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REVIEW ARTICLE

Pathophysiology, Diagnosis, and Management of the No-Reflow Phenomenon

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Abstract

Successful reperfusion of an infarct-related coronary artery by primary percutaneous intervention or fibrinolysis during acute ST-elevation myocardial infarction (STEMI) does not always restore myocardial tissue perfusion, a phenomenon termed "no-reflow." Herein we discuss the pathophysiology of this highly prevalent phenomenon and highlight the most salient aspects of its clinical diagnosis and management as well as the limitations of presently used methods. There is a great need for understanding the dynamic nature of no-reflow, as its occurrence is associated with poor cardiovascular outcomes. The no-reflow phenomenon may lend an explanation to the lack of further improvements in in-hospital mortality in STEMI patients despite decreases in door-to-balloon time. Hence, no-reflow potentially presents an important target for investigators interested in improving outcomes in STEMI.

Keywords Myocardial infarction · Microvascular disease · Cardiovascular disease · Ischemic heart disease

In the era of reperfusion, much effort has been made to decrease myocardial infarct (MI) size by implementing early reperfusion with primary percutaneous coronary intervention (P-PCI) or thrombolytic agents. Door-to-balloon times have improved substantially while concomitant in-hospital mortality improvements lag behind [1].

It is plausible that outcomes after successfully reperfused MI are determined by the initial size of myocardial ischemia, time from onset of ischemia to reperfusion, potential reperfusion injury, patency of the epicardial infarct-related artery, distal thromboembolization, adverse remodeling after infarction, and the microvascular no-reflow phenomenon (NRP). Herein we describe the dynamic pathophysiology of the NRP. Additionally, we present a comparison of clinical diagnostic and therapeutic strategies.

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Pathophysiology of Myocardial No-Reflow

Successful restoration of coronary blood flow in the infarct-related coronary artery during ST-elevation MI (STEMI) does not always lead to an improvement in myocardial perfusion. This has been termed NRP. Kloner et al. described the failure of subendocardial microvascular reperfusion, assessed by the injection of the fluorescent dye thioflavin-S into the coronary vasculature, after cessation of coronary artery occlusion in dogs without preexisting intra-arterial thrombus [2]. Death of previously ischemic cardiomyocytes preceded the onset of the NRP and capillary damage [3].

These zones with NRP evidenced microvascular damage. In addition, areas of endothelial disruption were present with platelet deposition and fibrin tactoids appearing to stem the capillary leak. Others described neutrophil plugs within areas of no-reflow, suggesting that an inflammatory component may worsen the phenomenon [4]. In addition to plugging the microvessels, neutrophils could also cause cellular injury and endothelial dysfunction by generating oxygen-derived free radicals, thus worsening the NRP. In the dog, the no-

reflow zone triples in area between 2 min and 8 h after reperfusion.

Ultrastructural evidence of microvascular damage does not seem to manifest until at least 60 to 90 min post-reperfusion, at least in the dog [5]. No-reflow impairs healing of necrotic areas: infarct thinning and expansion are correlated with the severity of no-reflow, which persisted for as long as 1 month in the rat [6].

Risk factors which have been independently linked to subsequent development of NRP include advanced age (≥ 70 years), diabetes mellitus, prolonged time from symptom onset to hospital presentation, and poor systolic function.

Clinical Descriptions of No-Reflow

A substantial proportion of patients demonstrate impaired myocardial reperfusion, portending worse prognosis, despite restoration of epicardial blood flow and absence of in situ thrombosis or vasospasm [7]. Clinical observations of the NRP have been reported copiously [3], and its presence after PCI is an adverse prognostic sign [8], associated with depressed left ventricular (LV) ejection fraction (LVEF) and adverse LV remodeling. Genetic and clinical risk factors likely influence individual susceptibility to no-reflow. No-reflow is more common in those with prolonged symptoms to device time, diabetes mellitus, larger ischemic myocardium at risk, and proximal left anterior descending artery (LAD) occlusion [9–11].

The microvascular obstruction [12] observed clinically is more complicated than the original observations in animal models. In patients with thrombotic occlusion overlying atherosclerotic plaques, embolization of microthrombi and debris from these plaques may further worsen microvascular damage during coronary revascularization (henceforth, referred to as "embolic no-reflow"). This thrombus embolization may result in microvascular spasm and microinfarcts. This effect, whether spontaneous or PCI-induced, is likely immediate and compounds upon the original non-embolic NRP, which develops and expands over the course of a few hours and relates to the ischemia-reperfusion injury of the myocardium and adjacent blood vessels (henceforth referred to as "non-embolic NRP").

The patient with no-reflow may have angina symptoms, chest pain, tachycardia, and even hypotension. Although microvascular obstruction (MVO) is reversible in about 50% of patients, persistent no-reflow and MVO should be considered in patients with post-PCI chest pain.

Diagnosis of No-Reflow

With remarkable variability in contemporary methods for assessing clinical no-reflow (Table 1), it is important to appreciate the mechanistic underpinnings and limitations of the common methods.

Angiography

Assessment of no-reflow after reperfusion in the catheterization laboratory is a routine clinical practice. However, standardized no-reflow assessments by coronary angiography are limited. No-reflow is a dynamic phenomenon, and angiography can only illustrate no-reflow early in its course in patients undergoing P-PCI. Furthermore, coronary angiography cannot truly delineate the microcirculation [13]. Given the earlier time point of angiography, it may not correlate with cardiac magnetic resonance (CMR) imaging, the current gold standard for assessing MVO, which is obtained later on. The prevalence of angiographic no-reflow in patients has been estimated to be about 2.3% [14].

TIMI-Flow Grade

Thrombolysis in Myocardial Infarction (TIMI)-flow grades are widely used to correlate angiographic and clinical outcomes after P-PCI and thrombolysis [15]. The assumption is that the fluidity of contrast in the epicardial coronary artery reflects the spontaneous coronary circulation and myocardial perfusion and thus, the success of coronary intervention.

TIMI-flow grades are assessed on a scale of 0 to 3. Higher TIMI-flow grades are associated with improved clinical outcomes and lower mortality [16]. Data from the TEAM-2 study showed that in patients undergoing streptokinase administration, early TIMI-flow grade 3 correlated with decreased peaks of cardiac biomarkers and ECG indices of MI, as well as lower hospital mortality [17]. Patients with TIMI-flow grade 2 did not differ significantly from those with grade 0 or 1 in relation to biomarker activity, ECG indices, or short-term survival in either study.

Interobserver variability limits the usefulness of operator-assessed TIMI-flow grades. Furthermore, a confounding factor with these associations is the improved survival observed with inferior MI compared with anterior MI [18].

In older studies of patients undergoing thrombolytic therapy, coronary angiography was carried out later and therefore, results are difficult to compare with those in the current P-PCI studies. Distal tissue perfusion may vary considerably despite TIMI grade 3 flow in the epicardial artery after reperfusion [7].

Corrected TIMI Frame Count

Corrected TIMI frame count (CTFC) is an attempt to more objectively assess the coronary circulation. CTFC represents the number of cine-frames required for radiocontrast dye to reach standardized distal landmarks in the epicardial arteries, corrected for the differing lengths of the arteries.

Table 1 Common methods for diagnosis of no-reflow

Diagnostic maneuver	Methodology
Surface ECG	The most used methods are (1) measuring the decrease of the sum of ST-segment elevation across leads (with complete resolution defined as a 50–70% decrease of this sum); (2) comparing the lead with the most prominent ST-segment deviation at baseline and post-reperfusion; and (3) measuring the maximum ST-segment deviation present at multiple time intervals.
TIMI-flow grade	TIMI grade 0 flow signifies occlusion; grade 1, minimal perfusion; grade 2, partial perfusion; grade 3 flow signifies a similar flow rate of an infarct-related artery compared with a non-culprit artery.
Corrected TIMI frame count	CTFC denotes the number of cine-frames required for contrast dye to reach standardized distal landmarks in the epicardial arteries, with frame count corrections based on the differing lengths of the arteries.
Myocardial blush grade	Myocardial blush grade 3 represents normal entry and exit of dye in the myocardium, similar to that achieved with a non-infarct-related epicardial artery; 2, moderate myocardial blush or contrast density but less than that of a non-infarct-related artery; 1, minimal contrast density or blush; 0, absence of blush or persistence of MBG, suggesting leakage into the extravascular space. Compared with TIMI-MPG, emphasis is on intensity, rather than on duration of blush.
TIMI-MPG	TIMI-MPG grade-3 blush indicates the beginning of blush clearance during washout (i.e., minimally persistent after 3 cardiac cycles of washout); grade 2 clears minimally or not at all during 3 cardiac cycles of washout; grade 1 denotes presence of myocardial blush without clearance from the microvasculature (i.e., stain was present during the next injection); grade 0 signifies no perfusion at the tissue level (i.e., myocardium opacification or no ground-glass appearance of blush) in the territory of the infarct-related artery. Compared with MBG, the emphasis is on *duration*, *rather than on intensity of the blush*.
Cardiac MRI	Microvascular obstruction (MVO) can be assessed by cardiac MRI after STEMI reperfusion, typically within a few days; this MVO assessment correlates well with mortality and heart failure hospitalizations at 1 year post-event.

TIMI, Thrombolysis in Myocardial Infarction; *CTFC*, corrected TIMI frame count; *MBG*, myocardial blush grade; *MPG*, myocardial perfusion grade; *ECG*, electrocardiogram; *MRI*, magnetic resonance imaging

Lower CTFC correlates with coronary blood flow velocity measured by intracoronary Doppler; although CTFC may accurately reflect blood flow, it does not accurately assess the extent of microvascular injury [19]. Although faster 90-min CTFC may correlate with better in-hospital and 30-day clinical outcomes, it may be that a subset of patients with supranormal CTFC (< 13) drives the observed improvement in outcomes [20].

Myocardial Blush Grade

Myocardial blush grade (MBG) is used to assess myocardial staining after P-PCI. The scale represents the entrance and disappearance of myocardial blush after radiocontrast injection. The original scale was described as 0 to 3: where 3 represents normal entry and exit of dye in the myocardium, similar to that achieved with a non-infarct-related epicardial artery; 2, moderate myocardial blush or contrast density but less than that of a non-infarct-related artery; 1, minimal contrast density or blush; 0, absence of blush or persistence of MBG, suggesting leakage into the extravascular space [21]. MBG ratings by the operator during P-PCI appear to independently prognosticate 1-year all-cause mortality, even in patients with TIMI-flow grade 3 [22].

However, more advanced investigations question these earlier findings. Neither TIMI-flow grade nor MBG correlated with LV function, unlike MVO assessed by CMR, in patients undergoing P-PCI [23]. Post hoc analysis of the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial found that ST-segment resolution (STR) 4 h after P-PCI and the degree of MBG are frequently discordant (in approximately 40% of cases), which may limit their use. After multivariable adjustment, STR was a stronger independent predictor of clinical outcomes at 30 days and 1 year, although both variables in combination appeared to have an incremental prognostic value [24].

TIMI Myocardial Perfusion Grade

An alternative method to assess myocardial perfusion is the TIMI myocardial perfusion grade (TIMI-MPG), which is also graded on a scale of 0 to 3. TIMI-MPG grade-3 blush indicates the beginning of blush clearance during washout (i.e.,

minimally persistent after 3 cardiac cycles of washout); TIMI-MPG grade-2 blush clears minimally or not at all during 3 cardiac cycles of washout; TIMI-MPG grade-1 blush denotes presence of myocardial blush without clearance from the microvasculature (i.e., stain was present during the next injection); grade-0 blush signifies no perfusion at the tissue level (i.e., myocardium opacification or no ground-glass appearance of blush) in the territory of the infarct-related artery [25, 26].

TIMI-MPG is a densitometric method that grades evolution (i.e., entry, endurance, and clearance) of contrast media at the myocardial level. It may be used in conjunction with TIMI-flow grade to grade no-reflow [27]. On the other hand, MBG focuses on intensity of the blush in the culprit artery distribution, relative to the contrast density in uninvolved territories. Impaired reperfusion described by TIMI-MPG grading system correlates to a higher risk of mortality, independent of epicardial blood flow restoration [25]. In a study of patients undergoing P-PCI, TIMI-MPG had the strongest relationship with MVO when assessed by CMR on day 3 post-STEMI, while MBG did not correlate with CMR-derived evaluation of MVO [28].

Impaired TIMI-MPG 3.5 days after fibrinolytic therapy for STEMI correlated with incidence of ventricular fibrillation and ventricular tachycardia [29]. Of note, analysis of data from The Randomized Trial to Evaluate the Relative PROTECTion against Post-PCI Microvascular Dysfunction and Post-PCI Ischemia among Anti-Platelet and Anti-Thrombotic Agents–Thrombolysis In Myocardial Infarction-30 (PROTECT-TIMI 30) trial found that abnormal TIMI-MPG, but not abnormal CTFC, correlated with increased death, MI, and ischemic events on Holter monitoring at 48 h after P-PCI [30].

A CMR imaging investigation of STEMI patients treated with P-PCI found that impaired TIMI-MPG was associated with larger infarct size, both at 7 days and 3 months [31]. TIMI-MPG has demonstrated a strong relationship with MVO assessed by CMR at 3 days post-STEMI, while MBG did not [28]. TIMI-MPG also predicted LVEF and wall motion score index at 90 days post-STEMI. The same group found that TIMI-MPG—not CTFC or MBG—predicted MVO on CMR 4 days POST-STEMI [32].

Electrocardiography

The most basic method of assessing for ongoing myocardial ischemia is the use of the surface electrocardiogram (ECG) with monitoring for changes in ST segments. There is some incongruence with regard to methods for measuring the so-called ST-segment resolution (STR) after STEMI. The most common method classifies STR as the decrease in the sum of ST elevation (STE) across all leads before and after reperfusion therapy. Complete STR is defined as a reduction of 50–70% of this sum [33].

Patients with persistent STE in ≥ 2 contiguous leads after reperfusion despite normal epicardial blood flow seem to be at higher risk for mortality. Early STR correlates with LVEF and enzymatic infarct size [34]. Persistent STE and myocardial blush grade (MBG) grades 0 to 1 independently predict long-term mortality after P-PCI, while CTFC—corrected Thrombolysis in Myocardial Infarction (TIMI) frame count—is a weaker predictor. Simultaneous use of these parameters may increase their predictive power [35]. Despite the ease and rapidity of obtaining STR, it at times presents itself as an inaccurate method to the diagnosis of no-reflow [36]. In another work, incomplete STR has been related to baseline LV function, but did not portend changes at follow-up [23].

Myocardial Contrast Echocardiography

Myocardial contrast echocardiography (MCE), though less frequently used in contemporary clinical practice, can be used to assess no-reflow. During MCE, echocardiograms are obtained after IV or IC injection of sonicated microbubbles [37]. The lingering of microbubbles within the myocardium indicates no-reflow. No-reflow in patients with acute MI has been estimated to be 29% with this technique [38].

Cardiac Magnetic Resonance Imaging

CMR is the gold standard for assessment and diagnosis of no-reflow. The degree of MVO detected by CMR portends worse prognosis with respect to mortality, heart failure hospitalizations, and LV remodeling, independent of the size of infarct [11, 39–42]. Specifically, the extent of MVO assessed by CMR several days after P-PCI correlates well with mortality and heart failure hospitalizations within 1 year of infarction.

Some amount of MVO was observed in 57% of 1688 patients in a pooled analysis of seven PCI trials [40], markedly greater than the prevalence noted in other studies [43, 44]. However, the time point of several days (24 h to 5 days) after reperfusion is different from that assessed in the animal models (several hours after reperfusion) and in the angiographic studies (minutes), and consequently may be affected by additional factors.

CMR assessment after STEMI is usually undertaken between 2 and 9 days post-reperfusion, as the extent of both MVO and infarction significantly increases during the first 48 h [45].

Gadolinium contrast can be used in two ways to describe MVO, as this agent clears slowly from infarcted regions. In first-pass-perfusion imaging, “early” MVO is measured through the simultaneous administration of contrast and acquisition of imaging. MVO is observed as a persistent area of hypoenhancement in the core of the infarcted myocardial

territory, which is seen soon after administration of the gadolinium. On the other hand, "late" MVO may be measured approximately 15 min after injection of the contrast agent.

Although it is thought that late MVO may underestimate the true extent of obstruction, early MVO is limited by poorer spatial resolution and incomplete assessment of the LV [46]. In a homogeneous population of STEMI patients undergoing P-PCI, Nijveldt et al. found that late MVO was the most powerful predictor of regional and global LV functional recovery compared with early MVO, STR, TIMI-flow grade, and MBG. Both early and late MVO were related to incomplete STR, but not TIMI-flow grade and MBG [23].

LVEF, infarct size, and extent of myocardial edema change significantly during the first week post-STEMI. CMR measurements obtained after 1 week more accurately predicted infarct size and LVEF at 3 months compared with imaging at 2 days [8].

Intramyocardial hemorrhage (IMH) which results from severe microvascular injury is defined as a hypointense infarct core with T_2* signal < 20 ms on CMR [47]. IMH is consistently linked with adverse LV remodeling and poor long-term clinical outcomes [48, 49].

Management of No-Reflow

Pharmacological Therapy

Achieving adequate epicardial coronary artery flow in the catheterization lab is paramount, and a handful of drugs have shown some benefit (Table 2). While no-reflow during STEMI is common, management with the therapies described below may be effective in restoring normal epicardial coronary flow [60].

Adenosine induces muscle relaxation in the coronary microcirculation [61]. Encouraged by positive results in animal models of reperfusion injury, the use of adenosine as adjunctive therapy to reperfusion during STEMI was evaluated in the Acute Myocardial Infarction STudy of ADenosine (AMISTAD)-1 trial [62]. Administration of adenosine within 6 h of STEMI onset reduced infarct size compared with that of placebo in patients receiving fibrinolytic therapy. The later AMISTAD-II trial [63] found that adenosine did not improve short-term or long-term clinical outcomes during evolving anterior STEMI managed with thrombolysis or P-PCI; this outcome occurred despite a significant reduction in infarct size with high-dose adenosine infusion. In a follow-up analysis of AMISTAD-II data, patients receiving early reperfusion in addition to adenosine had significantly reduced mortality and incidence of heart failure compared with those receiving early reperfusion and placebo, although no-reflow was not formally assessed, suggesting that the coupling of adenosine with early reperfusion may have a clinical benefit.

In the Intracoronary Nitroprusside Versus Adenosine in Acute Myocardial Infarction (REOPEN-AMI) trial, [56] intracoronary (IC) adenosine was compared with sodium nitroprusside (SNP) and placebo after performing thrombus aspiration. Adenosine as compared with sodium nitroprusside or placebo had favorable effects on STR. Meta-analyses have offered conflicting results on hard clinical outcomes, though all suggest possible improvement in surrogate measures of microvascular dysfunction, i.e., TIMI-flow grade and STR [64–66]. Sodium nitroprusside and calcium channel blockers (verapamil, diltiazem, nicardipine) are also frequently used as vasodilator therapy in the cardiac catheterization laboratory; evidence on their use is further described in Table 2.

The recent REperfusion Facilitated by LOcal adjunctive therapy in ST-Elevation Myocardial Infarction (REFLO-STEMI) trial [67] calls into question the benefit of adenosine and sodium nitroprusside on delayed microvascular injury. In patients undergoing P-PCI with observed TIMI grade 0/1 flow, infarct size, and MVO, assessed at 48–96 h post-PCI by CMR, there was a slight increase in major adverse cardiac events (MACE) at 30 days and 6 months with adenosine. Hence, high-dose adenosine may be contraindicated during STEMI, and even low doses should be reconsidered.

Routine use of GP IIb/IIIA inhibitors is currently not recommended or supported by clinical data in patients adequately pretreated with dual oral antiplatelet therapy, and these agents are only used as a bailout strategy. A multicenter CMR study of STEMI patients failed to show the benefit of IC vs IV abciximab on MVO or intramyocardial hemorrhage [68].

Other agents have also been investigated in small studies. There is some support for a plausible neural mechanism in no-reflow as α-adrenergic blockade after PCI showed a salutary effect on TIMI frame counts, post-ischemic systolic function, and regional systolic thickening [69]. Recent trial data do not support use of low-dose IC alteplase during P-PCI for STEMI [70].

Non-pharmacological Therapy

Presence of a thrombus is a major differentiator between experimental models of no-reflow and the clinical scenario. P-PCI itself may provoke embolization of thrombotic and atherosclerotic debris, leading to development of embolic no-reflow.

In patients with anterior STEMI treated with P-PCI, 30-day infarct size was not affected by aspiration thrombectomy in a background of IC abciximab and bivalirudin. [71] A recent meta-analysis corroborates the absence of clinical benefit with routine thrombus aspiration [72]. Hence, the ESC and the ACC/AHA guidelines do not recommend routine thrombus aspiration [73, 74]. The ACC/AHA focused update on P-

Table 2 Pharmacological therapies commonly used in managing no-reflow during PCI

Intervention	Mechanism	Pertinent literature
Sodium nitroprusside	Activation of guanylate cyclase, resulting in smooth muscle relaxation and vasodilation	In a group of 162 STEMI patients, intracoronary dosing of sodium nitroprusside in addition to tirofiban had favorable effects on ST-segment resolution, TIMI myocardial perfusion grade, and incidence of MACE at 6 months compared with tirofiban alone [50]. A small meta-analysis showed that intracoronary sodium nitroprusside reduces CTFC, improves left ventricular ejection fraction, and potentially reduces risk of rehospitalization due to cardiovascular events [51]. Another analysis found that intracoronary administration significantly reduces incidence of MACE [52].
Calcium channel blockers (nicardipine, verapamil, diltiazem)	Elicits smooth muscle relaxation and vasodilation	Non-dihydropyridine calcium channel blockers appear to mitigate no-reflow and 6-month MACE in a meta-analysis of randomized controlled trial data [53]. An intracoronary combination of nicardipine and adenosine was found to be safe and effective in reducing angiographic no-reflow during rotational atherectomy [54]. However, a Cochrane review found no evidence to support verapamil as no-reflow treatment with respect to all-cause mortality, non-fatal myocardial infarction, and angiographic no-reflow in patients with acute coronary syndromes [55].
Adenosine	Elicits smooth muscle relaxation in the coronary microcirculation; antiplatelet activity	The REOPEN-AMI trial [56] aimed to determine whether intracoronary (IC) adenosine or sodium nitroprusside after thrombus aspiration improves outcomes over thrombus aspiration alone. A total of 240 STEMI patients with TIMI 0/1 grade flow were given either adenosine, nitroprusside, or saline infusion. Aspirin and clopidogrel (600 mg) were given in the emergency room with IV abciximab (0.25 mg/kg bolus, 12-h infusion thereafter) and heparin (5000 IU) bolus given prior to PCI. The primary endpoint measured was ST-segment resolution (STR) on ECG at 90 min post-PCI. Adenosine, but not nitroprusside, improved STR, although angiographic microvascular obstruction (MVO) (TIMI-flow grade < 2 or 3 and myocardial blush (MBG) grade < 2) and major adverse cardiac events (MACE) at 30 days were not significantly different among the groups. One-year follow-up analysis of REOPEN-AMI data [57] revealed lower incidence of CHF, MI, and death with adenosine. Improved remodeling of the LV was observed.
GP IIb/IIIa receptor inhibitors	Inhibition of platelet aggregation and adhesion	In the CICERO trial, STEMI patients undergoing primary PCI with thrombus aspiration had improved MBG and smaller enzymatic infarct size with IC abciximab use [58]. IC bolus of abciximab during primary PCI for STEMI reduced MVO observed on CMR in another study [59].

ECG, electrocardiogram; *LVEF*, left ventricular ejection fraction: *STR*, ST-segment resolution; *GP IIb/IIIa*, glycoprotein IIb/IIIa

PCI for STEMI patients recommended against routine aspiration thrombectomy prior to P-PCI, while noting insufficient evidence to assess the benefit or selective use (class IIb) [75]. Most recently, pressure-controlled intermittent coronary sinus occlusion (PICSO) has been found to be a safe therapy, possibly associated with improvement in microvascular function in anterior STEMI [76].

Systematic analysis of randomized trials suggests that embolic protection devices do not reduce early mortality or reinfarction rates during P-PCI [77]. A recent study [78] found that the use of a distal embolic filter device decreased incidence of no-reflow (assessed by CTFC) in STEMI patients with attenuated plaques seen on intravascular ultrasound (IVUS), compared with conventional P-PCI. Nevertheless, long-term outcomes with such devices remain unclear [79].

Conclusions and Future Directions

The no-reflow zone develops over several hours to days, and non-embolic no-reflow, rather than the embolic no-reflow, instigated by provoked and spontaneous microthromboemboli, may be a more important pathophysiological target. This presentation intends to underline that no-reflow is truly a dynamic phenomenon, and many of the frequently used methods for diagnosis may by quite limited when analyzed in isolation. For instance, popular angiographic methods (TIMI-flow grade, CFTR, MBG, TIMI-MPG) and electrocardiographic methods are limited by subjectivity, and most importantly, these only attempt to capture early embolic epicardial no-reflow. Delayed evaluation of MVO by CMR several days after index infarct appears to be a more valuable tool in assessing no-reflow and predicting prognosis.

Understanding the evolution of the NRP may help to explain the disappointing results of several adjunctive pharmacological therapies with respect to meaningful clinical outcomes in STEMI. Further progress may likely depend on exploring diagnostics and therapeutics which modulate the pathophysiology of delayed microvascular damage during ischemia-reperfusion injury, and the field still remains ripe for inquiry.

Compliance with Ethical Standards

Conflict of Interest The authors declare that there are no conflicts of interest.

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