Review Article

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# No-Reflow Phoenomenon by Intracoronary Thrombus in Acute Myocardial Infarction

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Recently, percutaneous coronary intervention has been the treatment of choice in most acute myocardial infarction cases. Although the results of percutaneous coronary interventions have ben good, the no-reflow phenomenon and distal embolization of intracoronary thrombus are still major problems even after successful interventions. In this article, we will briefly review the deleterious effects of no-reflow and distal embolization of intracoronary thrombus during percutaneous coronary interventions. The current trials focused on the prevention and treatment of the no-reflow phenomenon and intracoronary thrombus.

**Key Words:** M*yocardial infarction; No-Reflow phenomenon; Thrombus; Percutaneous coronary intervention*



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## INTRODUCTION

Acute myocardial infarction (AMI) is one of the most common causes of death in modern society.[1] These days, percutaneous coronary intervention (PCI) is the preferred reperfusion method of treatment of AMI compared to thrombolytic therapy due to the superior patency rates in the target coronary artery.[2] Although the results for PCI in AMI are enough to achieve the desired patency of the target coronary artery, the major drawback is that the optimal perfusion is not achieved at the myocardial tissue level in some patients.[3] These phenomenon, so called "no-reflow (NR)", leaves myocardial tissue hypoperfusion despite the restoration of epicardial coronary artery patency following PCI.[4] There are several mechanisms that contribute to the development of NR, the main mechanism is thought to be the distal embolization of intracoronary thrombus.[5,6] NR and distal embolization of intracoronary thrombus occur frequently during PCI and worsen clinical outcomes.[7]

## NO-REFLOW AND DISTAL EMBOLIZATION OF INTRACORONARY THROMBUS

Through the past decade, PCI has been considered the standard treatment of AMI. Between 1999 and 2002, only 1/3 of patients with AMI who recieved reperfusion therapy underwent primary PCI in the National Registry of Myocardial Infarction (NRMI), with the remainder receiving thrombolytic therapy.[8] However, in 2007, the ACTION (Acute Coronary Treatment and Intervention Outcomes Network) registry reported nearly 90% of patients with AMI were treated using Primary PCI and only 4.3% using thrombolytic therapy.[9] Now, primary PCI is the standard treatment of AMI in most of the hospitals that are able to provide it. The success of angiographic reperfusion by PCI is routinely evaluated by the Thrombolysis in Myocardial Infarction (TIMI) flow grade,[10] myocardial blush scores[11,12] and TIMI frame count.[13,14] Despite high success rates of more than 95% for establishing epicardial artery patency after PCI,[15] 10 to 20 % of the patients leave the cath lab with reduced angiographical coronary flow(TIMI 0-2) descrbed as the no-reflow phenomenon(NR).[5,16,17] NR may occur at any point during PCI. Usually NR is induced by inflations with balloons or coronary stents, which presumably lead to more distal embolization of coronary thrombus.[18]

NR was first described in 1974.[19] The zone of NR was believed to be confined to areas of necrotic myocardium. It has been reported that myocardial cell death occurs before the disruption of the microvasculature.[20,21] NR predicts worse outcome in animal models and post-infarct patients.[22,23] A large zone of NR affects infarct healing, predicts infarct expansion and left ventricular dilatation.[24-26] Failure to ach-

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ieve the final TIMI 3 flow grades due to NR were reported in 20-40% of cases[27,28], with in-hospital mortality rates from 12%,[29] up to 40%.[30] Reduced TIMI flow grades are also associated with increased infarct size, worsening of left ventricular function, arrhythmias and substantially increased mortality rates compared to patients with adequate TIMI 3 flow.[31,32] Clinically, epicardial coronary flow shown by final coronary angiography after PCI has been considered to be an approximate surrogate for myocardial tissue perfusion. However, even in situations of restoration of normal TIMI-3 flow, marked reductions in myocardial tissue perfusion may be present.[14]

## PATHOPHYSIOLOGY OF MYOCARDIAL INJURY RELATED TO NO-REFLOW BY INTRACORONARY THROMBUS

Myocardial ischemia occurs immediately after coronary artery occlusion, resulting in structural and metabolic derangements by oxygen-derived free radicals, degradation of sarcolemma, and calcium overload within the mitochondria and cytoplasm, which further degrade the cell membrane.[33] Endothelial cell degradation, myocardial cell swelling and interstitial edema compress microvascular lumen and lead to tissue necrosis and cell death. Such ischemic cell death progresses from the subendocardial region towards the subepicardium.[34] PCI to open the occluded epicardial coronary artery is crucial to prevent further progression of ischemic injury and salvage myocardium. However, the damage to the myocardium at the time of reperfusion by PCI has been controversial for many years.[35] Infiltration of neutrophils and platelets into the coronary microcirculation at the time of reperfusion can obstruct the microcirculation.[36] Activated neutrophils release oxygen free radicals, proteolytic enzymes and pro-inflammatory mediators that can cause tissue and endothelial damage, particularly in critically injured myocytes.[37] Another mechanism for microvascular obstruction is the embolization of thrombus originating from unstable plaque during PCI. Using Doppler guidewires, multiple embolic particles were detected in patients who underwent PCI in an AMI setting.[38] In a non-infarct model, embolization causing about 50% obstruction of coronary capillaries results in an irreversible reduction of myocardial blood flow.[39] In animal models, distal coronary embolization produced severe regional contractile dysfunction, despite only 2-5% of minimal myocardial necrosis with leukocyte infiltration and preserved regional myocardial flow.[40] In these microinfarcts, the contractile dysfunction following distal coronary embolization does appear to recover over time.[41]

After NR and microvascular plugging by embolization of intracoronary thrombus and ruptured plaque debris, microvascular integrity is compromised by cell swelling, interstitial edema, and capillary plugging by red blood cells, neutrophils and microthrombi, leading to progressively increased microcirculatory flow resistance.[42] Also structural microvascular changes including tightly packed erythrocytes, platelets and fibrin thrombi occur and release vasoactive amines result in increased vascular tone and microvascular obstruction.[19] This microvascular obstruction manifests in angiography after PCI with a slowing of contrast progression in the infarct-related artery. It leads to myocardial ischemia and necrosis at tissue level.[8,20] Even angiographically successful reperfusion of the infarct-related artery does not guarantee adequate myocardial perfusion of the tissue levels, and the extent of microvascular obstruction correlate with infarct size and predicts worse outcome.[43-45] About 20-30% of AMI patients with final TIMI3 flow after PCI demonstrated significant microvascular hypoperfusion by myocardial contrast echocardiography which is associated with functional deterioration.[46]

## IMPACT OF NO-REFLOW AND DISTAL EMBOLIZATION OF INTRACORONARY THROMBUS

Distal embolization of intracoronary thrombus may have several worsening effects on myocardial infarct size and myocardial salvage strategies.[22,47] During early stages of AMI, there is patchy necrosis with some intervening areas of viable cardiomyocytes at the infarct zone. Embolization of intracoronary thrombus in small vessels will be detrimental to the survival of these vulnerable myocytes. The infarct area extends beyond its borders by blocking the small arterioles and microvessels of the surrounding myocytes.[21] Moreover, such NR and embolization of thrombus can prevent delivery of cardioprotective drugs to the myocytes in need. Consequently, distal embolization of intracoronary thrombus during PCI for AMI has been associated with inadequate tissue perfusion, poor reperfusion, larger infarct size and a more unfavorable prognosis.[48,49]

## PREDICTORS OF NO-REFLOW AND DISTAL EMBOLIZATION OF THROMBUS

Thrombus burden at initial coronary angiography is a predictor of subsequent NR and distal embolization.[50] High atheromatous burden, friability of the plaque and large lipid pool content are also known to contribute to NR in AMI patients undergoing PCI.[50] Implanation of a stent to the thrombus-burdened coronary lesion is known to be another possible cause of NR and distal emblolization, presumably due to the stent mesh crushing plaque and squeezing particles through stent struts.[18,51] In these lesions, distal embolization of thrombus was 3-fold higher after stenting in AMI compared to balloon inflations alone. Microemboli are frequently found in patients who died from ischemic heart disease and are associated with microinfarcts and an inflammatory reaction.[52] MRI in post-MI patients demonstrates a higher incidence of perfusion defects after Primary PCI compared to thrombolysis, strongly suggesting procedure-related DCE.[53] In current imaging studies, several grayscale IVUS features including greater plaque burden, plaque rupture, intracoronary thrombus, positive

remodeling, and tissue prolapse predict NR in AMI patients.[54,55] Also some virtual histology-IVUS features such as large necrotic core and thin-cap fibroatheroma were the independent predictors of NR in AMI patients.[56,57]

## THERAPIES FOR THE NO-REFLOW AND DISTAL EMBOLIZATION OF INTRACORONARY THROMBUS

Recovery of intact microvasculature within the infarction zone leads to myocellular viability and potential functional recovery.[45] Improved tissue perfusion to irreversibly damaged myocytes may have other benefits including prevention of infarct expansion or aneurysmal dilation and future development of collateral vessels.[22] There have been some mixed results from studies focused on the prevention and treatment of NR and distal embolization of intracoronary thrombus.

### 1. Pharmacological approaches

NR also may prevent the delivery of pharmaceutical agents such as anti-arrhythmics and cardioprotectants into the infarct zone. In past small group studies, several agents have been shown to reduce and treat NR, including vasodilators, nitroprusside, calcium channel blockers, adenosine, nicorandil, and platelet glycoprotein IIb/IIIa inhibitors.[58-71]

Calcium channel blockers, such as verapamil and diltiazem, may have several potentially beneficial effects in the setting of no-reflow in addition to attenuation of microvascular spasms and reduction of myocardial ischemia and infarct size.[61,62] Verapamil may inhibit platelet aggregation and thrombus formation in the microvasculature, and may have a direct effect on calcium flux across the sarcolemal membrane or within intracellular compartments that could protect injured myocytes.[63]

Adenosine affects intracellular calcium metabolism and inhibits neutrophil accumulation, superoxide generation, and intracellular acidification by affecting glucose utilization.[64,65] In the AMISTAD and AMISTAD-II trials, intravenous adenosine treatment significantly reduced infarct size.[66,67] Other studies report that administration of adenosine as an adjunct to primary angioplasty reduces the incidence of NR and improves ventricular function and clinical outcome.[68,69]

The ATP-sensitive potassium channel opening is known to be related to the development of the NR after PCI.[70] Nicorandil, an ATP-dependent potassium channel opener, may prevent reperfusion injury and protects cardiac myocytes by blocking the mitochondrial permeability transition pore, reducing the influx of calcium, and inhibiting neutrophil accumulation and activation.[71]

Glycoprotein IIB/IIIA inhibitors have shown modest clinical benefit in the prevention of NR and intracoronary thrombus embolization from PCI for AMI.[72-75] Some studies suggest that distal embolization sometimes reduces coronary blood flow only transiently, and is not associated with capillary obstruction.[17] Despite the use of glycoprotein IIB/IIIA inhibitors and clot extraction devices, NR and abnormal myocardial perfusion based on myocardial blush scores still occur.[76] Okamura reported 13% of patients had reduced TIMI-flow grades, despite routine use of clot extraction catheters and nicorandil to prevent R-NR.[18] When these interventions fail, NR treatment is based on the intracoronary administration of adenosine, nicodandil or nipride to induce maximal vasodilation in small distal coronary vasculature.[60-64,68,69] However, evidence of the beneficial effects of these agents on epicardial flow and myocardial salvage is still limited.

### 2. Device strategies for prevention of distal coronary embolization

Currently, clot extraction devices have shown modest clinical benefit resulting from PCI for AMI.[77-79] However, disappointing results have been reported in two major trials (EMERALD, PROMISE) testing the use of filter devices to prevent DCE.[78,80] Although the 100-micron pore size of the current filter devices may limit their effectiveness, the role of these filter devices on myocardial infarction is still questionable.

On the other hand, the thrombus burden has been thought to be a major cause of some of these adverse outcomes, so thrombus aspiration, at least macroscopically visible thrombi, is assumed to improve clinical outcome. Furthermore, the additional benefit of clot extraction by aspiration may be not only the removal of the thrombus but also vasoactive and chemotactic mediators released from platelets that may exacerbate tissue injury. On the basis of this assumption, mechanical thrombectomy and manual thrombus aspiration devices were evaluated, but showed little or no effect on clinical endpoints.[81] The major breakthrough came with the TAPAS (Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction Study) trial, which was a single-center, randomized, all-comer trial of routine thrombus aspiration versus conventional PCI.[82] The trial enrolled 1,071 patients, with thrombus aspiration being performed in 89% in the active arm and in 1% in the control arm. This TAPAS trial was positive not only with respect to the primary endpoint but also mortality at 1 year.

In two recent, large randomized trials, the Thrombus Aspiration in STElevation Myocardial Infarction in Scandinavia (TASTE)[83] and A Randomized Trial of Routine Aspiration ThrOmbecTomy with PCI Versus PCI alone in Patients With STEMI Undergoing Primary PCI (TOTAL) trial[84] reported different conclusions compared with the TAPAS trial. These trials were prospective, randomized, multicenter studies of 7,244 and 10,732 AMI patients with thrombus aspiration group or conventional PCI alone group, respectively. The results of both trials were negative including both the primary and secondary endpoints. Also, some disappointing findings wer reported in the TOTAL trial as the stroke rates increased in the thrombus aspiration group.[85] In the results of the trials, it seems that there

may be no clinical benefit to routine thrombus aspiration in patients with STEMI during PCI. However, the TASTE trial had shown that there was no clinical benefit from aspiration, whilst TOTAL had gone further confirming that aspiration does not provide benefits and in fact appears to cause harm. There may be several reasons for the different results between the TASTE and TOTAL trials relative to the TAPAS trial. Compared with the TAPAS trial, the TASTE and TOTAL trials included a lower risk population with a possibility of selection bias, fewer glycoprotein IIB/IIIA inhibitors were used in the aspiration arm in TOTAL trial and only 4.9% in TASTE and 7.1% in patients of TOTAL trial underwent bail-out thrombus aspiration. Therefore, a selection bias may be responsible for the lack of benefit in these two studies, despite the statistical analysis. Consequently, aspiration techniques may not be sufficient to remove the thrombus safely in patients with a high risk of microembolization. Lastly, although TAPAS was successful, it was still a single-center study, so extended to multicenter studies will be needed. It may be hard to draw any definite conclusions because the registry studies do not specify which patients were chosen for the thrombus aspiration, whether subjects were selected on the basis of TIMI flow grade, thrombus burden, time from PCI, or other criteria. Interestingly, another large, recent British registry study conflicted with the TASTE and TOTAL studies, by showing significant reduction of in-hospital and long term mortality in patients who underwent thrombus aspiration.[86]

Large randomized controlled registry studies thus show conflicting results of thrombus aspiration as a routine treatment in STEMI during PCI. However, most trials now find that there is no clinical benefit of *routine* thrombus aspiration in the treatment of STEMI patients.

The question remains as to whether the results from recent trials mean that there is no benefit of using thrombus aspiration in *selected high-risk* patients.

## SUMMARY

Coronary NR and distal embolization of intracoronary thrombus is a common complication of PCI which may severely compromise procedural outcomes. NR has a complex pathophysiology which relates to the patient's clinical and angiographic characteristics as well as PCI procedure. Preventive and treatment strategies have shown mixed results and the value of interventions such as distal protection or thrombus aspiration is still unclear. Further development of drugs and devices may lead to improved procedural outcomes in the future.

## CONFLICT OF INTEREST STATEMENT

None declared.

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