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The Phenomenon of No-Reflow: Physiological Processes and Management

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ABSTRACT

The no-reflow phenomenon is a serious microvascular complication characterized by inadequate myocardial perfusion despite successful restoration of epicardial coronary artery patency, most commonly following percutaneous coronary intervention (PCI) in acute coronary syndromes. This phenomenon is multifactorial in origin, involving microvascular obstruction due to distal embolization, ischemia–reperfusion injury, endothelial dysfunction, inflammation, and microvascular spasm. No-reflow is associated with larger infarct size, impaired left ventricular function, malignant arrhythmias, and increased short- and long-term mortality. Early recognition and prompt management are crucial, as timely pharmacological and mechanical strategies may partially restore microvascular flow and improve clinical outcomes..

Keywords: *No-reflow phenomenon; microvascular obstruction; percutaneous coronary intervention; myocardial reperfusion; acute myocardial infarction; coronary microcirculation.*

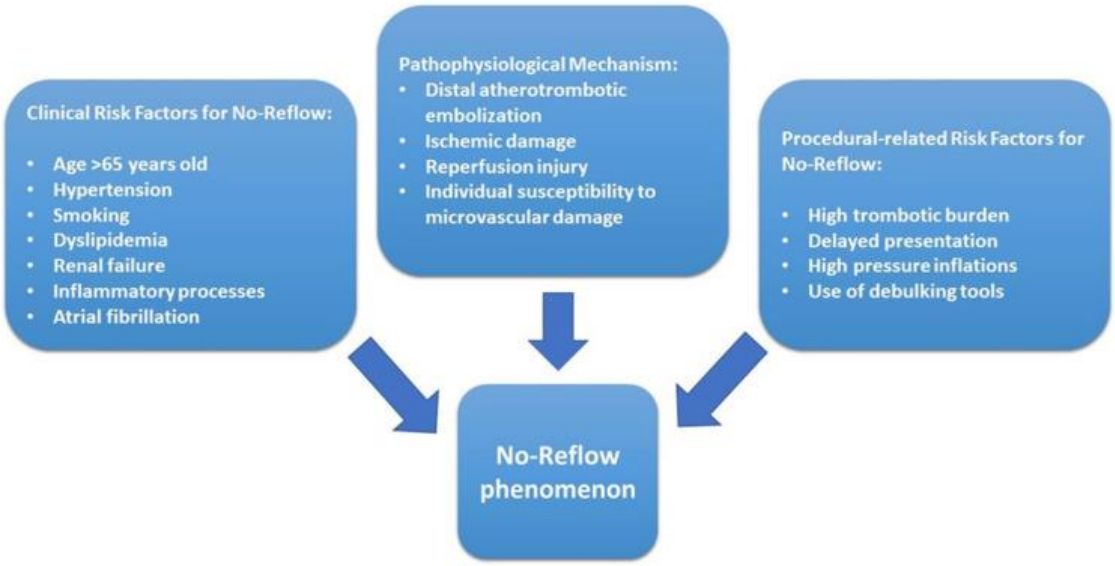
1. INTRODUCTION

Acute myocardial infarction with ST-segment elevation (STEMI) and other cardiovascular disorders are leading killers in developed nations. According to the latest worldwide recommendations from the European Society of Cardiology (ESC), the reperfusion technique recommended for patients with STEMI is primary percutaneous angioplasty (pPCI). Coronary reperfusion may still be inadequate (TIMI score <3) even after culprit vascular patency has been restored; this means that the damaged coronary artery may have delayed, partial, or nonexistent coronary flow (1).

This condition, known as "no-reflow" (NR) or microvascular obstruction (MVO), may exacerbate as many as 60% of STEMI cases, while it can resolve on its own in around 50% of instances. The structural and functional changes that cause NR in the coronary microcirculation might happen in either a patient with acute coronary syndrome or a patient who is stable. Furthermore, it is a standalone predictor of myocardial infarction and mortality, and it is linked to an elevated risk of rehospitalization, negative ventricular remodeling, malignant arrhythmias, and heart failure. Heart disease risk factors included being over the age of 65, having high blood pressure, smoking, having dyslipidemia, diabetes, kidney failure, inflammatory processes, and a history of atrial fibrillation. Procedural factors included having an increased thrombotic load, delayed presentation, high-pressure inflations, and debulking devices (2).

2. PHYSIOLOGICAL PROCESSES

NR is associated with changes in the structure and function of the coronary microcirculation, and four primary pathophysiological pathways have been identified: microvascular damage susceptibility, reperfusion injury, ischemia damage, and distal atherothrombotic embolization (Figure 1). During both the acute and procedure stages, a complex atherosclerotic plaque may cause distal embolization phenomena. This, in turn, might raise distal vascular resistance and cause more microinfarcts, which in turn encourage the production of chemicals that are both pro-inflammatory and vasoconstrictive (3)



The NR phenomenon was initiated by a multitude of causes, as shown in Figure 1 (4).

The length of time that an area is under ischemia has a direct correlation to how bad the ischemic damage is. Interstitial edoema, reduced nitric oxide generation, and microcirculation blockage promoted by vascular endothelial growth factor (VEFG) release that increases vascular permeability are all outcomes of ischemic injury. Cardiomyocytes and endothelial cells die as a consequence. In contrast, reperfusion injury occurs when damaged microcirculation suddenly receives blood flow again, damaging cardiomyocytes directly and triggering an inflammatory response that releases vasoactive substances, proteolytic enzymes, inflammatory cytokines, and free oxygen radicals. Microvascular dysfunction and no-reflow are more likely in those with a history of endothelial dysfunction or who have certain genetic alterations, such as the 1976TC polymorphism in the adenosine receptors and ion channel genes (5).

Undiagnosed Reflow

The most common way to diagnose NR is with coronary angiography during percutaneous coronary intervention (pPCI). This technique uses TIMI flow classification, which allows for the categorization of coronary flow on a scale from 0 (no flow) to 3 (normal flow). Alongside this, the TIMI frame count assesses how many frames are needed for the contrast agent to fill the coronary artery distalities. A proxy measure of NR is the total number of frames. Myocardial "blush" (MBG) evaluations were later included as an additional angiographic evaluation due to this one's low sensitivity and specificity. In reality, blush evaluates the speed with which contrast medium impregnation diminishes after injection into the epicardial coronary arteries and the intensity of myocardial tissue radiopacity. According to Ndrepepa and Kastrati (6), MBG may be used to diagnose NR when the value is between 0 and 1.

In contrast, flow or resistance metrics allow for a more precise intrusive evaluation. Factually, in the absence of epicardial stenosis, the microcirculation may be understood by calculating coronary flow reserve (CFR), which is the ratio of coronary flow at peak hyperemia to coronary flow at rest. A sensitivity of 79% was found to be connected with the existence of MVO when the value was less than 2.0. The characteristic flow pattern of NR, which includes early retrograde systolic flow and quick deceleration of diastolic flow, may also be detected by measuring the coronary blood flow velocity using intracoronary Doppler guidance. An evaluation of microcirculation that is not dependent on hemodynamic variables is provided by the microvascular resistance index (IMR), which is derived from the thermodilution principle and is defined as the product of the distal coronary pressure and the mean transit time of a bolus during maximum hyperemia with the use of a dual pressure and temperature guide. According to Annibali et al. (4), a post-procedure IMR more than 40 units has been linked to an increased risk of in-hospital complications, death, and readmission for heart failure at 1-year follow-ups. Additionally, an IMR value greater than 25 is connected with the existence of MVO.

In contrast, Doppler flow velocity is used to quantify flow in IMR under maximum hyperemia; results greater than 2.5 mmHg/cm/s indicate MVO. Recent research on angiography-derived IMR (IMRangio) has shown that it accurately predicts the existence of significant MVOs on cardiac MRI and an IMR > 40 units, two important diagnostic markers. Another innovative tool is the CorFlow TherapyTM (CoFlTM) system, which allows for the simultaneous administration of intracoronary medicines and real-time evaluation of microvascular function. This device measures distal pressure beyond balloon occlusion at the same time as it inflates the balloon to identify transitory coronary occlusion. It then incrementally injects crystalloid at a specified flow rate. Dynamic microvascular resistance and real-time microvascular malfunction detection are both made possible by the flow and pressure quotient. Positive safety, applicable, and rapid detection of MVO

after pPCI are some of the early outcomes of the MOCA I study, which was first validated in a pig model (7).

Without a doubt, the "gold standard" for NR diagnosis is gadolinium-enhanced cardiovascular MRI. The risk of death within a year is 1.14 times higher for every 1% increase in the extent of MVO. The endocardial nucleus does not get gadolinium enhancement because the coronary microvasculature becomes clogged by erythrocytes, neutrophils, and cellular debris. Various approaches, such as delayed gadolinium contrast enhancement (DGE) and T2-weighted imaging, may be used by cardiac magnetic resonance (CMR) to visualize myocardial damage (8).

Furthermore, by evaluating changes in T1, T2, and T2* release timings as well as extracellular volume, new parametric mapping methods enable precise measurement of cardiac injury. T2 sequences not only help identify regions of intramyocardial hemorrhage (IMH), but they are also essential for differentiating between acute and chronic myocardial infarction (edema usually goes away around four to six weeks after infarction). Ischemic myocardial infarction (IMF) is strongly linked to unfavorable outcomes and left ventricular remodeling regardless of infarct extent. Due to the presence of hemoglobin breakdown products, regions with attenuated signal inside high-signal edematous areas on T2-weighted images represent IMH. The contrast graphic approach is necessary for the detection of MVO locations (9).

Areas with increased extracellular/interstitial volume, such as necrosis (in the acute phase) or fibrosis (in the chronic phase), cause gadolinium to take longer to wash out because of its extravascular and extracellular distribution. To observe the myocardial ventricular outflow (MVO), which is a dark, hypointense region surrounded by the hyperintensity of necrotic myocardium, DGE is evaluated in T1-weighted images 10-15 minutes after gadolinium administration. As an alternative, T1-weighted acquisitions are carried out immediately after the injection of contrast medium (after 1-3 minutes) in early contrast graphic impregnation, a contrast-dependent approach. A thrombus or MVO is located in an area with a low signal strength. Last but not least, another contrast-dependent approach that can identify even tiny regions of MVO is the first-pass perfusion (FPP) method (10).

Fast pulse positron emission (FPP) imaging is a dynamic research that relies on seeing the temporal distribution of the paramagnetic contrast agent bolus during the first pass at the level of coronary microcirculation. Due to altered capillary microcirculation, a perfusion defect is consequently shown as an area of contrast graphic failure to impregnate cardiac tissue. On the other hand, FPP's predictive value is worse than DGE's, perhaps because FPP can also identify localized MVO (4).

It is possible to diagnose NR using an electrocardiogram (ECG). It is suggestive of NR if, 60 to 90 minutes after reperfusion, the ST-segment elevation resolution is less than 50% or 70%, according on the chosen cut-off. Nuclear imaging using positron emission tomography and single-photon emission computed tomography, as well as contrast-enhanced echocardiography, are further diagnostic tools used to evaluate NR. NR is detected by regions of hypoperfusion in contrast-enhanced echocardiography, a test that may be done at the patient's bedside after microbubbles of inert gas are usually delivered intravenously. According to Dawson et al. (11), these strategies are not as appealing for regular NR evaluations due to their lack of sensitivity and/or difficulty of implementation.

Management

Despite NR's long history of recognition, treatments that have shown promise in animal models have relatively limited success when applied to people, yielding positive effects on surrogate endpoints but little change in outcomes like cardiovascular mortality. To this day, intracoronary medicines that cause coronary artery vasodilation remain the mainstay of NR therapy. Potentially effective medications include vasodilators like adenosine, calcium channel blockers, and sodium nitroprusside, as well as antiplatelet medications such glycoprotein IIB/IIIA inhibitors. No therapy, alone or in combination, has been found to significantly improve clinical outcomes when it comes to reducing ischemia/reperfusion injury. This includes nonpharmacologic treatment strategies like coronary post-conditioning, remote ischemic conditioning, and tools to decrease embolization of thrombotic material and increase coronary flow (12).

Pharmaceutical therapy

• Antagonists

Protecting cardiomyocytes and extending infarcts have been the primary outcomes of research into this class of medicines. Nevertheless, pre-reperfusion administration of metoprolol decreased infarct extent and NR incidence in many animal models, suggesting an anti-inflammatory effect via suppression of neutrophil-platelet aggregation formation. Results showed that pre-PCI administration of metoprolol, which had a time-dependent action, decreased infarction extent, prevented adverse left ventricular remodeling, preserved systolic function, and decreased the rate of rehospitalization for heart failure, according to the METOCARD-CNIC study. Subsequent research by Niccoli et al. (13) found that metoprolol modulated the effect of neutrophils on MVO, suggesting that the two drugs interacted with one another and neutrophil count.

On the other hand, the EARLY-BAMI trial did not find any evidence of a decrease in infarct extension at 1 month in patients treated with intravenous metoprolol before percutaneous coronary intervention (pPCI), which is less appealing data. Some of the reasons mentioned were variations in medication dose, time of administration, and the specific patient group being studied (14).

Other compounds, including nebivolol and carvedilol, have shown that they can preserve the coronary microcirculation. Patients with ST-elevation myocardial infarction (STEMI) who are having percutaneous coronary intervention (pPCI) and who do not exhibit symptoms of acute heart failure are should be administered intravenous beta-blockers according to recent ESC recommendations (15).

Potential potassium channel blockers

One way to treat no-reflow is with calcium channel blockers (CCBs), such as verapamil, diltiazem, or nicardipine. Coronary vasodilation and smooth muscle relaxation are outcomes of their channel binding on vascular smooth muscle, cardiac myocytes, and nodal cells. Benefits of NR therapy for verapamil and diltiazem have been shown, with superior results in those treated intracoronary, despite various limitations of selection and measures. For the prevention of no-reflow, nicardipine has shown greater results when combined with rotational atherectomy. Nevertheless, there is a lack of evidence on CCBs that would indicate a substantial improvement in no-reflow (2).

1. Sodium nitroprusside

Nitric oxide, an active form of the non-selective medication sodium nitroprusside, is a powerful vasodilator in the peripheral and coronary microcirculation and in the prevention of platelet aggregation. Compared to other vasodilators, its onset of effect seems to be later. In addition, it has achieved a higher rate of left ventricular ejection fraction without significantly changing TIMI grade, a lower rate of adverse events, an improvement in TIMI frame count, and a more rapid resolution of ST-segment elevation compared to drugs like tirofiban. Despite the lack of evidence for NR's preventative capabilities, nitroprusside was shown to have decreased rates of revascularization, myocardial infarction, and mortality compared to placebo during 6-month follow-up. Nonetheless, it was essential for a more precise evaluation of nitroprusside's NR-prevention capabilities (16).

• Adrenergic

Intracoronary epinephrine is one of the pharmacological options available; it has less experience than some of the others, but it has lately shown promising results in treating NR that has not responded to other treatments or in cases where they are not applicable. The safety and effectiveness of epinephrine in non-respiratory STEMI patients compared to those receiving standard treatment were examined in the 2020 publication of the RESTORE trial, an observational research including many centers. Refractory NR patients with STEMI showed statistically significant improvements in coronary flow, left ventricular ejection fraction, ST-segment resolution, and clinical events after 30 days compared to the control group. Recent publications from the open-labeled COAR trial showed that intracoronary epinephrine enhanced end coronary flow and was relatively safe for normotensive individuals with acute coronary syndrome compared to adenosine. The development of malignant arrhythmias is the primary concern while using epinephrine. As shown in Figure 2, a situation where the center does not handle refractory reflow management (17).

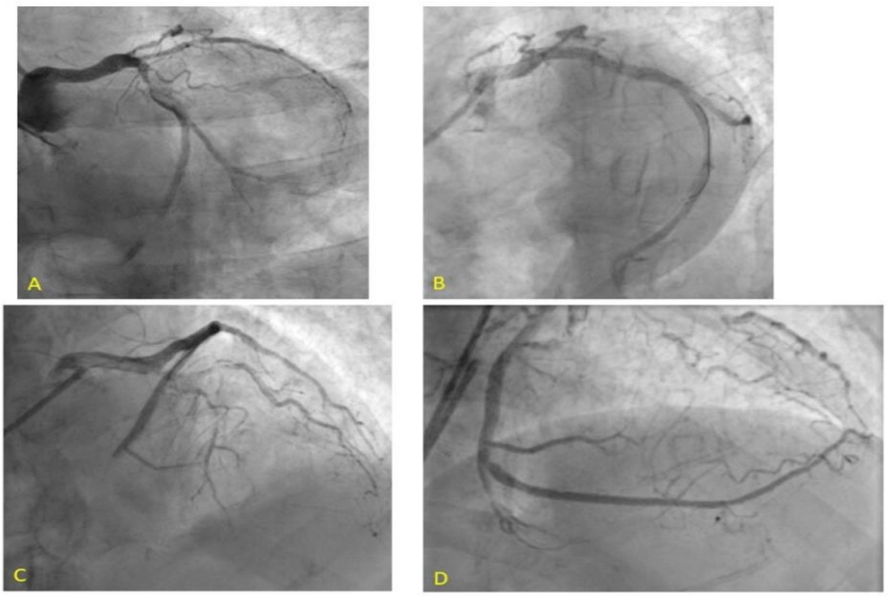


Figure 2: Our center's care of a refractory no-reflow case. A left circumflex coronary artery (A) thrombotic sub blockage and inferior-posterior STEMI were seen in a 93-year-old patient. Subsequent to effective thrombus aspiration and stenting (B), intracoronary epinephrine (D) alleviated the no-reflow phenomena, bradycardia, and hypotension that had developed (C). (4)II

• Nicoporandil

Nicorandil is a medication that widens blood vessels by influencing intracellular concentrations of cyclic GMP and potassium channels. As a result of its positive effects on myocardial perfusion and reduced no-reflow rates, it is prescribed to patients in Japan and other Asian and European nations experiencing acute coronary syndromes for the treatment of angina pectoris (18).

• Blood-thinning medication

Regarding the major antiplatelet drugs, sub-analysis of the PLATO study found no NR or myocardial perfusion benefits. This was in accordance with the results of the ATLANTIC study and the REDUCE-MVI study, which measured the effectiveness of ticagrelor in reducing microvascular dysfunction in acute myocardial infarction (19).

But new data from the PLEIO trial shows that ticagrelor is more effective than clopidogrel in restoring microcirculation function. This confirms what a previous meta-analysis found: ticagrelor reduces NR and incidence of MACE more effectively than clopidogrel, with no discernible increase in the risk of bleeding. Cangrelor, an innovative antiplatelet drug, was waiting for results from the PITRI study, which tested whether or not it might decrease the extent of acute myocardial infarction and myocardial vascular occlusion (MVO) as measured by CT (20).

Prior to the widespread use of dual antiplatelet medication, glycoprotein IIB/IIIA inhibitors were effective antiplatelet medicines that prevented platelet aggregation. Adding glycoprotein IIB/IIIA inhibitors to conventional treatment has been shown to provide compelling advantages in studies conducted so far. Nevertheless, according to the On-TIME-2 research (21), bolus tirofiban started before hospital arrival might enhance clinical outcomes during percutaneous coronary intervention (pPCI) and lead to ST-segment resolution.

Information on the intravenous or intracoronary route of delivery is also contradictory. Despite the positive effects of intracoronary abciximab administration on reducing infarct area in the CICERO trial and the INFUSE-AMI study, the AIDA STEMI study found no difference in the rates of major adverse cardiovascular events after 90 days and 1 year between the two administration modalities (22).

Recently, a cohort of 71 STEMI patients treated with pPCI shown that NR rates were lowered when glycoprotein IIB/IIIA inhibitors were used in conjunction with aspiration and balloon inflation. At last, if there is evidence of NR or thrombotic consequence, recent ESC recommendations state that GP IIb/IIIa inhibitors should be evaluated (class of recommendation IIa, degree of evidence C) (23).

intracoronary fibrinolysis

Research on fibrinolytic treatment is also ongoing. When it came to myocardial reperfusion, in reality, it had not validated the preliminary promising findings that had shown advantages. One such study is the randomized T-TIME experiment, which found that intracoronary alteplase at low doses did not enhance MVO. Thus, the available evidence does not yet support its use as an adjuvant treatment to enhance NR. Yet, a recent meta-analysis by Alyamani et al. shown that a targeted thrombolytic IC strategy seems to be both safe and capable of increasing the effectiveness of percutaneous coronary intervention (pPCI) (24).

• Rations

It seems that statin medication has favorable benefits in the treatment and prevention of NR, perhaps due to pleiotropic effects that are separate from the impact on lipid metabolism. Statin loading at high dosages increased angiographic MVO but did not extend infarct in the STATIN STEMI trial compared to low doses, however infarct extension was not as affected. The results were corroborated by the SECURE-PCI research, which found that high-dose atorvastatin reduced cardiovascular events by almost 50% at 30 days compared to placebo (25).

Furthermore, compared to naïve individuals, those who were already taking statins at the time of the event had lower NR rates, better cardiac functional recovery at follow-up, and less infarction. Table 1 summarizes all of the primary NR pharmaceutical therapies along with their adverse effects (6).

Table 1: Main drugs and dosages for the treatment of No-Reflow (4)

Medication	Dosage	Side Effects
Adenosine	Intravenous: 70 µg/kg/min infusion Intracoronary: 100–200 µg bolus	Bradycardia, hypotension, chest pain, dyspnea
Sodium Nitroprusside	Intracoronary: 60–100 µg bolus	Bradycardia and hypotension

Verapamil	Intracoronary: 100–500 µg bolus (max 1 mg)	Bradycardia, transient heart block
Diltiazem	Intracoronary: 400 µg bolus (max 5 mg)	Bradycardia, hypotension
Nicardipine	Intracoronary: 200 µg (max 1 mg)	Bradycardia, hypotension
Epinephrine	Intracoronary: 80–100 µg bolus	Malignant arrhythmias
Nicorandil	500 µg (max: 5 mg)	Malignant arrhythmias
Streptokinase	250 kU over 3 min	Bleeding
Tenecteplase	5 mg (max: 25 mg)	Bleeding
Tissue plasminogen activator (tPA)	0.025–0.5 mg/kg/h	Bleeding
Abciximab	0.25 mg/kg bolus, then 0.125 µg/kg/min (max 10 µg/min) infusion for 12 h	Bleeding
Eptifibatide	180 µg/kg bolus, then further 180 µg/kg bolus 10 min later, then 2 µg/kg/min infusion for up to 18 h. If CrCl < 50 mL/min, reduce infusion by 50%	Bleeding
Tirofiban	25 µg/kg over 3 min, then 0.15 µg/kg/min infusion for up to 18 h If CrCl < 30 mL/min, reduce infusion by 50%	Bleeding

CrCl: creatinine clearance.

Figure shows an algorithm of management and treatment of the no-reflow phenomenon applied at center (4).

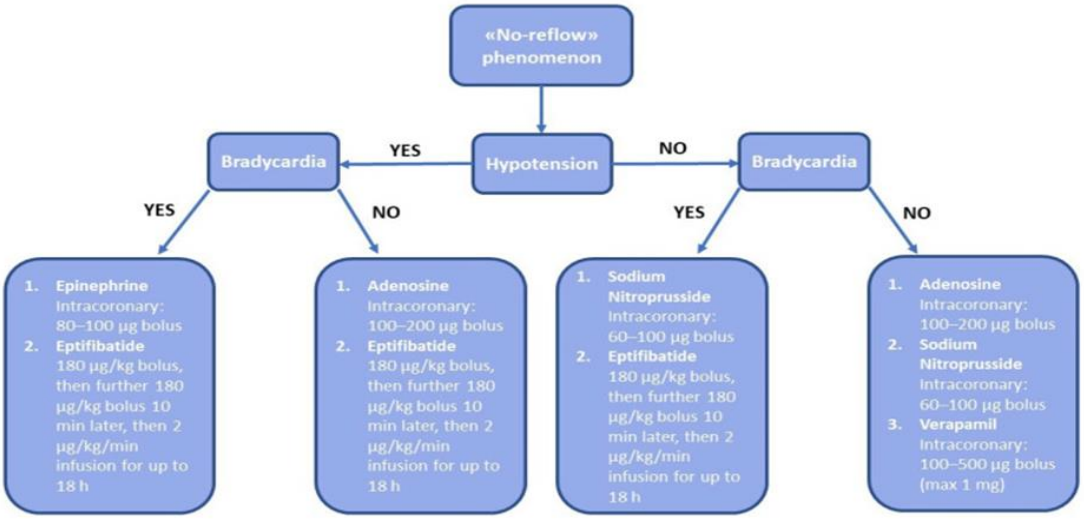


Figure 3: Algorithm of management and treatment of the no-reflow phenomenon applied at our center (4)

Adenosine is a

Adenosine, a nucleoside that is purine in nature, has a short half-life of less than 2 seconds and several pleiotropic effects, such as relaxing smooth muscles and causing the coronary microcirculation to widen by binding to A2 receptors. In addition to exhibiting anti-apoptotic and pro-angiogenic actions, it inhibits platelet aggregation and neutrophil inflammation, enhances ischemia preconditioning by reducing reperfusion damage, and so on. Hypotension, dyspnea, flushing, bronchospasm, and bradycardia with atrioventricular block are among of the side effects (26).

Major cardiovascular events were reduced and left ventricular remodeling was favorable one year after the event in the REOPEN-AMI (Intracoronary Nitroprusside Versus Adenosine in Acute Myocardial Infarction) trial, which showed a

significant improvement in MVO and peak troponin compared with placebo or sodium nitroprusside (17).

complementary and alternative medicine

• Conditioned ischemia

Through repeated cycles of coronary balloon occlusion and reperfusion, ischemic preconditioning is the most effective endogenous mechanism that may lessen the severity of myocardial infarction. Despite this, ischemia preconditioning did not improve clinical outcomes in the most recent CONDI-2/ERIC-PPCI trial. A new randomized experiment confirmed the positive findings of earlier big studies when it came to the incidence of NR caused by extended balloon inflation during stent placement. Results from POST, DANAMI-3-iPOST, POSTEMI, and LIPSIA CONDITIONING do not support the use of ischemic postconditioning in clinical practice, despite the fact that it has been shown to decrease no -reflow (27).

• Phlebitis aspiration

One of the etiopathogenetic processes of NR is distal embolization damage; coronary filters or thrombus aspiration are techniques developed to decrease this risk. While thrombus aspiration was once thought to improve clinical outcomes for STEMI patients, it has now been de-emphasized due to its failure to lower 30-day mortality in trials conducted in later years. In fact, according to the most recent ESC guidelines (recommendation class III) (22), it is even contraindicated as a routine maneuver.

Another mechanical method to decrease distal embolization in STEMI is to use filters, which are devices that are inserted prior to stent deployment. Despite this, there is no evidence that these methods enhance microvascular flow, infarct extension, or clinical outcomes. The device known as pressure-controlled intermittent coronary sinus occlusion (PICSO) was one of the ones that passed the test. The goal of this transitory occlusion device is to increase heart venous pressure and, by extension, microcirculation perfusion by blocking the flow in the coronary sinus. Patients with an IMR greater than 40 were enrolled in the OxAMI-PICSO trial, which examined the use of PICSO before stent release. At 6 months, patients treated with PICSO had less infarction extension compared to the control group (28).

Using saline as a therapy for the no-reflow phenomena during percutaneous coronary intervention

The major treatment objective in patients with ST-segment elevation myocardial infarction (STEMI) is the timely reopening of the infarct-related artery using primary percutaneous coronary intervention (pPCI). Inadequate myocardial perfusion despite successful recanalization of the infarcted associated artery is known as microvascular obstruction (MVO), and it may complicate percutaneous coronary intervention (pPCI) in 30–50% of STEMI cases. If there are no PCI-related problems with the epicardial vessels, a ST resolution (STR) of less than 70% within 60-90 minutes, a TIMI flow of less than 3, and/or a myocardial blush grade (MBG) of 0-1 in the event of a TIMI flow of 3 (8), then myocardial vein occlusion (MVO) can be postulated after percutaneous coronary intervention (pPCI).

Researchers have spent a lot of time trying to figure out how to treat and avoid MVO since it is a big indicator of bad clinical outcomes. While several of the evaluated techniques for ischemia-reperfusion damage did show some improvement, particularly when used in conjunction with one another, this particular approach outperformed the others by a wide margin (29).

A significant void in decision-making arises when no-reflow occurs since ESC guidelines do not provide a particular therapeutic approach for addressing this complication after STEMI and pPCI, taking into account these inconsistent findings on the resolution of MVO. Using the thrombus aspiration catheter, the SALINE approach included injecting saline into the no-reflow channel in a very targeted and aggressive manner. Figure 4 summarizes the SALINE protocol's step-by-step method (30).

The SALINE approach was used after conventional angiography showed no reflow. In Step 1, a thrombus aspiration catheter was used to superselectively inject contrast media beyond the site of stopped flow in TIMI 0 flow, or at the mid coronary artery segment in TIMI 1-2 flow, or normal TIMI 3 but MBG 0-1 in normal TIMI 3. This was done to define distal angiography. (2) After that, the external transducer was attached to the thrombus aspiration catheter so that it could monitor the pressure at its tip while performing a pullback operation. Step 2 included recording an intracoronary pressure reading from the far end of the coronary artery to the near end in order to determine the optimal location for the angiographic pressure decrease. In Step 3, a 10-milliliter bolus of saline solution was manually injected intracoronaryly over the course of three to four seconds using the thrombus aspiration catheter. (5) In order to evaluate TIMI flow, distal angiography was done again. If no reflow was seen, Step 4 was performed two or three times in a row. Step 6 included repeating conventional coronary angiography to determine treatment effectiveness, and Step 5 involved measuring intracoronary pressure from the distal to the proximal coronary channel using a different pullback procedure (30).

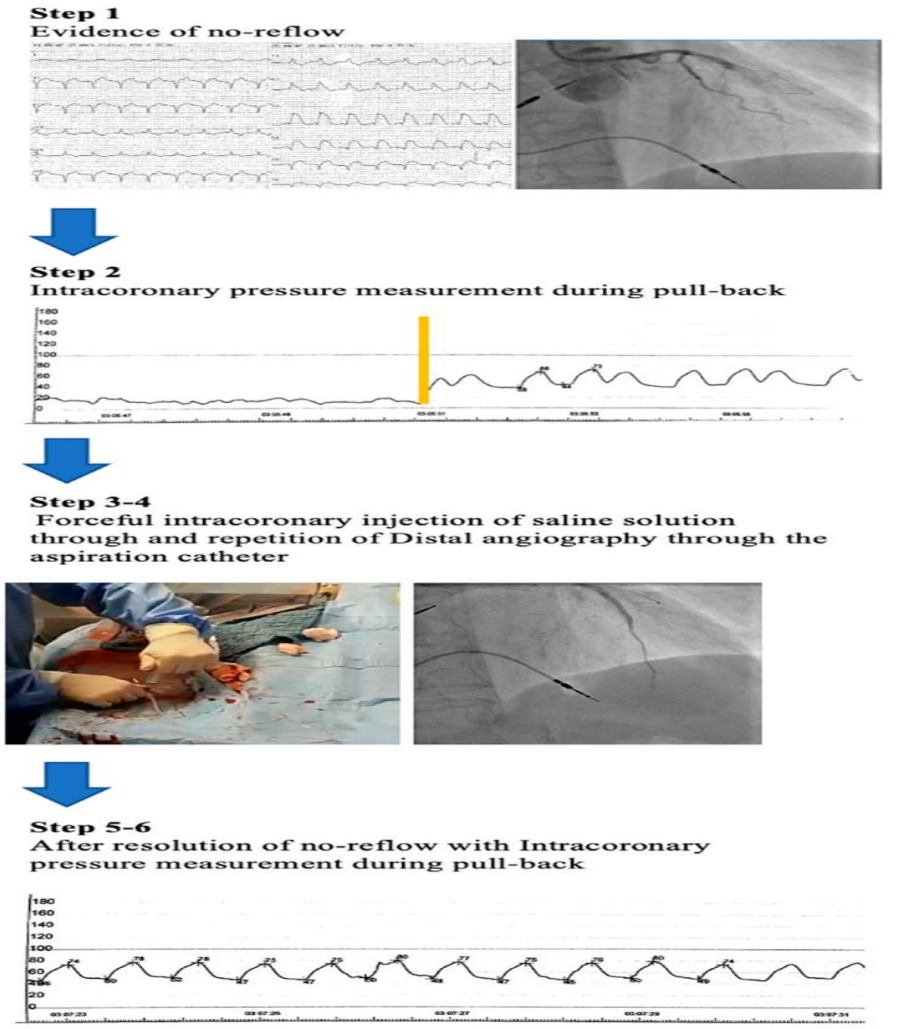


Figure 4: Stepwise flowchart of a successful patient treated using SALINE (30)

Research has shown that in the event of no-reflow after percutaneous coronary intervention (pPCI), the SALINE technique—a super-selective manual forceful injection of saline solution using a thrombus aspiration catheter—is a safe and effective way to restore myocardial perfusion. Either a quick resolution of the ST-segment or normalization of the final TIMI flow in most patients indicates that this method is beneficial (31).

Significant independent risk factors for death and heart failure in the long run after STEMI include ischemia/reperfusion damage, myocardial vascular obstruction (MVO), and ultimate infarct size. Immediate post-PCI diagnosis of MVO is made when post-procedural angiographic TIMI flow is less than 3, TIMI flow equal to 3 when MBG is less than or equal to 1 (angiographic MVO), or when ST resolution is less than 70% within 60-90 minutes after the operation. Despite cardiac magnetic resonance (CMR) being the go-to for measuring myocardial vascular oxygen saturation (MVO) and infarct size, other invasive and flow-related metrics measured just after percutaneous coronary intervention (pPCI), including TIMI flow grade and invasive magnetic resonance imaging (IMR), shown a strong association with MVO as identified by CMR (32).

Optimal treatment method for no-reflow post-pPCI remains contentious due to the lack of consensus reached in several clinical and randomized studies that compared various approaches. Gupta and Gupta (33) found that individuals with early start of symptoms had a larger improvement in microcirculatory perfusion after intracoronary injection of adenosine compared to nitro prussiate. This improvement was measured by the resolution of ST-segment elevation.

These findings provide significant evidence against doctors avoiding reperfusion damage during percutaneous coronary intervention (pPCI) by administering a large dosage of intracoronary adenosine. The use of epinephrine improved coronary flow patterns and increased the prevalence of ST-related complications by more than 70% compared to SC alone (75.0% vs. 28.5%), according to a recent multicenter observational study. There was also a significant decrease in the composite of death and heart failure within 30 days, and the left ventricle ejection fraction improved early after percutaneous coronary intervention (pPCI) (30).

Although several theories are likely involved in the ultimate outcome, the pathophysiological mechanism of action of the SALINE approach is still unclear. It is possible that the quick wash-out of osmotically active molecules from the interstitial space is the basis of SALINE's effectiveness, which is improved by strong, super-selective, and repeated saline injection. This, in turn, considerably enhances the clearance impact on interstitial edema. Another possible outcome of forceful perfusion is the initiation of vasomotor adjustments in coronary tone as a myogenic response to changes in intraluminal pressure. However, Candreva et al. (34) note that the processes of intracoronary saline-induced hyperemia remain unknown.

New research suggests that using a specialized intracoronary infusion catheter (RayFlow®) to induce hyperemia with saline causes intravascular hemolysis in the local area. Local release of vasodilatory compounds like ATP or NO is likely to cause microvascular dilatation in that specific area. Nevertheless, Gallinoro et al. (35) showed that the hyperemic effect did not occur when saline was administered via a single distal hole from the same microcatheter or at lower infusion rates.

The final myocardial flow could have been increased due to the dilation of these distal tiny arterioles (~120 μm) caused by the injection of intracoronary adenosine prior to SALINE administration. The metabolic aspects of the GpIIb/IIIa inhibitors may not have affected the restoration of coronary blood flow after no-reflow, but major tissue pressure and myogenic small vessel regulation likely had a far larger role in restoring myocardial blood flow. Last but not least, it is challenging to determine in post-no-reflow studies whether endothelial and neurohumoral variables facilitate or modulate the restoration of cardiac flow (30).

Safety, cheap cost, and facility applicability are the benefits of a procedure based on the injection of saline. Many intracoronary drugs, such epinephrine and others that don't seem to be well-tolerated, have adverse effects that may be mitigated by using SALINE, as somewhat discussed before. Safety, cheap cost, and facility applicability are the benefits of a procedure based on the injection of saline. While certain intracoronary drugs, such epinephrine, do not seem to be well-tolerated, the administration of SALINE mitigates their adverse effects (36).

To sum up, the SALINE approach is an affordable, straightforward, safe, and promising strategy that should be used in all catheterization laboratories. Significant improvements in TIMI flow grade and STR indicate that SALINE is a safe and effective method to address the "no-reflow" problem in STEMI patients treated with pPCI. whether we want to know whether this method works, if it can be replicated, and if it will improve prognoses, we need to do randomized control trials (30).

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