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Coronary No-Reflow During Primary Percutaneous Coronary Intervention: Current Concepts, Prevention, and Management

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Abstract

Coronary no-reflow is a serious complication of primary percutaneous coronary intervention (PCI) in patients with ST-segment elevation myocardial infarction (STEMI). It is characterized by inadequate myocardial tissue perfusion despite successful restoration of epicardial coronary artery patency in the absence of a mechanical obstruction. Although advances in reperfusion therapy have substantially improved clinical outcomes, coronary no-reflow remains associated with larger infarct size, impaired recovery of left ventricular function, adverse ventricular remodeling, heart failure, ventricular arrhythmias, and increased mortality. The pathophysiology of coronary no-reflow is multifactorial and involves prolonged myocardial ischemia, distal embolization, endothelial dysfunction, inflammation, oxidative stress, microvascular spasm, intramyocardial hemorrhage, and ischemia–reperfusion injury. Early recognition of patients at increased risk is essential for timely intervention and optimization of procedural strategy during primary PCI. Diagnosis relies primarily on coronary angiography using TIMI flow grade, myocardial blush grade, and TIMI frame count, while cardiac magnetic resonance imaging has become the reference standard for detecting microvascular obstruction and assessing its prognostic significance. Current management focuses on the rapid exclusion of mechanical causes, optimization of coronary perfusion, individualized intracoronary vasodilator therapy, and appropriate antithrombotic treatment. Despite numerous pharmacological and mechanical approaches, no single intervention has consistently demonstrated superiority in preventing or reversing no-reflow. This review summarizes the current evidence regarding the definition, pathophysiology, risk factors, diagnosis, prevention, and contemporary management of coronary no-reflow during primary PCI. Particular emphasis is placed on practical catheterization laboratory strategies aimed at improving myocardial reperfusion and clinical outcomes.

Keywords: Coronary No-Reflow; Primary Percutaneous Coronary Intervention; ST-Segment Elevation Myocardial Infarction; Microvascular Obstruction; Myocardial Reperfusion; Coronary Microcirculation; Reperfusion Injury; Intracoronary Vasodilators

Abbreviations

PCI: Percutaneous Coronary Intervention; STEMI: ST-Segment Elevation Myocardial Infarction; TIMI: Thrombolysis in Myocardial Infarction; MBG: Myocardial Blush Grade; TFC: TIMI Frame Count; CMR: Cardiac Magnetic Resonance Imaging; MVO: Microvascular Obstruction; ROS: Reactive Oxygen Species; mPTP: Mitochondrial Permeability Transition Pore; IMR: Index of Microcirculatory Resistance.

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Introduction

Primary percutaneous coronary intervention (PCI) is the preferred reperfusion strategy for patients presenting with ST-segment elevation myocardial infarction (STEMI). Advances in antithrombotic therapy, stent technology, and regional STEMI networks have substantially improved the restoration of epicardial coronary artery patency and clinical outcomes [1]. Nevertheless, successful recanalization of the infarct-related artery does not always translate into adequate myocardial tissue perfusion.

The coronary no-reflow phenomenon is defined as inadequate myocardial perfusion despite successful restoration of epicardial coronary artery patency in the absence of an identifiable mechanical obstruction, such as residual stenosis, coronary dissection, epicardial vasospasm, or distal vessel occlusion [2,3]. It represents the angiographic manifestation of severe coronary microvascular dysfunction and remains one of the most challenging complications encountered during primary PCI [2,4].

The incidence of no-reflow varies depending on the diagnostic method used. Although angiographic assessment remains the standard tool in the catheterization laboratory, it may underestimate tissue-level reperfusion abnormalities, as clinically significant microvascular obstruction can occur even in patients with TIMI grade 3 epicardial flow [3,5]. Consequently, no-reflow is now recognized as a spectrum of coronary microvascular injury rather than merely an angiographic finding.

The pathophysiology of no-reflow is multifactorial and involves prolonged myocardial ischaemia, distal embolization, endothelial dysfunction, inflammation, oxidative stress, microvascular spasm, and ischaemia–reperfusion injury [2,3]. These mechanisms contribute to impaired myocardial perfusion and explain the variable response to currently available therapies.

Clinically, no-reflow is associated with larger infarct size, impaired recovery of left ventricular function, adverse ventricular remodelling, heart failure, ventricular arrhythmias, and increased mortality [3,5,6]. Despite considerable advances in interventional cardiology, no single therapy has consistently proven effective in preventing or reversing this phenomenon [1,7].

This review summarizes the current evidence regarding the pathophysiology, risk factors, diagnosis, prevention, and contemporary management of coronary no-reflow during primary PCI, with particular emphasis on practical strategies applicable in the cardiac catheterization laboratory.

Definition, Classification, and Epidemiology

Coronary no-reflow is defined as inadequate myocardial tissue perfusion despite successful restoration of epicardial coronary artery patency in the absence of an identifiable mechanical obstruction, such as residual stenosis, coronary dissection, significant epicardial vasospasm, or distal vessel occlusion [2,3]. It reflects severe coronary microvascular dysfunction and represents a failure of myocardial reperfusion rather than unsuccessful coronary revascularization.

Angiographically, no-reflow is most commonly defined as a final Thrombolysis in Myocardial Infarction (TIMI) flow grade ≤2 without an evident mechanical cause [8]. However, epicardial coronary flow does not necessarily reflect myocardial tissue perfusion. Additional parameters, including Myocardial Blush Grade (MBG) and corrected TIMI Frame Count (TFC), improve the assessment of microvascular perfusion, although patients with TIMI grade 3 flow may still have significant microvascular obstruction [9,10].

Coronary no-reflow may be broadly classified as structural or functional. Structural no-reflow results from irreversible microvascular injury caused by prolonged ischaemia, distal embolization, endothelial destruction, capillary obstruction, interstitial oedema, and intramyocardial haemorrhage. Functional no-reflow is characterized predominantly by reversible microvascular dysfunction mediated by vasoconstriction, platelet activation, inflammation, oxidative stress, and endothelial dysfunction [3,4].

Cardiac magnetic resonance imaging (CMR) has further expanded the concept of no-reflow through the identification of microvascular obstruction (MVO), which is considered the reference standard for evaluating irreversible microvascular injury. The extent of MVO correlates closely with infarct size, adverse left ventricular remodelling, and long-term cardiovascular outcomes [6].

The reported incidence of no-reflow varies according to the diagnostic modality. Angiographic no-reflow occurs in approximately 5–15% of patients undergoing primary PCI for STEMI, whereas impaired myocardial perfusion assessed by myocardial blush grade is observed in up to one-third of patients [3,11].

CMR detects microvascular obstruction in as many as 50–60% of STEMI patients despite successful epicardial reperfusion, demonstrating that conventional angiography substantially underestimates the true burden of microvascular injury [6,12].

Overall, angiographic no-reflow and CMR-defined microvascular obstruction should be regarded as

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complementary manifestations of the same pathological process, with angiography guiding immediate procedural management and CMR providing superior tissue characterization and prognostic assessment.

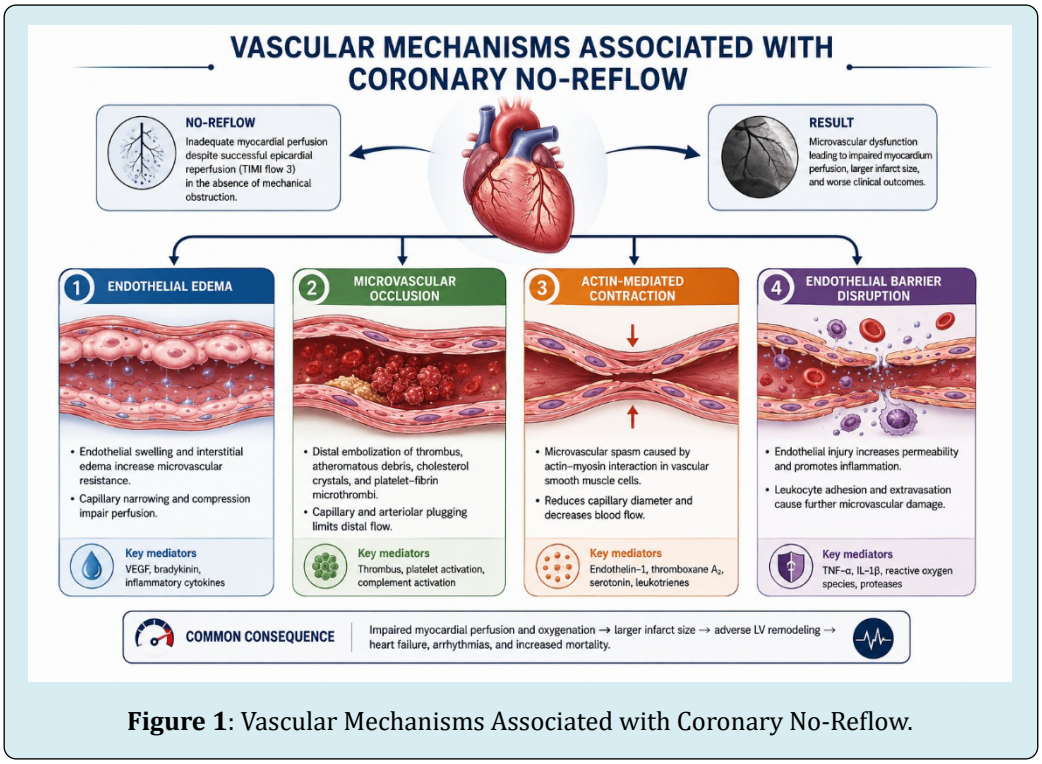

Figure 1: Vascular Mechanisms Associated with Coronary No-Reflow.

Pathophysiology of Coronary No-Reflow

The pathophysiology of coronary no-reflow is complex and multifactorial, involving structural and functional alterations of the coronary microcirculation. Rather than resulting from a single mechanism, no-reflow develops through the interaction of prolonged myocardial ischemia, distal embolization, endothelial injury, inflammation, oxidative stress, and ischemia–reperfusion injury [3,4,13]. The relative contribution of each mechanism varies among patients and may change throughout the course of reperfusion.

Prolonged Ischemic Injury

Microvascular damage begins before reperfusion is established. During prolonged coronary occlusion, endothelial cells become swollen, intracellular calcium accumulates, ATP stores are depleted, and capillary integrity progressively deteriorates. Persistent ischemia also promotes interstitial edema, capillary compression, and disruption of endothelial barrier function, reducing capillary lumen diameter and increasing vascular resistance [13].

The duration of coronary occlusion is therefore one of the strongest determinants of subsequent microvascular obstruction. Delayed presentation after STEMI is consistently associated with a higher incidence of no-reflow because irreversible injury develops not only within cardiomyocytes but also throughout the coronary microvascular network [1,3].

Distal Embolization

During primary PCI, disruption of a ruptured atherosclerotic plaque and manipulation of thrombotic material frequently release embolic debris into the distal coronary circulation. Platelet aggregates, fibrin, cholesterol crystals, foam cells, inflammatory cells, and fragments of necrotic plaque may obstruct small arterioles and capillaries, resulting in abrupt impairment of tissue perfusion [4,14].

Distal embolization is particularly common in patients presenting with a high thrombus burden, delayed reperfusion, large infarct size, and ulcerated lipid-rich plaques. Although contemporary antithrombotic therapy has reduced thrombus formation, distal embolization remains one of the principal mechanisms responsible for angiographic no-reflow.

Endothelial Dysfunction and Microvascular Spasm

The coronary endothelium plays a central role in regulating vascular tone. Ischemia and reperfusion impair

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endothelial nitric oxide production while simultaneously increasing endothelin-1, thromboxane A_2, serotonin, and other potent vasoconstrictors. The resulting imbalance promotes intense microvascular vasoconstriction, particularly at the level of pre-arterioles and arterioles, thereby reducing myocardial blood flow despite successful restoration of epicardial coronary patency [3,15].

Functional vasoconstriction is potentially reversible and represents one of the principal targets of intracoronary vasodilator therapy.

Inflammation and Oxidative Stress

Reperfusion rapidly activates the innate inflammatory response. Neutrophils adhere to damaged endothelial cells through upregulated adhesion molecules, migrate into the interstitium, and release proteolytic enzymes, reactive oxygen species (ROS), and inflammatory cytokines including tumor necrosis factor-α and interleukin-1β [16].

Simultaneously, platelet activation amplifies local inflammation through interactions with leukocytes and endothelial cells, further increasing microvascular obstruction. Excessive ROS production contributes to lipid peroxidation, endothelial apoptosis, mitochondrial dysfunction, and reduced nitric oxide bioavailability, perpetuating microvascular injury.

Ischemia–Reperfusion Injury

Paradoxically, restoration of coronary blood flow itself may exacerbate myocardial injury. Reperfusion triggers calcium overload, rapid normalization of intracellular pH, mitochondrial permeability transition pore (mPTP) opening, oxidative stress, and activation of apoptotic pathways [17]. These processes contribute not only to cardiomyocyte death but also to irreversible damage of the coronary microcirculation.

Experimental studies suggest that reperfusion injury may account for a substantial proportion of the final infarct size, making it an attractive therapeutic target. However, despite promising preclinical results, most pharmacological interventions aimed at attenuating reperfusion injury have failed to demonstrate consistent clinical benefit in large randomized trials.

Intramyocardial Hemorrhage

In severe STEMI, profound disruption of the microvascular architecture may permit erythrocyte extravasation into the infarcted myocardium following reperfusion. Intramyocardial hemorrhage represents an advanced stage of microvascular injury and frequently coexists with extensive microvascular obstruction identified on cardiac magnetic resonance imaging [6].

Patients with intramyocardial hemorrhage demonstrate larger infarct size, more pronounced adverse left ventricular remodeling, reduced recovery of systolic function, and worse long-term prognosis than patients with isolated microvascular obstruction.

Overall, coronary no-reflow should be regarded as the final common pathway resulting from multiple simultaneously acting mechanisms rather than a single pathological process. This concept explains why no individual pharmacological or mechanical intervention has proven universally effective and supports a multimodal therapeutic approach targeting several components of microvascular injury.

Risk Factors and Predictors

Several clinical, angiographic, and procedural characteristics increase the risk of coronary no-reflow during primary PCI. Delayed presentation after symptom onset, anterior STEMI, prolonged ischemic time, diabetes mellitus, renal dysfunction, and advanced age are consistently associated with a higher incidence of microvascular obstruction [1,3].

Angiographic predictors include a large thrombus burden, total occlusion of the infarct-related artery, long lesion length, complex plaque morphology, and impaired initial TIMI flow. Procedural factors such as repeated balloon inflations, aggressive stent deployment, and distal embolization further increase the likelihood of no-reflow [3,14].

Several risk scores combining clinical and angiographic variables have been proposed; however, none has achieved widespread routine clinical use. Careful recognition of high-risk patients before PCI remains essential for individualized procedural planning and preventive strategies.

Diagnosis

Coronary no-reflow is primarily diagnosed during coronary angiography by impaired myocardial perfusion despite successful reopening of the epicardial artery. Angiographic criteria include TIMI flow grade ≤2, reduced myocardial blush grade (MBG), increased corrected TIMI frame count, and persistent ST-segment elevation despite restoration of coronary patency [8-10].

Because angiography may underestimate microvascular dysfunction, cardiac magnetic resonance (CMR) has

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become the reference standard for detecting microvascular obstruction (MVO). Late gadolinium enhancement imaging accurately identifies non-perfused myocardial regions and provides important prognostic information regarding infarct size, ventricular remodeling, and long-term clinical outcomes [6,12].

Invasive physiological assessment using the Index of Microcirculatory Resistance (IMR) offers an additional method for quantifying coronary microvascular dysfunction immediately after PCI and has emerged as a promising tool for risk stratification in selected patients [3].

Prevention

Preventing coronary no-reflow begins with minimizing total ischemic time through rapid reperfusion. Early primary PCI, adequate antithrombotic therapy, and meticulous procedural technique remain the cornerstones of prevention. Patients with a large thrombus burden require particular attention. Contemporary PCI strategies emphasize gentle lesion manipulation, avoidance of unnecessary balloon inflations, optimization of stent deployment, and selective rather than routine thrombus aspiration, in accordance with current guideline recommendations [1,7].

Although numerous pharmacological agents—including adenosine, calcium-channel blockers, glycoprotein IIb/IIIa inhibitors, nicorandil, and sodium nitroprusside—have been investigated, evidence supporting their routine prophylactic administration remains inconsistent. Current preventive strategies therefore rely primarily on appropriate patient selection, careful procedural planning, and prompt recognition of patients at increased risk for microvascular injury [3,7].

Management of Coronary No-Reflow

Management of coronary no-reflow requires immediate recognition and a systematic approach aimed at restoring microvascular perfusion while excluding mechanical causes of impaired coronary flow. Before initiating pharmacological therapy, operators should first rule out coronary dissection, significant residual stenosis, stent underexpansion or thrombosis, severe epicardial vasospasm, distal vessel perforation, and air embolism. Once mechanical complications have been excluded, intracoronary vasodilator therapy represents the cornerstone of treatment. Adenosine remains one of the most frequently used agents because of its potent microvascular vasodilatory, anti-inflammatory, and antiplatelet effects. Calcium-channel blockers, particularly verapamil and nicardipine, effectively relieve microvascular spasm and improve coronary flow in selected patients. Intracoronary sodium nitroprusside is another valuable option owing to its direct nitric oxide-mediated vasodilatory properties [3,7].

In patients with persistent no-reflow despite standard vasodilator therapy, intracoronary epinephrine has emerged as an effective rescue treatment by improving coronary perfusion pressure and microvascular blood flow. Recent observational studies have demonstrated favorable angiographic and hemodynamic results, although randomized evidence remains limited [19].

Adjunctive pharmacological therapy should include optimization of antithrombotic treatment. In patients with a large residual thrombus burden, intravenous glycoprotein IIb/IIIa inhibitors may be considered to reduce platelet aggregation and distal microembolization, particularly in bailout situations. Supportive measures are equally important. Systemic hypotension should be corrected promptly to maintain adequate coronary perfusion pressure. Intravenous fluids, vasopressors when appropriate, correction of hypoxemia, and treatment of ventricular arrhythmias should accompany intracoronary therapy. In patients with cardiogenic shock, temporary mechanical circulatory support may be considered according to current guideline recommendations. Despite numerous therapeutic options, no single intervention has consistently demonstrated superiority in randomized clinical trials. Therefore, successful management of coronary no-reflow relies on rapid diagnosis, exclusion of mechanical complications, individualized intracoronary pharmacotherapy, optimization of coronary perfusion, and meticulous PCI technique.

Drug	Main mechanism	Typical intracoronary dose	Clinical role
Adenosine	Microvascular vasodilation	60–240 μg	First-line
Verapamil	Calcium-channel blockade	100–500 μg	Microvascular spasm
Nicardipine	Calcium-channel blockade	100–300 μg	Alternative first-line
Nitroprusside Na	Nitric oxide donor	50–200 μg	Persistent no-reflow
Epinephrine	Increases coronary perfusion pressure	50–200 μg	Rescue therapy
Tirofiban	GP IIb/IIIa inhibition	Standard IV regimen	Large thrombus burden

Table 1: Pharmacological Management of Coronary No-Reflow.

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Conclusion

Coronary no-reflow remains one of the most challenging complications of primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. Although restoration of epicardial coronary artery patency is the primary goal of reperfusion therapy, successful PCI does not necessarily ensure adequate myocardial tissue perfusion. Coronary no-reflow reflects severe microvascular injury resulting from multiple interacting mechanisms, including prolonged ischemia, distal embolization, endothelial dysfunction, inflammation, oxidative stress, and ischemia–reperfusion injury.

The occurrence of no-reflow is consistently associated with larger infarct size, impaired recovery of left ventricular function, adverse ventricular remodeling, heart failure, malignant ventricular arrhythmias, and increased mortality. Early identification of patients at increased risk and prompt recognition during primary PCI are therefore essential for improving clinical outcomes.

Despite considerable advances in pharmacological and interventional therapies, no single treatment has demonstrated consistent superiority in preventing or reversing no-reflow. Contemporary management should therefore emphasize meticulous PCI technique, optimization of antithrombotic therapy, rapid exclusion of mechanical causes, individualized intracoronary vasodilator treatment, and maintenance of adequate coronary perfusion pressure.

Recent developments in coronary physiology, cardiac magnetic resonance imaging, and artificial intelligence-based risk prediction have improved our understanding of coronary microvascular dysfunction and may facilitate more personalized therapeutic strategies in the future. Further randomized clinical trials are required to establish standardized treatment algorithms and identify novel therapies capable of effectively preserving the coronary microcirculation during reperfusion.

Ultimately, successful treatment of STEMI should no longer be defined solely by restoration of TIMI grade 3 epicardial flow but also by achieving complete myocardial reperfusion. Recognition and effective management of coronary no-reflow remain essential components of contemporary interventional cardiology practice.

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