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METHODS

Current concepts in the pathogenesis and management of coronary no-reflow phenomenon

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Epicardial coronary arteries are the subject of the majority of research attention and treatment techniques. This is because interventional cardiologists focus on relieving the obstructions in epicardial coronary arteries which are easily seen on angiography. On the contrary, the coronary microvasculature receives less attention. The heart microvasculature, which consists of capillaries and arterioles, is negatively affected when the epicardial coronary artery becomes blocked. When the occlusion is relieved, sometimes the blood flow to the ischemic tissue still remains impeded, a phenomenon known as no-reflow. This review article aims to provide an in-depth understanding of the pathophysiology and management strategies needed to tackle this life-threatening phenomenon.

Keywords: coronary no-reflow, pathogenesis, management

1. Introduction

Ischemic disease is the leading cause of mortality worldwide, accounting for 1.4 and 5.7 million deaths in industrialized and developing countries, respectively, according to the Worldwide Burden of Disease study (1). Various modes of coronary intervention have also increased to combat this looping surge. The recommended strategy for percutaneous coronary intervention (PCI) is used to treat acute myocardial infarction (AMI) (2). However, catheter-based interventions are associated with numerous periprocedural complications. Coronary no-reflow (NR), a condition that results in suboptimal cardiac reperfusion despite the infarct-related artery's effective epicardial recanalization, with angiographic absence of dissection, spasm, obstruction, and thrombus, is the most significant PCI-related complication. The phenomenon of NR has multifactorial pathogenesis and grave consequences. There has been a paucity of clear-cut guidelines for the management of NR. This makes it the need of the hour to review this preventable catastrophic hurdle.

2. Incidence and historical review

Myocardial blush grade, TIMI flow grade, and ST resolution have all been used to estimate an incidence of 1 to 3% in large registries (3). Cardiovascular magnetic resonance imaging (CMRI) and myocardial contrast echocardiography (MCE), which show a higher incidence (10–30%) of NR and microcirculatory dysfunction, are two more recent and sensitive ways of diagnosing these conditions (2, 3).

In 1974, Kloner et al. coined the term no-reflow (NR), which developed following a brief epicardial coronary artery closure for 90 min (3). NR during primary percutaneous transluminal coronary angioplasty (PTCA) for acute myocardial infarction (AMI) was first observed by Feld et al. in 1992 (3). Blood flow through myocardial tissue

at flow rates less than 40 ml/min/100 g of tissue results in lethal ischemia and permanent cardiomyocyte and endothelial damage.

3. Postulated mechanisms of NR

Among the various postulated mechanisms, ischemia/reperfusion injury (2, 3), myocardial dysfunction, and athero-embolism are the cardinal pre-disposing mechanisms (**Figure 1**). During AMI, the hypo-perfused myocardial zone is the area at risk (AAR). In addition to microvascular damage, interstitial hemorrhage, and inflammation, the usual morphological hallmarks of reperfusion injury include contraction bands, karyolysis, mitochondrial enlargement and disruption, and membrane rupture in cardiomyocytes (1–3).

The myocardial infarct size is determined by the following:

1. Size of the AAR
2. Duration of myocardial ischemia
3. Amount of residual blood flow through collaterals
4. Temperature of the tissue during ischemia
5. Hemodynamics during ischemia
6. Heart rate, which controls the coronary blood flow and myocardial demand

Activated neutrophils release vasoconstrictors and inflammatory mediators promoting oxygen-free radical formation, which cause the release of bioactive molecules such as nitric oxide, prostacyclins, endothelins, and adhesion molecules (3). In a nutshell, increased inflammatory mediators and endothelial injury cause microvascular plugging and microvascular dysfunction which result in coronary NR phenomenon.

4. Risk factors and predictors

Hyperglycemia and other chronic inflammatory states inhibit endothelium-dependent vasodilatation, reduce collateral blood flow, aggravate thrombotic risk, and inhibit nitric oxide availability leading to microvascular spasm and microvascular dysfunction. A somewhat objective indicator of the risk of no-reflow (NR) is the shock index (SI), which is calculated as the ratio of heart rate to systolic blood pressure. With SI 0.66 functioning as a limit for the clinical prediction of NR, several studies have shown a strong association between SI and in-hospital mortality in patients with acute coronary syndrome (ACS) following initial percutaneous coronary intervention (PCI). PCI-related slow/NR is also connected to the PCI method itself, and it has been shown that the length of implanted stent and overexpansion of the stent were related to the elevated risk of NR (2–4). The plaques are crushed by the balloon or stent expansion, which also causes the lipid core to break. The lipid fraction then promotes the development of thrombosis, and the fragments block the distal microcirculation.

4.1. No-reflow score

An eight-variable scoring system was constructed (5) to predict the risk of coronary NR (**Table 1**). When patients with acute ST-elevation myocardial infarction (STEMI) were detected as having NR during primary percutaneous coronary intervention (PCI), the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value were reported to be 80, 92, 86, 89, and 85%, respectively.

5. Clinical implication and prevention

The incidence of this dreaded preventable complication can surely be decreased by adequate metabolic control, appropriate management of hypotension, adequate anticoagulation, decreasing time to reperfusion, optimal balloon inflation, and stent implantation. Clinically, NR may result in recurrent malignant arrhythmias, acute dyspnea, chest discomfort, cardiogenic shock, and acute heart failure. NR is a gradual phenomenon, and it may take time before it manifests. After PCI, angiographic NR is linked to increased infarct size and lesser myocardial salvage, which subsequently results in higher short- and long-term mortality.

6. Diagnosis

6.1. Electrocardiography [ST segment resolution (STR)]

The segment resolution (STR) should be more than 70% at 60 min after percutaneous coronary intervention (PCI). A sign of no-reflow (NR) is STR less than 70% after 60 min. The ST segment elevation that resolves quickly is an extremely sensitive (77%) and very specific (91%) myocardial reperfusion indicator.

6.2. Coronary angiography

The quickest technique to diagnose no-reflow (NR) is via coronary angiography. The dye should immediately enter the artery that is connected to the infarct after a successful PCI (IRA). TIMI flow, myocardial blush grade, corrected TIMI frame count, and TIMI myocardial perfusion grade are only a few of the basic and complicated angiographic

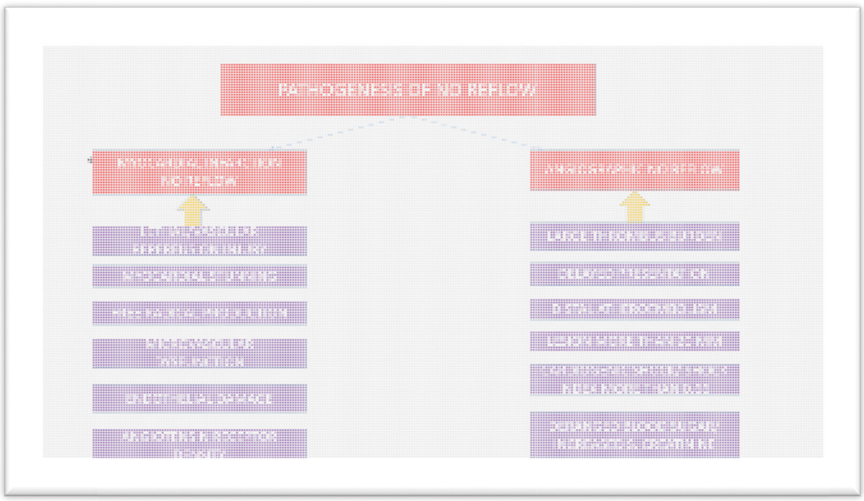

FIGURE 1 | Different pathogenic mechanisms of coronary no-reflow phenomenon.

TABLE 1 | No-reflow score.

Factor	Points
Age > 60 years	1
Delayed reperfusion time > 4 h	2
Large luminal diameter ≥ 2.8 mm	2
Long target lesion ≥ 20 mm	4
High thrombus burden	1
Initial TIMI flow ≤ 1	3
Positive CK-MB on admission	2
Elevated D-dimer ≥ 500 ng/ml	1

Total score = 16 points.
Score ≥ 10, most likely to have NR phenomenon.
Sensitivity is 86% and specificity is 73%, $P < 0.001$.

methods that may be used to assess epicardial and myocardial perfusion. TIMI-3 flow with an MBG score of 2/3 indicates successful reperfusion.

6.3. Intracoronary guidewires

Using an intracoronary Doppler guidewire, coronary flow reserve (CFR) and coronary flow velocity (CFV) are assessed. The three characteristics that set NR apart from other cardiac rhythms are forward diastolic flow with a steep deceleration slope, decreased systolic antegrade flow, and systolic flow reversal. No-reflow (NR) patterns on CFV are brought on by extensive capillary damage and elevated capillary resistance. The lack of gradient also excludes NR.

6.4. Cardiovascular MRI

To detect the presence of no-reflow (NR) phenomenon and predict the prognosis of patients with revascularized acute myocardial infarction (AMI), MRI with conventional gadolinium chelates has proven to be useful. The microvascular blockage is indicated by the necrotic myocardial core's lack of late gadolinium enhancement. Studies have demonstrated a correlation between MRI indices of microvascular blockage and poor functional recovery in the left ventricle. The delayed phase shows the degree of myocardial necrosis, whereas the early phase reflects NR. CMRI is used to diagnose intramural hemorrhage and infarct size (2–4).

6.5. Myocardial contrast echocardiography

In recent times, myocardial contrast echocardiography has been taken as the most important tool to diagnose no-reflow (NR) using microbubbles (<5 μm) having similar rheology to erythrocytes (1–3). In a study involving patients with anterior wall MI who were receiving thrombolysis for the first time, congestive cardiac failure and pericardial effusion were seen more frequently in individuals with NR on myocardial contrast echocardiography (MCE) compared to patients with normal flow on MCE.

6.6. Biochemical markers

Serial tests of blood creatine kinase-MB, troponin I/T, or myoglobin can be used to test the patency of infarct-related arteries at baseline, 60 min after reperfusion, or 90 min after reperfusion. Studies have demonstrated the functions of the von Willebrand factor (vWF) and ADAMTS-13. VWF, an adhesive GP that transports factor VIII and captures platelets at sites, is crucial for bleeding after vascular damage. The metalloproteinase ADAMTS-13 controls the shape and activity of VWF (2, 3).

7. Management

7.1. Non-pharmacological management

7.1.1. Thrombus aspiration

During initial percutaneous coronary intervention (PCI), manipulating the plaque with balloons and stents frequently causes distal thrombus embolization, which may result in no-reflow (NR). During PCI, aspiration thrombectomy is linked to decreased distal embolization and enhanced microvascular reperfusion, which would result in better clinical outcomes like reduced mortality and reinfarction (1–3). Various meta-analyses and trials have not found the clinical benefit of routine thrombus aspiration in all cases of acute myocardial infarction (AMI); however, in cases of high thrombus burden, it is likely to be useful (6).

7.1.2. Direct stenting

It has been suggested that direct stenting without first balloon dilatation will lower the incidence of NR. Direct stenting after thrombus aspiration has been recommended by Dudek et al. (7), which improved microvascular perfusion as measured by the mean blood glucose (MBG). But these observations have to be confirmed in larger randomized trials.

7.1.3. Defer stenting

Delaying stenting in some high-risk individuals may reduce the chances of no-reflow (NR). In high-risk ST-elevation myocardial infarction (STEMI) patients, DEFER-STEMI TRIAL (8) showed that delaying stenting during primary percutaneous coronary intervention (PCI) decreased NR and enhanced myocardial salvage. However, compared to traditional PCI, regular postponed stent insertion in STEMI patients did not lower the incidence of mortality, heart failure, myocardial infarction, or repeat revascularization (9). Neither the microvascular obstruction (MVO) nor the infarct size decreased. These findings go against accepted wisdom regarding delayed stenting in STEMI patients getting PCI.

7.1.4. Miscellaneous

Besides thrombus aspiration and other aforementioned prevention strategies, other, less established, non-pharmacological management strategies for NR have been described. There are studies that have demonstrated the role of induced hypothermia in the reduction of myocardial infarct size. Herring et al. (3) demonstrated a marked reduction in NR with the use of induced hypothermia in animal models of myocardial infarction. However, we do not have any human data on NR to suggest the use of this induced hypothermia routinely in MI patients. Moreover, there is a risk of prolonging the door-to-balloon time. Second, few smaller trials have suggested the use of ischemic post-conditioning to reduce NR (3). However, the lack of phase III trials and long-term follow-up data limits its routine use in clinical practice.

7.2. Pharmacological treatment

7.2.1. Adenosine

Adenosine has vasodilating and antiplatelet properties and reduces intracellular calcium overload and oxygen-free radical generation. Adenosine also exhibits negative dromotropic and chronotropic effects. When used during therapies for ST-elevation myocardial infarction (STEMI), high-dose adenosine (70 μg/kg/min delivered for 3 h) demonstrated a significant reduction in infarct size in the Acute Myocardial Infarction STudy of ADenosine (AMISTAD) and AMISTAD-II trials (10, 11). However, the use of adenosine did not improve clinical outcomes, such as congestive heart failure, re-hospitalization for congestive heart failure, or mortality.

When compared to placebo or sodium nitroprusside, high-dosage intracoronary (IC) adenosine reduced STR and infarct size in STEMI patients in the REOPENAMI study (12). On the contrary, the REFLOSTEMI trial, which compared the IC administration of adenosine with the IC administration of nitroprusside or a placebo, did not discover a significant difference in infarct size or microvascular obstruction (MVO), as measured by CMRI. Data from 15 RCTs including 1,736 participants were retrieved by Gao et al. in a meta-analysis, and the data showed that following adenosine, STR and TIMI flow grade improved, but there was no appreciable change in the left ventricular ejection fraction or death (13).

7.2.2. Calcium channel blockers

The positive benefits of verapamil, diltiazem, and nicardipine in NR have been investigated. These drugs function by blocking L-type channels in the cardiac cell membrane, which causes endothelium-dependent microvascular relaxation, a drop in oxygen consumption, and a decrease in oxygen-free radical-induced damage. Rezkalla et al. examined the effects of nitroprusside, verapamil, and nicardipine on coronary blood flow following first PCI (14). They discovered that pharmacologic treatment was equally beneficial in enhancing coronary flow as measured by TIMI flow and MBG (p-values of both are 0.0001). [78] In the RECOVER AMI trial, verapamil, diltiazem, and nitroglycerin were shown to significantly improve coronary flow compared to nitroglycerin in acute MI patients and resulted in a lower incidence of NR (3). A recent meta-analysis of 8 RCTs with 494 participants found that intracoronary verapamil + diltiazem injection is secure, and it considerably lowers NR when compared to the control group (RR 0.3; $p = 0.0002$) (3). Verapamil was linked to a lower frequency of angiographic MVO than sodium nitroprusside (SNP) (13.3 vs. 40%; $p = 0.02$), as well as a greater rate of STR 70% (33.3 vs.

6.7%; $p = 0.01$), in a study comparing the two drugs' impact on MVO in 60 patients with STEMI (2–4).

7.2.3. Nicorandil

Nicorandil relaxes vascular smooth muscle as a nitric oxide donor and dual-action potassium channel opener by hyperpolarizing the membrane, increasing transmembrane potassium conductance, and increasing the concentration of cyclic guanosine monophosphate (GMP) inside cells. In addition, nicorandil has the ability to control plasma nitric oxide and endothelin-1 (3). Patients who received intravenous nicorandil demonstrated greater coronary perfusion and fewer NR than control participants in a meta-analysis of myocardial infarction patients (3). The majority of small-scale and/or single-center clinical trials indicate positive outcomes of supplementary nicorandil therapy.

7.2.4. Sodium nitroprusside

Sodium nitroprusside activates guanylate cyclase in vascular smooth muscle cells, which results in strong vasodilation and enhances microvascular performance by avoiding arteriolar spasm and regulating endothelial function. A direct source of nitric oxide is nitroprusside (2, 3). A total of 49 patients with STEMI and NR participated in a research study, and SNP outperformed nicorandil in terms of lowering the corrected TIMI frame count (2, 3).

7.2.5. Epinephrine

Along with the more well-known beta-1 agonist qualities that heighten inotropic and chronotropic stimulation of the heart, epinephrine also possesses strong beta-2 receptor agonist capabilities that promote arteriolar vasodilatation (2, 3). Twelve individuals with refractory NR were the subjects of a single, short retrospective research that examined intracoronary epinephrine. Nine out of twelve patients improved after receiving 100 to 400 μg of epinephrine in the distal coronary bed (2, 3).

8. Conclusion

As previously stated, percutaneous coronary intervention (PCI) is the most commonly used technique for revascularization wherever indicated and feasible; however, its efficacy is constrained by serious but avoidable complications like NR. Interventional cardiologists should always be vigilant and armor their guards at each and every phase of PCI to avoid the complication of NR.

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