage by primary PCI, large scintigraphic infarct size, deteriorated left ventricle ejection fraction at six months, and increased risk of first-year mortality. During primary PCI, intracoronary infusion of diltiazem and verapamil can reverse no-reflow more effectively than nitroglycerin.

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Introduction

No-reflow refers to a state of myocardial tissue hypo-perfusion in the presence of a patent epicardial coronary artery. The underlying cause of no-reflow is microvascular obstruction, which may be developed by various mechanisms. Reperfusion no-reflow occurs after primary Percutaneous Coronary Intervention (PCI) for reperfusion of an infarct-related artery in the setting of Acute Myocardial Infarction (AMI), which may be asymptomatic or clinically present with uncontrolled chest pain and ST-segment elevation. Reperfusion no-reflow is preceded by ischemic cell injury, confined to the irreversibly damaged necrotic zone, which can exacerbate at the time of reperfusion.

Reperfusion no-reflow is an independent predictor of adverse clinical outcome after AMI regardless of the infarct extent. Although Electrocardiogram (ECG) analysis of ST-segment is an available marker of tissue-level reperfusion, persistence of ST-segment elevation in an AMI patient may reflect either epicardial artery occlusion or microvascular obstruction. Coronary angiography allows a semi-quantitative grading of epicardial coronary flow according to the Thrombolysis in Myocardial Infarction (TIMI) flow grades.

The no-reflow phenomenon is recognized by angiography in 20% of patients undergoing primary angioplasty for AMI and in 2% of elective PCI cases.

Reduced coronary arterial flow after primary angioplasty (TIMI flow: 0-2) is associated with worse outcome than normal flow (TIMI: 3), even when no significant epicardial obstruction remains (1).

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A number of sensitive markers of tissue perfusion are than TIMI flow grade. TIMI frame count assesses the number of angiographic frames required for the contrast medium to reach standardized distal landmarks of the coronary tree. Myocardial blush grade, on the other hand, is a quantitative detector of myocardial contrast density. Angiographic epicardial flow is a poor surrogate indicator of tissue perfusion, which is the clinically important endpoint of coronary interventions, and microvascular no-reflow occurs much more commonly than estimated. Myocardial contrast ECG is an advanced non-invasive method for assessment of myocardial perfusion and can demonstrate microvascular no-reflow, even among patients with angiographic TIMI grade 3 flow after primary PCI, which predicts adverse outcomes (2).

Tissue hypo-enhancement in contrast-enhanced magnetic resonance imaging and computed tomography scan reflects impaired myocardial perfusion, which is associated with histological evidence of microvascular obstruction. A rise in cardiac serum biomarkers after PCI reflects myocardial identified, which provide more prognostic information necrosis secondary to tissue hypo-perfusion and ischemia. More than 70% of patients may exhibit elevated troponin values after a successful elective PCI (3).

Materials and Methods

The search was carried out using the following keywords: “no-reflow phenomenon”, “percutaneous coronary intervention”, and “acute myocardial infarction (AMI)”. All the included articles (n=4) were retrieved from MEDLINE and ScienceDirect databases (up to October 2014). The studies were controlled trials, and had focused on no-reflow phenomenon after primary PCI, diagnosed and graded by TIMI grading system. In these studies, the risk factors, predictors, therapeutic interventions, and outcomes of no-reflow were reviewed and compared with each other. The results and the study characteristics of the articles were reviewed and the collected data are presented in Table 1.

Table1: The results and characteristics of the reviewed articles

Author	Year	Type of study	No. of patients	Selected group characteristics	No reflow confirming method	Objectives
Gjin Ndrepepa	2009	Prospective, controlled study	1140 (108 patients with no-reflow)	Patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI) and paired scintigraphic examinations	Thrombolysis In Myocardial Infarction (TIMI) grading system	Determining the predictive factors, persistence in time, and impact of no reflow on myocardial salvage, ventricular function, and mortality
Itsuro Morishima	2000	Retrospective, controlled study	476 (120 patients were included in the study)	1) Patients with initial episode of acute myocardial infarction (AMI); 2) A single-culprit lesion; 3) The infarct-related artery was recanalized with direct or rescue-PTCA within 6 h of the disease onset or between 6 h and 24 h if evidence showed continuing ischemia; 4) Residual stenosis not more than 50%; and 5) Absence of apparent dissection or thrombosis that might restrict coronary flow despite multidirectional observations on cineangiograms	TIMI flow grades	Elucidate the long-term prognostic importance of angiographic no-reflow phenomenon after percutaneous transluminal coronary angioplasty (PTCA) for acute myocardial infarction (AMI)
Dong Huang	2006-2009	Prospective, randomized, 2-center trial study	608 (102 patients with no-reflow)	Patients with no-reflow in primary PCI were randomized to receive intracoronary infusion of diltiazem, verapamil, or nitroglycerin (n=34 in each group) through selective microcatheter	TIMI grading system	Compare different vasodilators for treating no-reflow during primary PCI for ST-segment elevation acute myocardial infarction
Giampaolo Niccoli	2008-2009	A placebo-controlled, randomized, open-label, blind-examination, multicenter trial	240	1) Symptoms onset less than 12 h prior to enrollment. 2) ST-segment elevation of at least 2 mm in two or more contiguous leads. 3) TIMI flow 0–1 at baseline angiography	TIMI grading system	Compare the effect of intracoronary nitroprusside, adenosine versus placebo in patients with no-reflow phenomenon

Results

In a study by Gjin Ndrepepa, 1140 patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI and paired scintigraphic examinations (pre- and 7-14 days post-intervention) were included. After primary PCI, 108 patients had no-reflow and 1032 patients had normal coronary flow.

The median salvage index was 0.34 (interquartile range: 0.15-0.49) in the patients with no-reflow, while it was 0.55 (interquartile range: 0.29-0.81) in the patients with normal flow (P<0.001). LVEF at six months after PCI was 47.7±13.1% in the no-reflow group, whereas it was 54.2±13.9% in the group with normal flow after PCI (P<0.001).

In 80.3% of the patients with no-reflow, normalization of blood flow occurred more than six months after PCI, which was correlated with improvement in LVEF. Independent predictors of no-reflow were residual flow in the infarct-related artery (P<0.001), initial perfusion defect (P=0.03), C-reactive protein (P<0.001), and history of myocardial infarction (P=0.013). Kaplan–Meier estimate of one-year mortality was 16.7% (n=18) in the patients with no-reflow, while it was 5.5% (n=56) in the patients with normal flow (hazard ratio: 3.35; 95% confidence interval (CI): 1.97-5.69; P<0.001) (4).

In a study by Itsuro Morishima 120 consecutive patients with first AMI, treated by percutaneous transluminal coronary angioplasty (PTCA), and without flow-restricting lesions were studied. The patients were classified as no-reflow (n=30) and reflow (TIMI: 3) (n=90), based on post-PTCA cineangiograms to follow-up (5.8±1.2 years) for cardiac death and non-fatal events. The results showed that the patients with no-reflow sustained congestive heart failure (P< 0.0001), malignant arrhythmia (P=0.038), and cardiac death (P=0.002) more often than those with reflow.

Kaplan-Meier curves showed lower cardiac survival and cardiac event-free survival (P<0.0001) in the patients with no-reflow than in those with reflow.

Multivariate analyses exhibited that no-reflow phenomenon was an independent predictor of long-term cardiac death (relative risk (RR): 5.25, 95% CI: 1.85-14.9; P=0.002) and cardiac events (RR: 3.71, 95% CI: 1.79-7.69; P=0.0004). During follow-ups, survivors with no-reflow had higher end-diastolic and end-systolic left ventricle (LV) volume indices and higher plasma brain natriuretic peptide level, and lower LVEF (P=0.0002, P< 0.0001, P=0.002, and P<0.0001, respectively) than those with reflow, indicating that no-reflow may be involved in LV remodeling (1).

A prospective, randomized, two-site trial was designed by Dong Huang to compare the effect of three different vasodilators on coronary no-reflow. A total of 102 patients with no-reflow after primary PCI were randomly selected to receive intracoronary infusion of diltiazem, verapamil, or nitroglycerin (n=34 for each group) through selective microcatheter. The primary endpoint was coronary flow improvement of corrected TIMI frame count (CTFC) after administration of the agents.

Results of the aforementioned study showed a significant improvement in CTFC after drug infusion in the diltiazem and verapamil groups, compared to the nitroglycerin group (42.4 frames vs. 28.1 and 28.4 frames, P<.001). The improvement in CTFC was similar in the diltiazem and verapamil groups (P=0.9). Compared to the nitroglycerin group, the diltiazem and verapamil groups achieved more complete ST-segment resolution at three hours after PCI, lower peak troponin T level, and lower N-terminal pro-B-type natriuretic peptide level at 1 and 30 days after PCI. After drug infusion, the reduction in heart rate and systolic blood pressure in the verapamil group was greater than the diltiazem and nitroglycerin groups (5).

Giampaolo Niccoli carried out a study to compare the effect of intracoronary nitroprusside and adenosine injection after PCI on the prevention of no-reflow phenomenon in AMI patients referring to six hospitals in Italy. For this purpose, 240 consecutive patients with AMI undergoing primary or rescue PCI and thrombus aspiration were randomly allocated to equal-sized groups to receive intracoronary nitroprusside, adenosine, or placebo. The primary endpoint was achievement of ST resolution greater than 70% on surface ECG 90 minutes after the procedure.

Moreover, secondary endpoints were: incidence of angiographic no-reflow (TIMI flow<-2 or 3 with myocardial blush grade<2); change in LV volume during follow-up (in two-dimensional ECG); and increased rate of major cardiac adverse events (e.g., cardiac death, myocardial infarction, target lesion revascularization, and heart failure requiring hospitalization) (6).

Discussion

Myocardial infarction reperfusion no-reflow

Myocardial ischemia-reperfusion injury and endothelial damage underlie development of reperfusion no-reflow. This phenomenon is associated with considerable reduction of myocardial salvage through primary PCI in patients with STEMI. Infarct size and microvascular hypo-perfusion might increase at the time of coronary reperfusion beyond those observed during the ischemic period. Endothelial injury is induced by acute inflammatory response, generation of reactive oxygen species, intracellular calcium overload, and opening of the mitochondrial permeability transition pore.

Ultrastructural changes, which are confined to the necrotic zone, first appear in the subendocardium, and subsequently progress toward the subepicardium after long-term occlusion. Endothelial cellular swelling and protrusion, as well as myocyte swelling and tissue edema, may occlude the microvasculature. Moreover,

vasospasm and downstream embolization of thrombus compound the microvascular obstruction.

Patients with no-reflow more commonly experience malignant arrhythmia, chronic heart failure, and cardiac death than those with reflow. They also have more advanced LV remodeling, as shown in ECG findings. Therefore, angiographic no-reflow phenomenon strongly predicts cardiac complications, independent of other well-known early predictors of long-term outcome after AMI such as age, Killip class, and LVEF.

Predictors of no-reflow

The degree of reperfusion no-reflow, developing after infarct angioplasty, is associated with the duration of the preceding myocardial ischemia, infarct size, procedural variables, and patient characteristics. Absence of residual blood flow in the infarct-related artery, large infarct size, history of myocardial infarction, and elevated level of C-reactive protein at baseline are independent predictors of development of no-reflow after primary PCI. Coronary stenting may reduce tissue perfusion more than balloon angioplasty (7).

Two putative mechanisms may be proposed to explain less inevitable continuation of myocardial necrosis in patients with no-reflow. First, persistence of microvascular obstruction, the key mechanism of no-reflow phenomenon, hampers tissue perfusion and leads to continuation of tissue ischemia and progressive cell loss. Second, restoration of less-than-optimal blood flow may indicate reperfusion injury, which might play an important role in development of no-reflow and further promote cell death (8, 9).

Large plaque area and eccentric or fissured plaque can predict no-reflow. These findings reflect the importance of distal embolization in this setting. Diabetes mellitus, absence of pre-infarction angina, and advanced age can predict no-reflow, which demonstrate the impact of preexisting microvascular damage and dysfunction, as well as ischemic preconditioning on subsequent development of no-reflow. Interventional no-reflow more commonly occurs after angioplasty in degenerated saphenous vein grafts, thrombotic lesions, and coronary atherectomy. Angiographic no-reflow phenomenon strongly predicts cardiac complications independent of other well-known early predictors of long-term outcome after AMI such as age, Killip class, and LVEF.

Prevention and treatment of no-reflow

Multiple treatment modalities for no-reflow have been examined in animals and to a lesser degree in humans. Efficacious interventions for treatment of no-reflow in preclinical studies often are not translated into effective human therapies owing to the limitations of available animal models. Most studies have focused attention on AMI, and randomized, clinical trials have been confined to preventive therapies. Consequently, data related to reversal of established no-reflow are limited. Since no-reflow is dynamic by nature and may spontaneously resolve over time, the contribution of non-randomized studies to the current understanding of treatment options is limited.

Several pharmacological agents have been studied for reversal of no-reflow. Adenosine is an endogenous purine nucleoside, which decreases the arteriolar resistance and activates intracellular cardioprotective signaling pathways. Its mechanism of action may involve opening adenosine 5′-triphosphate-sensitive potassium (KATP) channels, inhibition of neutrophil migration, prevention of superoxide generation, or blockade of coronary endothelin release.

Nitroprusside and nitroglycerin are nitric oxide donors that vasodilate conductance vessels; however, microvessels are unable to metabolize nitroglycerin to nitric oxide, and nitroprusside does not require metabolism. Intracoronary nitroprusside can significantly reduce the incidence of angiographic no-reflow during primary PCI and major adverse cardiovascular events. It seems to be a promising adjunctive therapy for no-reflow after primary PCI (10).

Nicorandil is a hybrid of KATP channel opener and nitrate, which may prevent reperfusion injury by blocking the mitochondrial permeability transition pore. Calcium channel blockade has several potentially beneficial effects in the setting of no-reflow in addition to attenuation of the risk of microvascular spasm.

Reduction of heart rate and blood pressure may lower myocardial ischemia and infarct size. Verapamil can inhibit platelet aggregation and thrombus formation in the microvasculature, and might have a direct impact on calcium flux across the sarcolemmal membrane or within intracellular compartments that can protect reversibly injured myocytes. Platelet inhibition with glycoprotein IIb/IIIa inhibitors reduces downstream embolization and in situ microvascular generation of thrombus and diminishes the release of vasoactive and chemotactic mediators from platelets.

Myocardial infarction reperfusion no-reflow

Randomized trials have suggested that verapamil and adenosine may reduce the risk of no-reflow development after primary PCI. Prevention of upstream and in situ microvascular thrombosis with intravenous abciximab and intracoronary thrombolysis was shown to improve microvascular perfusion (11, 12).

Mechanical devices for prevention of embolization and removal of plaque and thrombus may play a role in the setting of primary PCI. Unlike distal arterial protection device, thrombus aspiration improves tissue perfusion (13, 14).

The concept of ischemic pre- and post-conditioning refers to a variety of pharmacological and non-pharmacological cardioprotective interventions implemented before the onset of ischemia or at the time of reperfusion. Intracellular signaling is complex and

incompletely defined and appears to involve the activation of various survival protein kinase cascades (e.g., ERK1/2 and PI3K-Akt), anti-apoptotic pathways (e.g., Bcl-2 and BAX), protein kinases C and G, intracellular generation of nitric oxide, mitochondrial generation of reactive oxygen species, opening mitochondrial (and possibly sarcolemmal) KATP, and blockade of the mitochondrial permeability transition pore (11).

These various events culminate in lowering necrotic and apoptotic cell death, the degree of no-reflow and infarct size, and the risk of diabetes and hyperlipidemia.

Intravenous nicorandil, started before PCI, and myocardial post-conditioning after direct coronary stenting by intermittent low-pressure balloon inflations in the infarct-related artery were shown to improve tissue perfusion, reduce infarct size, and improve patient outcome (15, 16). Papaverine, nitroprusside, and abciximab were reported to be effective in reversal of existing no-reflow after primary PCI; however, no randomized trials have been performed in this regard.

Conclusion

In summary, development of no-reflow in patients with STEMI after primary PCI is associated with significant reduction in myocardial salvage by primary PCI, large scintigraphic infarct size, deteriorated LVEF at six months, and increased risk of one-year mortality.

The extent of initial area at risk, absence of residual blood flow in the infarct-related artery, previous history of MI, and elevated level of C-reactive protein are independent predictors of no-reflow.

In a vast majority of patients with no-reflow after PCI, normalization of blood flow occurred within six months after reperfusion. Persistence of compromised tissue perfusion is associated with worse LV function in patients with no-reflow, compared to patients in whom normal blood flow is restored within six months after PCI. Angiographic no-reflow phenomenon after PTCA predicts adverse long-term outcome in patients with AMI. Patients with no-reflow may be at risk of LV remodeling, which leads to progressive heart failure and cardiac death. Therefore, the angiographic no-reflow phenomenon, which is the simplest clinical diagnostic tool for assessing myocardial reperfusion, is indispensable in early clinical decision-making for treating patients with AMI.Based on the reviewed studies, the efficacy and safety of intracoronary nitroprusside and adenosine, as adjunctive treatments for PCI after thrombus aspiration in patients with acute myocardial infarction, is approvable. Intracoronary infusion of diltiazem or verapamil could reverse no-reflow more effectively than nitroglycerin during primary PCI for acute myocardial infarction. The efficacy of diltiazem and verapamil was similar, while administration of diltiazem seemed to be safer.

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