Pathophysiology, diagnosis and management of no reflow

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Abstract

Successful reperfusion of an infarct-related coronary artery during acute ST elevation MI (STEMI) does not always bring about improvements in myocardial tissue perfusion, a phenomenon termed “no-reflow.” In this article we present the pathophysiology of this phenomenon. In addition we highlight the most salient aspects of clinical diagnosis and management of myocardial no-reflow, as well as limitations of presently used methods. There is a great need for understanding dynamic nature of no-reflow, as its presence is associated with poor cardiovascular outcomes.
Cardiovascular disease still remains a primary cause of mortality and morbidity through both myocardial ischemia and reperfusion injury. In the era of reperfusion therapy, much effort has been made to decrease myocardial infarct (MI) size by prioritizing early reperfusion with primary percutaneous coronary intervention (PCI) or thrombolytic agents. Both therapies have indubitably improved clinical outcomes, but attempts to further reduce infarct size have been hampered by lack of success in clinical trials. Door-to-balloon times improved substantially in the Cath PCI registry, although in-hospital mortality was largely unchanged.\(^1\)

It is plausible that outcomes after successfully reperfused MI are determined by the initial size of myocardial necrosis (cell death during active ischemia), potential reperfusion injury, patency of the epicardial infarct-related artery, the microvascular no-reflow phenomenon and adverse remodeling after infarction. Herein we describe the dynamic pathophysiology of the no-reflow phenomenon. Additionally, we present a comparison of clinical methods of diagnosis and therapy.

**PATHOPHYSIOLOGY OF MYOCARDIAL NO REFLOW**

It has been observed that successful restoration of coronary blood flow in the infarct-related epicardial coronary artery during acute ST-elevation MI (STEMI) does not always lead to an improvement in microvascular perfusion of the myocardium. This has been termed the “no reflow” phenomenon. The first descriptions of no reflow were of the kidney\(^2\), the brain\(^3\), and the heart\(^4\) several decades ago. Kloner et al. expounded upon the no-reflow phenomenon in detailing 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 canine experimental models without preexisting thrombus.\(^5\) Death of previously ischemic cardiomyocytes preceded the onset of the no-reflow phenomenon and capillary damage.\(^6\)\(^7\)

Exposing transverse sections of the heart to ultraviolet light revealed zones of myocardium that were completely devoid of the fluorescent dye, even though the epicardial coronary artery was patent after a 90-minute ischemia time. These no reflow zones evidenced microvascular damage under electron microscopy. In addition, areas of endothelial disruption were present with platelet deposition and fibrin tactoids appearing to stem the capillary leak.\(^8\) Some investigators have described neutrophil plugs within areas of no reflow, suggesting that an inflammatory component may worsen the phenomenon.\(^9\)

In the canine model, the no reflow zone triples in area between 2 minutes and 8 hours after reperfusion. Regional blood flow is hyperemic immediately upon reperfusion, roughly halving within several hours.\(^10\) In sum, these animals, without preexisting atherosclerosis or thrombotic occlusion, developed an initial hyperemic response and a subsequent decline in tissue perfusion following the release of mechanical coronary artery occlusion.

The no reflow phenomenon seems to be associated with reperfusion injury or post reperfusion inflammatory reaction,\(^11\)\(^12\) as the no reflow zone was seen to increase during the first few hours following coronary reperfusion. Ultrastructural evidence of microvascular damage does not seem to manifest until at least 60 to 90 minutes post-reperfusion, at least in the canine model.\(^7\) No reflow zones are confined to the ischemic risk zone within the area of necrosis. No reflow may impair healing of necrotic areas: infarct thinning and expansion are correlated with the severity of no-reflow, which persisted for as long as one month in a rat model.\(^13\)

**CLINICAL DESCRIPTIONS OF NO REFLOW**
A substantial proportion of patients demonstrate impaired myocardial reperfusion, portending worse prognosis, despite restoration of epicardial blood flow.\(^{14}\) Clinical observations of the no-reflow phenomenon have been reported copiously,\(^{6}\) and its presence after PCI is an adverse prognostic sign,\(^{15,16}\) 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 symptom to device time, diabetes mellitus, larger ischemic myocardium at risk, and proximal left anterior descending artery (LAD) occlusion.\(^{8,17,18,19}\) Incidence of no reflow is markedly higher in patients with STEMI compared to those with non ST-elevation MI (NSTEMI) or those undergoing elective PCI.\(^{20}\)

The microvascular obstruction observed clinically is more complicated than the original observations in animal models. In patients with thrombotic occlusion of atherosclerotic plaques, embolization of microthromboemboli 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 multiple micro-infarcts. This effect, whether spontaneous or PCI-induced, is likely immediate and compounds upon the original non-embolic no-reflow phenomenon described by Kloner et al., which develops and expands over the course of a few hours, and relates to the ischemic-reperfusion injury of the myocardium and adjacent blood vessels (henceforth referred to as “non-embolic no reflow”).

**METHODS FOR DIAGNOSIS OF NO REFLOW**

There is remarkable variability in contemporary methods for assessing clinical no reflow. It is important for both the practicing clinician and investigator to realize the mechanistic underpinnings as well as the limitations of each of the methods outlined below.

**Electocardiography**

*Surface ECG*

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. As such, it is also commonly used to gauge myocardial reperfusion and no-reflow. There is some incongruence with regards to methods for measuring so-called ST-segment resolution (STR) after STEMI. The most common methodology classifies STR as the sum of ST-segment elevation across all leads before and after reperfusion therapy.\(^{21}\) An alternative method is to compare the ECG lead with the most prominent ST-segment deviation at baseline and after reperfusion. A third technique is to measure the maximum ST-segment deviation present at multiple time intervals.

Van’t Hof et al. found that patients with persistent ST segment elevation (STE) after reperfusion seem to be at higher risk for mortality despite normal epicardial blood flow. Early resolution of STE has been correlated to LVEF and enzymatic infarct size.\(^{22}\) A later study demonstrated that persistent STE and myocardial blush grade (MBG) grade 0 to 1 independently predict long-term mortality after PCI for STEMI, while CTFC—corrected Thrombolysis in Myocardial Infarction (TIMI) TIMI frame count—is a weaker predictor. Simultaneous use of these parameters may increase their predictive power.\(^{23}\) Despite the ease and rapidity of
obtaining STR, it at times presents itself as an inaccurate method to the diagnosis of no-reflow.\textsuperscript{20} In another work, incomplete STR has been related to baseline LV function, but did not portend changes at follow-up.\textsuperscript{24} In addition, other factors can contribute to STE besides transmural ischemia, such as pericardial involvement, conduction abnormalities, and heart rate.

\textit{Intracoronary ECG}

In uncontrolled clinical scenarios, surface ECG readings are often only undertaken at long time intervals after reperfusion. Interference of lead cables with imaging precludes the use of continuous 12-lead ECG monitoring.

Thus intracoronary ECG (IC-ECG) was developed as a technique to produce real-time information for the operator in the catheterization lab.\textsuperscript{25} The angioplasty guide-wire is passed distal to the stenotic segment of the coronary vessel and positioned with the lumen of the infarct related artery while the proximal end is connected to the ECG recorder.\textsuperscript{26}

In a small study, IC-ECG was seen to be a more sensitive marker of myocardial ischemia during balloon angioplasty compared to surface ECG readings.\textsuperscript{27} Although this technique provides a steady flow of information to the operator, the question remains as to how one ought to respond to the stream of data. The duration of monitoring is limited to the time the guide-wire is positioned in the coronary artery (only during the PCI).

Most recently, intracoronary STR, defined as >1mm improvement compared to baseline, was a strong predictor of microvascular obstruction (MVO) assessed by CMR (cardiac magnetic resonance) imaging 4 days post-STEMI. At 3 months, it was seen to correlate also with infarct size and LV remodeling parameters. Late MVO was the strongest predictor of LVEF at 90 days post-STEMI, when compared to other variables derived from CMR and angiography.\textsuperscript{28} Robust studies which directly correlate the use of adjunctive pharmacological therapies in the management of patients demonstrating evidence of ischemia on IC-ECG are lacking.

\textbf{Angiography}

Assessment of no reflow after reperfusion in the catheterization lab has come to be routine clinical practice. However, no-reflow assessments by coronary angiography are limited. No reflow is a dynamic phenomenon, as illustrated by the microspheres techniques in the laboratory, and angiography can only illustrate no-reflow early in its course. Furthermore, coronary angiography is a planar technique, and the dye used during fluoroscopy does not linger in the intravascular space and hence cannot truly delineate the microcirculation.\textsuperscript{29} Distal tissue perfusion may vary considerably despite TIMI grade 3 flow in the epicardial arteries after reperfusion, the traditional angiographic gold standard.\textsuperscript{14}

\textit{TIMI flow grade}

TIMI flow grades have come to be widely used to correlate angiographic and clinical outcomes after primary PCI and thrombolysis.\textsuperscript{30} 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; 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 to a non-culprit artery. Higher TIMI flow grades have been associated with improved clinical outcomes, such as mortality.\textsuperscript{31} Data from the TEAM-2 study
showed that in patients undergoing streptokinase administration, early TIMI grade 3 flow correlated with decreased peaks of cardiac biomarkers and ECG indices of MI. In-hospital mortality was markedly reduced in STEMI patients undergoing thrombolysis and achieving TIMI grade 3 flow.\textsuperscript{32} It should be noted that 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 greatly limits the usefulness of operator-assessed TIMI flow grades. Furthermore, a large confounding factor with these associations is the improved survival observed with inferior MI\textsuperscript{33} compared to anterior wall MI. TIMI grade 2 flow is more frequently noted in the left anterior descending artery (LAD) due to its longer length while TIMI grade 3 flow is more commonly seen in the right coronary artery (RCA).

**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. Frame counts are corrected for the differing lengths of the arteries (e.g. frame counts for the LAD are divided by 1.7).

Lower CTFC has been observed to correlate with coronary blood flow velocity measured by intracoronary Doppler, but not with diastolic deceleration time and the averaged systolic peak velocity in a group of STEMI patients after PCI. This suggests that although CTFC may accurately reflect blood flow, it does not accurately assess the extent of microvascular injury.\textsuperscript{35} Although faster 90-minute CTFC may correlate with in-hospital and 30-day clinical outcomes in retrospective studies, it may be that a subset of patients with supranormal CTFC (<13) is driving the observed improvement in outcomes.\textsuperscript{36}

**Myocardial blush grade**
Van’t Hof et al. introduced the myocardial blush grade (MBG) technique to assess myocardial staining after primary PCI for STEMI. 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.\textsuperscript{37} The appearance of MBG was independently correlated to long-term mortality.

MBG appears to correlate with long-term mortality and LVEF.\textsuperscript{41} At one hospital, MBG ratings by the operator during primary PCI for STEMI appeared to independently prognosticate 1-year all-cause mortality, even in patients rated as TIMI flow grade 3.\textsuperscript{45} This association of MBG with short and long-term mortality was observed in another investigation of patients having undergone PCI for first anterior MI, with success having been graded as TIMI flow grade 3,\textsuperscript{46} further suggesting that high TIMI flow grade alone does not give a full prognostic picture. However, more advanced investigations question these earlier findings. Neither TIMI flow grade nor MBG correlated with LV functional outcome, unlike MVO assessed by CMR, in study of STEMI patients undergoing primary PCI.\textsuperscript{47} Post-hoc analysis of CADILLAC trial data found that STR 4 hours after primary PCI and the degree of MBG are frequently discordant (in approximately 40% of cases), which may limit their use in routine practice. Multivariate analysis
suggested STR to be the stronger prognostic factor for clinical outcomes at 30 days and 1 year though there appeared to be incremental prognostic value when both factors were combined.\textsuperscript{48}

*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.\textsuperscript{38,39} The emphasis with TIMI MPG is on duration of the blush; 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.\textsuperscript{38} In a study of STEMI patients undergoing primary PCI, TMPG had the strongest relationship with MVO when assessed via CMR on day 3 post-STEMI, while MBG did not correlate to CMR derived evaluation of MVO.\textsuperscript{40}

Impaired TIMI MPG visualized 3.5 days after fibrinolytic therapy for STEMI correlated with increased incidence of ventricular fibrillation and ventricular tachycardia.\textsuperscript{42} Of note, analysis of data from the PROTECT-TIMI 30 trial found that abnormal TIMI MPG, but not abnormal CTFC, was correlated with increased occurrence of death, MI, and ischemic events on Holter monitoring at 48 hours after PCI in STEMI patients.\textsuperscript{43} A cardiac magnetic resonance (CMR) imaging investigation of STEMI patients treated with primary PCI found that impaired TIMI MPG was associated with larger infarct surface area and infarct complexity, both at seven days and 3 months.\textsuperscript{44} Wong et al. 2012\textsuperscript{49} found that TIMI MPG demonstrated a strong relationship with MVO assessed by CMR at 3 days post-STEMI, while MBG did not. 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.\textsuperscript{28}

*Coronary flow reserve*
Coronary flow reserve (CFR) represents the maximum increase in coronary blood flow above the resting volume in response to a vasoactive substance. This can be measured through the use of intracoronary Doppler flow wire. Techniques also exist for measurement of this parameter through \textsuperscript{99m}Tc-sestamibi single photon emission computed tomography (SPECT), Doppler echocardiography, and CMR.\textsuperscript{50} However, studies relating CFR to STEMI outcomes after reperfusion are inconclusive. This is likely because measurement of CFR largely represents an assessment of coronary macrocirculation rather than microcirculation.\textsuperscript{51,52}

*Index of microcirculatory resistance*
The most recent attempt to quantify the no-reflow phenomenon in the coronary angiography suite is the use of index of microcirculatory resistance (IMR). In this technique, a coronary pressure wire records mean pressure in the distal two thirds of the arterial lumen.\textsuperscript{26} A small study has correlated IMR to LVEF and elevation of cardiac biomarkers after STEMI.\textsuperscript{53}
Most recently, the OxAMI-PICS0 study found that IMR-guided treatment was associated with reduced infarct size at six months; however, the study was small and used a historical cohort control. Presently the relationship of IMR to harder clinical outcomes is unknown.

**Cardiac magnetic resonance imaging**

The degree of MVO detected by advanced imaging portends worse prognosis with respect to mortality and LV remodeling, independent of the size of infarct. Specifically, the extent of MVO assessed by CMR several days after percutaneous coronary intervention (PCI) in the setting of STEMI correlates well with mortality and heart failure hospitalizations within 1 year of the sentinel event. MVO is also associated with more frequent cardiovascular complications after MI, even after controlling for infarct size. Some amount of MVO was observed in 57% of 1688 patients in a pooled analysis of seven PCI trials, markedly greater than the prevalence noted in other studies. However, the time point of several days (24h 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 hours. 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 minutes 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. In a homogeneous population of STEMI patients undergoing primary PCI, Nijveldt et al, found that late MVO was the most powerful predictor of regional and global LV functional recovery compared to 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.

An important study by Mather et al. illustrated that 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 to imaging at 2 days.

**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 in dealing with no reflow during PCI. (Table 1). Distal coronary administration of the vasodilator therapies through a microinfusion catheter may be preferred in order to avoid systemic side effects of injection through the guiding catheter.
While no reflow during STEMI is common, management with the therapies described below may be equally effective in restoring normal epicardial coronary flow.\textsuperscript{66}

Adenosine induces muscle relaxation in the coronary microcirculation.\textsuperscript{67} The use of adenosine as adjunctive therapy to reperfusion during STEMI was evaluated in the AMISTAD I trial.\textsuperscript{68} Administration of adenosine within 6 hours of STEMI onset, reduced infarct size compared to placebo in patients receiving fibrinolitic therapy. The later AMISTAD II trial,\textsuperscript{69} found that adenosine did not improve short-term or long-term clinical outcomes during evolving anterior STEMI managed with thrombolysis or primary angioplasty. Later, the REOPEN-AMI trial,\textsuperscript{70} trial showed intracoronary (IC) adenosine improved outcomes over thrombus aspiration alone, with favorable effects on STR. Meta-analyses have offered conflicting results on hard clinical efficacy, though all suggest possible improvement in surrogate measures of microvascular dysfunction (i.e. TIMI grade flow, STR;\textsuperscript{71-73} only with the adenosine intervention group. 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 1.

The recent REFLO-STEMI trial\textsuperscript{74} calls into question the benefit of adenosine and sodium nitroprusside on delayed microvascular injury. STEMI patients undergoing primary PCI with observed TIMI grade 0/1 flow, infarct size and MVO assessed at 48-96 hours post-PCI by CMR were not decreased by adenosine or sodium nitroprusside. There was a slight increase in major adverse cardiac events (MACE) at 30 days and 6 months with adenosine.

The 2017 European Society of Cardiology (ESC) guidelines for the management of STEMI state that GP IIb/IIIa inhibitors may be considered for bailout if there is evidence of no-reflow or a thrombotic complication during coronary angiography (Class IIa recommendation, Level of evidence: C). In the comparison of IC vs IV abciximab administration during emergency reperfusion of STEMI trial (CICERO), STEMI patients undergoing primary PCI with thrombus aspiration evidenced improved MBG and smaller enzymatic infarct size with IC abciximab.\textsuperscript{75} In another study, IC bolus of abciximab during primary PCI for STEMI reduced the MVO observed on CMR.\textsuperscript{76} However, the strategy of using GP IIb/IIIA inhibitors when large thrombus burden or no-reflow is perceived angiographically has not been studied in a randomized controlled trial. Routine use of GP IIb/IIA inhibitors is currently not recommended or supported by clinical data.

Nonpharmacological therapy
Presence of a thrombus presents a major differentiator between experimental models of no reflow and clinical scenarios. PCI itself may provoke embolization of thrombotic debris, leading to development of embolic no reflow. Data from the ATTEMPT investigation support the use of thrombus aspiration during PCI for STEMI patients However, routine aspiration thrombectomy prior to primary PCI was not correlated with improvement in long-term survival or clinical outcomes in a recent meta-analysis.\textsuperscript{77} Hence, the ESC does not recommend routine thrombus aspiration; the procedure may be considered in cases of large residual thrombus burden after opening the culprit vessel with a balloon or guidewire.

Systematic analysis of randomized trials suggests that anti-embolic devices do not reduce early mortality or reinfarction rates during primary PCI for MI.\textsuperscript{78} A recent study\textsuperscript{79} found that 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 to conventional PCI. Nevertheless, long-term outcomes with such devices remain unclear.\textsuperscript{80}
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 be 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 the 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 significance of timing of the “no-reflow” phenomenon may help to explain the disappointing results of several adjunctive pharmacological therapies with respect to meaningful clinical outcomes in ischemic heart disease. 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.
### Table 1. Pharmacological therapies commonly used in managing no reflow during PCI.

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<tr>
<th>Intervention</th>
<th>Mechanism</th>
<th>Pertinent literature</th>
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<tr>
<td>Sodium nitroprusside</td>
<td>Activation of guanylate cyclase, resulting in smooth muscle relaxation and vasodilation</td>
<td>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 to tirofiban alone.(^{81}) 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.(^{82}) Another analysis found that intracoronary administration significantly reduces incidence of MACE.(^{83})</td>
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<tr>
<td>Calcium channel blockers (nicardipine, verapamil, diltiazem)</td>
<td>Elicits smooth muscle relaxation and vasodilation</td>
<td>Non-dihydropiridine calcium channel blockers appear to mitigate no reflow and 6-month MACE in a meta-analysis of randomized controlled trial data.(^{84}) An intracoronary combination of nicardipine and adenosine was found to be safe and effective in reducing angiographic no reflow during rotational atherectomy.(^{85}) However, a Cochrane review found no evidence to support verapamil as no-reflow treatment with respect all-cause mortality, non-fatal myocardial infarction, angiographic no-reflow in patients with acute coronary syndromes.(^{86})</td>
</tr>
<tr>
<td>Adenosine</td>
<td>Elicits smooth muscle relaxation in the coronary microcirculation; antiplatelet activity</td>
<td>The REOPEN-AMI trial,(^{70}) aimed to determine whether intracoronary (IC) adenosine or sodium nitroprusside after thrombus aspiration improve outcomes over thrombus aspiration alone. 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 hour infusion thereafter) and heparin (5000 IU) bolus given prior to PCI. The primary endpoint measured was ST segment resolution (STR) on ECG at 90 minutes post-PCI. Adenosine, but not nitroprusside, improved STR, although angiographic microvascular obstruction (MVO) (TIMI flow grade &lt;2 or 3 and myocardial blush (MBG) grade &lt;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(^{87}) revealed lower incidence of CHF, MI, and death with adenosine. Improved remodeling of the LV was observed.</td>
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<tr>
<td>GP IIb/IIIa receptor inhibitors</td>
<td>Inhibition of platelet aggregation and adhesion</td>
<td>In the CICERO trial, STEMI patients undergoing primary PCI with thrombus aspiration had improved MBG and smaller enzymatic infarct size with IC abciximab use.(^{75}) IC bolus of abciximab during primary PCI for STEMI reduced MVO observed on CMR in another study.(^{76})</td>
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**Abbreviations:** ECG- electrocardiogram; LVEF- left ventricular ejection fraction; STR– ST segment resolution; GP IIb/IIIa – glycoprotein IIb/IIIa
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