State of the Art
No-Reflow Phenomenon

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KEYWORDS

• No-reflow • Primary PCI • Microvascular obstruction

KEY POINTS

- The term no reflow describes inadequate myocardial perfusion of a given segment without angiographic evidence of persistent mechanical obstruction of epicardial vessels.
- No reflow represents an independent predictor of death and myocardial infarction.
- Several strategies have been tested to treat the no-reflow phenomenon but none has been shown to be effective to revert it.

INTRODUCTION

The term no reflow refers to a state of myocardial tissue hypoperfusion in the presence of a patent epicardial coronary artery.[1] The underlying mechanism is microvascular obstruction (MVO). It can typically occur during primary percutaneous coronary intervention (PCI) in the setting of acute myocardial infarction (AMI) or, less frequently, during a PCI on a non–infarct-related artery.[2]

The coronary no-reflow phenomenon is an independent predictor of adverse clinical outcomes after AMI regardless of infarct size and is associated with heart failure, increased mortality, and malignant arrhythmias.[3,4] The incidence of the no-reflow phenomenon varies widely depending on available studies, patient complexity,[5,6] and the diagnostic methods used.

PREDISPOSING FACTORS

Several cardiovascular risk factors have been identified to portend a higher risk of no reflow, such as hypertension, smoking, dyslipidemia, diabetes, renal insufficiency, and other inflammatory processes.[7,8] Recent studies investigating the relationship between the inflammatory profile and the no-reflow phenomenon showed that elderly patients (>65 years old) have higher rates of no reflow, owing to their pronounced proinflammatory state.[9]

The concept that a higher thrombotic burden is associated with a higher risk of slow/no reflow has been confirmed by Kaya and colleagues,[10] showing that the presence of atrial fibrillation is associated with a 2-fold increase of risk to develop no reflow in patients with ST-segment elevation myocardial infarction (STEMI). However, other

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patient-specific factors are more closely related to the no-reflow phenomenon, such as delayed presentation to the catheterization laboratory during STEMI.[11] Based on this, evidence has been accumulated that a shorter door-to-balloon time is associated with less myocardial injury and a lower incidence of no reflow.[12]

Polymorphisms of the gene coding for vascular endothelial growth factor A were shown to be associated with impaired microvascular tone.[13]

Barman and colleagues[14] showed an association between CHA2DS2-VASc (congestive heart failure; hypertension; age $\geq$75 years; diabetes mellitus; prior stroke, transient ischemic attack, or thromboembolism; vascular disease; age 65–74 years; sex category) score and a higher risk of no reflow in patients with non–ST-elevation myocardial infarction undergoing PCI.

MECHANISMS OF NO REFLOW

The no-reflow phenomenon was first described by Krug and colleagues[15] in 1966. Later, it was shown in experimental animal models that prolonged ischemia impairs perfusion and leads to damage of the arterial microvasculature, which is proportionally greater for longer time periods of ischemia.[16] Such impairment is caused by the swelling of endothelial cells of the small blood vessels leading to obstruction and consequent slow flow. As a consequence of the ischemia-reperfusion damage, the endothelial dysfunction, and the distal thromboembolism, the clearance of debris by macrophages is inhibited and this event results in poor healing of the infarcted area and adverse remodeling.[17] Infarct size is a major determinant of patients' prognosis and is associated with clinical events and cardiovascular mortality.[18] The angiographic feature of no reflow was first reported by Bates and colleagues[19] as abnormal slow antegrade flow of contrast in a culprit vessel, whereas the first clinical case of no reflow during PCI for myocardial infarction (MI) was reported by Feld and colleagues[20]. It has been widely shown that the no-reflow phenomenon is significantly correlated with poor clinical outcomes and, although advances in interventional techniques have reduced its incidence,[21] still represents an independent predictor of death and MI.[3,4]

Distal embolization has been identified as one of the most intuitive causes of no reflow. Thromboembolic material can originate from epicardial coronary thrombus and from fissured plaques during primary PCI (pPCI).[22] As an experimental confirmation of this, old studies have shown that myocardial blood flow decreases irreversibly when microspheres obstruct more than 50% of coronary capillaries.[23] Another mechanism subtending the no-reflow phenomenon has been identified with prolonged ischemia. The ischemic injury produces morphologic changes of the endothelial cells (protrusions and membrane-bound bodies), which can contribute to luminal obliteration. The consequent loss of vascular tone causes extravasation of erythrocytes, resulting in interstitial edema further compressing the microvascular circulation.[15] Reperfusion after ischemia represent a traumatic stage for coronary microcirculation, with platelets and neutrophils extensively infiltrating it and forming aggregates that obstruct capillaries and consequently block flow.[24] Reperfusion-related injury develops from this step, with activated neutrophils releasing oxygen free radicals and proinflammatory mediators that can directly cause tissue and endothelial damage. Also, damaged endothelial cells, neutrophils, and platelets contribute to sustained vasoconstriction of coronary microcirculation.[25]

Therefore, based on the underlying mechanisms, 2 types of no reflow can be identified: structural and functional no reflow.

Structural no reflow occurs when microvessels within the necrotic myocardium region under prolonged ischemia show damage and loss of capillary integrity with endothelial swelling, edema, and MVO. Structural no reflow is largely irreversible.[26]

Functional no reflow is observed when the patency of microvasculature is compromised because of spasm, microthrombotic embolization, and reperfusion injury, with accumulation of neutrophils and platelets and activation of the neurohumoral system. At variance with the structural counterpart, functional no reflow may be reversible to a varying degree.[26]

DIAGNOSTIC METHODS

Angiographic Methods

Not all no-reflow types are created equal. The causes subtending this phenomenon can be various and multifactorial, and their identification has an effect on the following therapeutic options. The classification of different grades of angiographic coronary blood flow has been established according to the Thrombolysis in Myocardial Infarction (TIMI) scale.[27] No reflow can initially be shown by the analysis of TIMI flow grade. TIMI flow grade 0 to 2, observed in 5% to 10% of patients, is predictably associated with no reflow. However, no reflow also occurs in a sizable proportion of patients with apparently successful large epicardial vessel reopening resulting in TIMI

flow grade 3, caused by microvasculature and not epicardial vessel involvement. In addition to the TIMI scale, another imaging technique can be useful to confirm the angiographic diagnosis and assess myocardial microvasculature, and this is the myocardial blush grade (MBG).[28] With this method, angiographers assess the myocardial tissue opacification intensity with longer angiographic runs, performed until the venous phase of contrast passage. According to visual or computerized signal intensity automatic assessment, myocardial blush is graded using a scale with 4 intensity grades: 0, no myocardial blush; 1, minimal myocardial blush or contrast density; 2, moderate myocardial blush or contrast density, but less than that obtained during angiography of a contralateral non–infarct-related coronary artery; 3, normal myocardial blush or contrast density, similar to that obtained during angiography of a contralateral non–infarct-related coronary artery. Using the combined angiographic criteria of TIMI and MBG, no reflow can be classified as TIMI flow grade less than or equal to 2 and with MBG from 0 to 1.

Non Angiographic Methods

Several noninvasive diagnostic methods have been shown to be able to identify MVO, among them ST resolution at electrocardiogram (ECG), myocardial contrast echocardiography, cardiac magnetic resonance (CMR), and coronary flow velocity and coronary flow reserve (by means of intracoronary Doppler wires).[19] ST resolution at ECG is an easy bedside method of assessing myocardial perfusion following PCI. An ST resolution less than 70% at 60 minutes is a marker of no reflow.[29] Myocardial contrast echocardiography uses ultrasonography to visualize contrast microbubbles that flow through patent coronary microvessels. Lack of intramyocardial contrast can reveal MVO and correlates with the extent of no reflow.[30] CMR is regarded as the most sensitive and specific method to assess the extent of no reflow. The best timing, in terms of predictive value, seems to be 1 week after MI, when the resolution of the MI-related edema occurs.

No reflow can be diagnosed as (1) lack of gadolinium enhancement during the first pass; and (2) lack of gadolinium enhancement within a necrotic region, identified by late gadolinium hyperenhancement.[31]

Intracoronary Doppler guidewire is used to measure coronary flow velocity and coronary flow reserve. These parameters are standard methods for assessing microvascular function. During no reflow, this technique usually shows systolic flow reversal, reduced antegrade flow, and forward diastolic flow with rapid deceleration slope.[32]

STAGES OF NO-REFLOW AND THERAPEUTIC MEASURES

Prevention Before Reperfusion

Different therapeutic strategies can be implemented in a temporal phase occurring before and during no-reflow onset (**Fig. 1**). They are based on the treatment of predisposing factors of no reflow, such as increased lipid levels and glucose plasma concentrations, and smoking cessation. After chest pain onset, in patients with STEMI the goal is to reduce the time to ischemia, shortening the arrival to the catheterization laboratory to guarantee timely reperfusion with pPCI.

Within this temporal phase, the adoption of noninvasive therapies as remote ischemic preconditioning (IPC) may offer some degree of cardioprotection. Brief ischemia in an organ that is distant or remote from the heart, such as a limb, also reduces MI in experimental models. Cycles of intermittent limb ischemia provide an acceptable method for inducing cardioprotection, and early experimental studies have confirmed the effectiveness of remote IPC in cardiac surgery and coronary angioplasty, as assessed by reduced markers of cardiac injury.[33,34]

In the Catheterization Laboratory

Identified procedural predictors of angiographic no reflow are high thrombus burden,[35] predilatation,[36] long coronary lesions (>15 mm),[37] and reperfusion time greater than 6 hours.[38,39] During the primary PCI, distal microvascular plugs in the microcirculation, local inflammation, and hemorrhage can occur, leading to the angiographic appearance of no reflow. To counteract this significant flow impairment, both interventional and pharmacologic therapies have been tested.

NON PHARMACOLOGIC THERAPIES

Among procedural strategies for no-reflow prevention, direct stenting, nominal pressure stent deployment, stent postdilation avoidance, and manual thrombectomy before the intervention are included. Manual thrombectomy has been shown to be correlated to lower no-reflow incidence in several studies, although a positive significant impact on clinical outcomes is still debated.[40–42] Some recent meta-analyses and trials questioned its beneficial effect on mortality, raising safety concerns in terms of stroke.[43,44] For this reason, manual thrombectomy is not recommended as a routine approach during STEMI and should

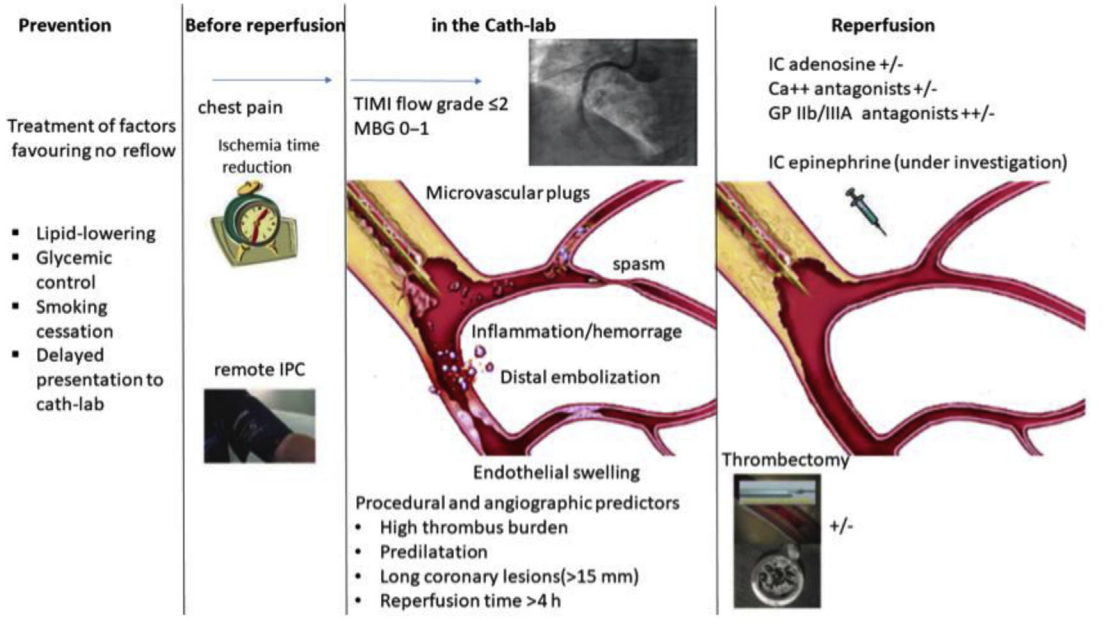

Fig. 1. Therapeutic measures applied at different stages to prevent or treat the no-reflow phenomenon. Cath-lab, catheterization laboratory; GP, glycoprotein; IC, intracoronary; IPC, ischemic preconditioning.

probably be limited to the presence of angiographically large thrombotic burden.[45] Also, different devices for embolic protection have been tested in the past but the effectiveness of their routine use during primary PCI for STEMI in terms of microvascular flow improvement has not been shown.[46,47] Of note, in a recent randomized trial, the use of distal embolic protection applied with a filter device decreased the incidence of the no-reflow phenomenon after revascularization compared with conventional PCI in patients with acute coronary syndrome with attenuated plaque identified by intravascular ultrasonography[48] (**Table 1**).

PHARMACOLOGIC THERAPIES

Pharmacologic management has probably been the most used therapeutic option for functional slow-flow/no-reflow phenomenon and still represents the most effective strategy in the catheterization laboratory to counteract no reflow in the acute setting (**Table 2**). Antiplatelet therapy is a cornerstone for AMI management and is essential as baseline therapy in order to prevent no reflow.[49]

Common oral antiplatelet drugs such as aspirin, clopidogrel, prasugrel, and ticagrelor are of paramount importance in order to counteract the early phase of thrombus formation.[50–52] However, they may not be sufficient as preventive therapies, and some evidence exists in favor of glycoprotein (GP) IIb/IIIa inhibitors as bailout therapy in the event of angiographic evidence of a large thrombus, slow flow, or no reflow, and a mortality reduction is observed with the intracoronary compared with the intravenous administration.[53–55] No evidence is available with regard to the new intravenous P2Y12 receptor inhibitor cangrelor on this topic.

Adenosine and sodium nitroprusside (SNP) are probably the most evaluated adjunctive therapies designed to attenuate MVO and infarct size.

Adenosine produces smooth muscle relaxation in the coronary circulation, although evidence also suggests antiplatelet properties[56] as well as reduction of oxygen free radical formation. Initial studies focused on the use of adenosine following intervention for STEMI. The AMISTAD (Acute Myocardial Infarction Study of Adenosine) and AMISTAD-II trials (**Table 3**)[57,58] showed a significant reduction in infarct size, with high-dose adenosine administration not translating into better clinical outcomes. Recent meta-analyses reported discordant findings,[59,60] whereas the most recent randomized trial on the topic, the REFLO-STEMI (Reperfusion Facilitated by Local Adjunctive Therapy in STEMI) trial, comparing intracoronary administration of adenosine or SNP following thrombus aspiration, found that high-dose intracoronary adenosine and SNP during pPCI did not reduce infarct size or MVO measured by CMR imaging.[61] When sodium nitroprusside is injected distally in the coronary artery, it has negligible systemic effect on the blood pressure but

Table 1
Clinical and angiographic outcomes of interventional studies for prevention of coronary no-reflow phenomenon following primary percutaneous coronary intervention

	Intervention	Study	Study Type	Patients (n)	Results
Nonpharmacologic therapies	Thrombus aspiration/ thrombectomy	Svilaas et al,[40] 2008	Randomized trial	1071	Lower myocardial blush grade of 0 or 1 in the thrombus-aspiration group
		De Vita et al,[41] 2009	Meta-analysis	2686	Lower all-cause mortality, reduced MACE, death, and MI rate Improved survival in patients treated with GP IIb/IIIa inhibitors
		Mongeon et al,[42] 2010	Meta-analysis	4299	Less no-reflow phenomenon, higher ST-segment resolution in the thrombus-aspiration group No 30-d benefit on mortality, reinfarction, and stroke
		Jolly et al,[43] 2015	Randomized trial	10,732	No 180-d benefit on CV death, recurrent MI, cardiogenic shock, or NYHA class IV Increased rate of stroke within 30 d
		Elgendy et al,[44] 2015	Meta-analysis	20,960	No benefit on clinical end points. Possible increase of risk of stroke
		De Luca et al,[45] 2013	Meta-analysis	18,306	Clinical outcomes not improved. Patients with thrombus grade >3: trend toward reduced CV death and increased stroke or transient ischemic attack
	Distal protection	Stone et al,[47] 2005	Randomized trial	501	Similar ST-segment resolution, infarct size, and clinical outcomes between groups (balloon occlusion and aspiration distal microcirculatory protection system vs angioplasty without distal protection)
		Kelbaek et al,[46] 2008	Randomized trial	626	Similar microvascular perfusion, infarct size, MACCE between groups (pPCI with distal protection vs conventional pPCI)
		Hibi et al,[48] 2018	Randomized trial	200	Lower incidence of no-reflow phenomenon, fewer serious adverse cardiac events in patients with ACS and attenuated plaque $\geq$5 mm in length at IVUS in the distal protection group vs conventional PCI

Abbreviations: ACS, acute coronary syndrome; CV, cardiovascular; GP II/b/IIIa, glycoprotein IIb/IIIa inhibitors; IVUS, intravascular ultrasonography; MACCE, major adverse cerebral and cardiovascular events; MACE, major adverse cardiovascular events; NYHA, New York Heart Association.
Data from Refs.[40–48]

Table 2
Pharmacologic agents currently used for no-reflow phenomenon treatment and principal characteristics

Drug	Dose	Mechanism of Action	Effects on Coronary Circulation	Side Effects
Antiplatelet Therapy				
Anti-GP IIb/IIIa Abciximab Eptifibatide Tirofiban	 IV bolus: 0.25 mg/kg; IV infusion: 0.125 μg/kg/min IV bolus: 180 μg/kg; IV infusion: 2 μg/kg/min IV bolus: 25 μg/kg; IV infusion: 0.15 μg/kg/min	Inhibition of GP IIb-IIIa receptors	• Inhibition of platelet activation • Reduction of downstream embolization/local thrombus • No release of vasoactive-chemotactic mediators	Bleeding
Vasodilators				
Adenosine	IV: 70 μg/kg/min for 3 h IC: 48–200-μg bolus	Adenosine receptors activation	• Vasodilatation • PLTs: neutrophils inhibition • Reduction Ca^{2+} overload: ROS	Bradycardia, transient AV block, chest pain, dyspnea, headache, flushing, bronchospasm
Verapamil Diltiazem Nicardipine	IC: 100–250-μg bolus or 100-μg/min up to 1000 μg IC: 400 μg IC: 50–200-μg bolus (up to 500 μg)	Calcium-channel blocker	• Vasodilatation endothelium mediated • Reduction of myocardial O_2 demand	Hypotension, heart block
Nitroprusside	IC: 50–200-μg bolus	Nitric oxide donor Activation of guanylate cyclase	• Vasodilatation • Antiplatelet effects	Hypotension, cyanide toxicity
Nicorandil	IV: 8-mg/h infusion IC: 2-mg bolus	KATP channel opener Nicotinamide nitrate	• Vasodilatation • Reduction of Ca^{2+}overload • Neutrophil inhibition	Headaches, nausea, vomiting, flushing
Hormones				
Epinephrine	IC: 50–200 μg	β2-receptor activation	• Reduction of Ca^{2+}overload • Coronary vasodilatation	Arrhythmias
Mitochondrial Permeability Transition Pore Blocker				
Cyclosporine-a	IC: 2.5–10 mg/kg	Inhibition of opening of mitochondrial permeability transition pores	• Protective effect on mitochondrial function • Reduction of ROS	Kidney damage, hypertension, infection

Novel Therapies				
Liraglutide	• Before reperfusion 1.8 mg • 0.6 mg/2 days • 1.2 mg/2 days • 1.8 mg/3 days	Glucagonlike peptide-1 analogue	• Inflammation reduction • Vasodilatation, endothelial dependent • Reduced monocyte adhesion • Improved endothelial viability	Nausea, loss of appetite, runny nose, rash

Abbreviations: AV, atrioventricular; IC, intracoronary; IV, intravenous; PLTs, platelets; ROS, reactive oxygen species.

Table 3
Clinical and angiographic outcomes of pharmacologic studies for prevention and/or treatment of coronary no-reflow phenomenon following primary percutaneous coronary intervention

	Drug	Study	Study Type	Patients (n)	Results
Pharmacologic therapies	GP IIb/IIIa inhibitors	Navarese et al,[53] 2012	Meta-analysis	1246	Intracoronary administration of abciximab is associated with significant benefits in mortality at short-term follow-up compared to IV abciximab administration, in STEMI patients undergoing PPCI
		Van't Hof et al,[54] 2008	Randomized trial	984	Routine prehospital initiation of high-bolus-dose tirofiban improved ST-segment resolution and clinical outcome after PCI
	Vasodilators (adenosine, nitroprusside)	Mahaffey et al,[57] 1999	Randomized trial	236	Adenosine resulted in a significant reduction in infarct size
		Ross et al,[58] 2005	Randomized trial	2118	Adenosine did not improve clinical outcomes in patients with STEMI undergoing reperfusion; infarct size was reduced
		Navarese et al,[59] 2012	Meta-analysis	3821	Adenosine showed beneficial effect on postprocedural coronary flow not associated with consistent advantages on clinical outcomes
		Polimeni et al,[60] 2016	Meta-analysis	1487	Intracoronary adenosine associated with lower incidence MACE
		Nazir et al,[61] 2016	Randomized trial	247	High-dose intracoronary adenosine and SNP during pPCI did not reduce infarct size or MVO measured by CMR. Adenosine may adversely affect midterm clinical outcome
		Zaho et al,[62] 2014	Meta-analysis	781	Intracoronary nitroprusside reduces the incidence of no-reflow during pPCI as well as the incidence of MACE
	Nicorandil	Iwakura et al,[63] 2009	Meta-analysis	1337	Nicorandil reduced the incidence of TIMI flow grade $\geq$2
	Cyclosporine	Cung et al,[64] 2015	Randomized trial	970	IV cyclosporine did not show better clinical outcomes and did not prevent adverse left ventricular remodeling at 1 y
	Liraglutide	Chen et al,[66] 2016	Randomized trial	284	Lower no-reflow prevalence

Data from Refs.[53,54,57–64,66]

induces marked improvement in coronary flow and myocardial tissue blush. Recent meta-analyses confirmed a clear benefit of nitroprusside in the management of no reflow during PCI.[62] Calcium-channel blockers, nicorandil, cyclosporine-A, and dabigatran have also been investigated as pharmacologic therapy in the context of no reflow, but no definitive conclusions exist regarding their efficacy.[63–65] Recently, the results of a small randomized trial have been reported, showing a potential for the glucagonlike peptide (GLP)-1 analogue liraglutide to reduce no reflow.[66] Adrenaline (epinephrine) also represents an interesting drug in the context of the no-reflow phenomenon, given its potent β2-receptor agonist properties that mediate coronary vasodilatation, increasing coronary blood flow. Several observational data show the significantly positive impact on coronary circulation mediated by adrenaline.[67] For these reasons, intracoronary adrenaline might have the potential to revert no-reflow instances.

SUMMARY

The occurrence of the no-reflow phenomenon still represents an important clinical issue during pPCI and can negate the benefits of restoring culprit-vessel patency. Novel promising therapeutic options are on the horizon, such as intracoronary adrenaline, which will be tested in future studies.

DISCLOSURE

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REFERENCES

1. Rezkalla SH, Kloner RA. Coronary no-reflow phenomenon: from the experimental laboratory to the cardiac catheterization laboratory. Catheter Cardiovasc Interv 2008;72(7):950–7.
2. Rezkalla SH, Stankowski RV, Hanna J, et al. Management of no-reflow phenomenon in the catheterization laboratory. JACC Cardiovasc Interv 2017;10(3):215–23.
3. Ndrepepa G, Tiroch K, Fusaro M, et al. 5-year prognostic value of no-reflow phenomenon after percutaneous coronary intervention in patients with acute myocardial infarction. J Am Coll Cardiol 2010;55:2383–9.
4. Wu KC, Zerhouni EA, Judd RM, et al. Prognostic significance of microvascular obstruction by magnetic resonance imaging in patients with acute myocardial infarction. Circulation 1998;97:765–72.
5. Morishima I, Sone T, Okumura K, et al. Angiographic no-reflow phenomenon as a predictor of adverse long-term outcome in patients treated with percutaneous transluminal coronary angioplasty for first acute myocardial infarction. J Am Coll Cardiol 2000;36:1202–9.
6. Durante A, Camici PG. Novel insights into an "old" phenomenon: the no-reflow. Int J Cardiol 2015;187:273–80.
7. Iwakura K, Ito H, Ikushima M, et al. Association between hyperglycemia and the no-reflow phenomenon in patients with acute myocardial infarction. J Am Coll Cardiol 2003;41:1–7.
8. Navarese EP, Kowalewski M, Andreotti F, et al. Meta-analysis of time-related benefits of statin therapy in patients with acute coronary syndrome undergoing percutaneous coronary intervention. Am J Cardiol 2014;113(10):1753–64.
9. Del Turco S, Basta G, De Caterina AR, et al. Different inflammatory profile in young and elderly STEMI patients undergoing primary percutaneous coronary intervention (PPCI): its influence on no-reflow and mortality. Int J Cardiol 2019;290:34–9.
10. Kaya A, Keskin M, Tatlisu MA, et al. Atrial fibrillation: a novel risk factor for no-reflow following primary percutaneous coronary intervention. Angiology 2020;71(2):175–82.
11. Rezkalla SH, Dharmashankar KC, Abdalrahman IB, et al. No-reflow phenomenon following percutaneous coronary intervention for acute myocardial infarction: incidence, outcome, and effect of pharmacologic therapy. J Interv Cardiol 2010;23:429–36.
12. Magro M, Springeling T, Jan van Geuns R, et al. Myocardial 'no-reflow' prevention. Curr Vasc Pharmacol 2013;11:263–77.
13. Yoshino S, Ciluffo R, Best PJ, et al. A single nucleotide polymorphism associated with abnormal coronary micro-vascular function. Coron Artery Dis 2014;25:281–9.
14. Barman HA, Kahyaoglu S, Durmaz E, et al. The CHADS-VASc score is a predictor of no-reflow in patients with non-ST-segment elevation myocardial infarction. Coron Artery Dis 2020;31(1):7–12.
15. Krug A, de Rochemont WM, Korb G. Blood supply of the myocardium after temporary coronary occlusion. Circ Res 1996;19:57–62.
16. Kloner RA, Ganote CE, Jennings RB. The "no-reflow" phenomenon after temporary coronary occlusion in the dog. J Clin Invest 1974;54:1496–506.
17. Bolognese L, Carrabba N, Parodi G, et al. Impact of microvascular dysfunction on left ventricular remodeling and long-term clinical outcome after primary coronary angioplasty for acute myocardial infarction. Circulation 2004;109:1121–6.
18. Stone GW, Selker HP, Thiele H, et al. Relationship between infarct size and outcomes following primary PCI: patient-level analysis from 10 randomized trials. J Am Coll Cardiol 2016;67:1674–83.

19. Bates ER, Krell MJ, Dean EN, et al. Demonstration of 'no-reflow' phenomenon by digital coronary arteriography. Am J Cardiol 1986;57:177–8.
20. Feld H, Lichstien E, Schachter J, et al. Early and late angiographic findings of the 'no-reflow' phenomenon following direct angioplasty as the primary treatment for acute myocardial infarction. Am Heart J 1992;123:782–4.
21. Salinas P, Jimenez-Valero S, Moreno R, et al. Update in pharmacological management of coronary no-reflow phenomenon. Cardiovasc Hematol Agents Med Chem 2012;10(3):256–64.
22. Skyschally A, Leineweber K, Gres P, et al. Coronary microembolization. Basic Res Cardiol 2006;101:373–82.
23. Hori M, Inoue M, Kitakaze M, et al. Role of adenosine in hyperemic response of coronary blood flow in microembolization. Am J Physiol 1986;250:H509–18.
24. Tantry US, Navarese EP, Myat A, et al. Combination oral antithrombotic therapy for the treatment of myocardial infarction: recent developments. Expert Opin Pharmacother 2018;19:653–65.
25. Ito BR, Schmid-Schönbein G, Engler RL. Effects of leukocyte activation on myocardial vascular resistance. Blood Cells 1990;16:145–63.
26. Galiuto L. Optimal therapeutic strategies in the setting of post-infarct no-reflow: the need for a pathological classification. Heart 2004;90:123–5.
27. The TIMI Study Group. The Thrombolysis in myocardial infarction [TIMI] trial. Phase I findings. N Engl J Med 1985;312:932–6.
28. Van't Hof AW, Liem A, Suryapranata H, et al, Zwolle Myocardial Infarction Study Group. Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction: myocardial blush grade. Circulation 1998;97:2302–6.
29. Schroder R. Prognostic impact of early ST-segment resolution in acute ST-elevation myocardial infarction. Circulation 2004;110:e506–10.
30. Iliceto S, Marangelli V, Marchese A, et al. Myocardial contrast echocardiography in acute myocardial infarction. Pathophysiological background and clinical applications. Eur Heart J 1996;17:344–53.
31. Albert TS, Kim RJ, Judd RM. Assessment of no-reflow regions using cardiac MRI. Basic Res Cardiol 2006;101:383–90.
32. Yamamuro A, Akasaka T, Tamita K, et al. Coronary flow velocity pattern immediately after percutaneous coronary intervention as a predictor of complications and in-hospital survival after acute myocardial infarction. Circulation 2002;106:3051–6.
33. Kharbanda RK, Mortensen UM, White PA, et al. Transient limb ischemia induces remote ischemic preconditioning in vivo. Circulation 2002;106:2881–3.
34. Kharbanda RK, Nielsen TT, Redington AN. Translation of remote ischaemic preconditioning into clinical practice. Lancet 2009;374:1557–65.
35. Yip HK, Chen MC, Chang HW, et al. Angiographic morphologic features of infarct-related arteries and timely reperfusion in acute myocardial infarction: predictors of slow-flow and no-reflow phenomenon. Chest 2002;122:1322–32.
36. Piscione F, Piccolo R, Cassese S, et al. Is direct stenting superior to stenting with predilation in patients treated with percutaneous coronary intervention? Results from a meta-analysis of 24 randomised controlled trials. Heart 2010;96(8):588–94.
37. Tasar O, Karabay AK, Oduncu V, et al. Predictors and outcomes of no-reflow phenomenon in patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. Coron Artery Dis 2019;30(4):270–6.
38. Mazhar J, Mashicharan M, Farshid A. Predictors and outcome of no-reflow post primary percutaneous coronary intervention for ST elevation myocardial infarction. Int J Cardiol Heart Vasc 2015;10:8–12.
39. Nallamothu BK, Bradley EH, Krumholz HM. Time to treatment in primary percutaneous coronary intervention. N Engl J Med 2007;357:1631–8.
40. Svilaas T, Vlaar PJ, van der Horst IC, et al. Thrombus aspiration during primary percutaneous coronary intervention. N Engl J Med 2008;358:557–67.
41. De Vita M, Burzotta F, Biondi-Zoccai GG, et al. Individual patient-date meta-analysis comparing clinical outcome in patients with ST-elevation myocardial infarction treated with percutaneous coronary intervention with or without prior thrombectomy. ATTEMPT study: a pooled Analysis of Trials on ThrombEctomy in Acute Myocardial infarction based on individual PatienT data. Vasc Health Risk Manag 2009;5:243–7.
42. Mongeon FP, Bélisle P, Joseph L, et al. Adjunctive thrombectomy for acute myocardial infarction: a Bayesian meta- analysis. Circ Cardiovasc Interv 2010;3:6–16.
43. Jolly SS, Cairns JA, Yusuf S, et al. Stroke in the TOTAL trial: a randomized trial of routine thrombectomy vs. percutaneous coronary intervention alone in ST elevation myocardial infarction. Eur Heart J 2015;36:2364–72.
44. Navarese EP, Tarantini T, Musumeci G, et al. Manual vs mechanical thrombectomy during PCI for STEMI: a comprehensive direct and adjusted indirect meta-analysis of randomized trials. Am J Cardiovasc Dis 2013;3(3):146–57.
45. De Luca G, Navarese EP, Suryapranata H. A meta-analytic overview of thrombectomy during primary angioplasty. Int J Cardiol 2013;166(3):606–12.
46. Kelbaek H, Terkelsen CJ, Helqvist S, et al. Randomized comparison of distal protection versus conventional treatment in primary percutaneous coronary intervention: the drug elution and distal protection

in ST-elevation myocardial infarction (DEDICATION) trial. J Am Coll Cardiol 2008;51:899–905.
47. Stone GW, Webb J, Cox DA, et al. Distal microcirculatory protection during percutaneous coronary intervention in acute ST-segment elevation myocardial infarction: a randomized controlled trial. JAMA 2005;293:1063–72.
48. Hibi K, Kozuma K, Sonoda S, et al, VAMPIRE 3 Investigators. A randomized study of distal filter protection versus conventional treatment during percutaneous coronary intervention in patients with attenuated plaque identified by intravascular ultrasound. JACC Cardiovasc Interv 2018;11(16): 1545–55.
49. Gurbel PA, Jeong YH, Navarese EP, et al. Platelet-mediated thrombosis: from bench to bedside. Circ Res 2016;118(9):1380–91.
50. Adamski P, Adamska U, Ostrowska M, et al. Evaluating current and emerging antithrombotic therapy currently available for the treatment of acute coronary syndrome in geriatric populations. Expert Opin Pharmacother 2018;19(13):1415–25.
51. Navarese EP, Buffon A, Kozinski M, et al. A critical overview on ticagrelor in acute coronary syndromes. QJM 2013;106(2):105–15.
52. Tantry US, Navarese EP, Myat A, et al. Selection of P2Y12 inhibitor in percutaneous coronary intervention and/or acute coronary syndrome. Prog Cardiovasc Dis 2018;60(4–5):460–70.
53. Navarese EP, Kozinski M, Obonska K, et al. Clinical efficacy and safety of intracoronary vs. intravenous abciximab administration in STEMI patients undergoing primary percutaneous coronary intervention: a meta-analysis of randomized trials. Platelets 2012;23(4):274–81.
54. Van't Hof AW, Ten Berg J, Heestermans T, et al, Ongoing Tirofiban in Myocardial infarction Evaluation (On-TIME) 2 Study Group. Prehospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): a multicentre, double-blind, randomised controlled trial. Lancet 2008;372(9638):537–46.
55. De Luca G, Navarese E, Marino P. Risk profile and benefits from Gp IIb-IIIa inhibitors among patients with ST-segment elevation myocardial infarction treated with primary angioplasty: a meta-regression analysis of randomized trials. Eur Heart J 2009;30:2705–13.
56. Johnson-Cox HA, Yang D, Ravid K. Physiological implications of adenosine receptor- mediated platelet aggregation. J Cell Physiol 2011;226:46–51.
57. Mahaffey KW, Puma JA, Barbagelata NA, et al. Adenosine as an adjunct to thrombolytic therapy for acute myocardial infarction: results of a multicenter, randomized, placebo-controlled trial: the Acute Myocardial Infarction STudy of Adenosine (AMISTAD) trial. J Am Coll Cardiol 1999;34:1711–20.
58. Ross AM, Gibbons RJ, Stone GW, et al. AMISTAD-II Investigators. A randomized, double-blinded, placebo- controlled multicenter trial of adenosine as an adjunct to reperfusion in the treatment of acute myocardial infarction (AMISTAD-II). J Am Coll Cardiol 2005;45:1775–80.
59. Navarese EP, Buffon A, Andreotti F, et al. Adenosine improves post-procedural coronary flow but not clinical outcomes in patients with acute coronary syndrome: a meta-analysis of randomized trials. Atherosclerosis 2012;222:1–7.
60. Polimeni A, De Rosa S, Sabatino J, et al. Impact of intracoronary adenosine administration during primary PCI: a meta-analysis. Int J Cardiol 2016;203: 1032–41.
61. Nazir SA, Khan JN, Mahmoud IZ, et al. The REFLO-STEMI (REperfusion Facilitated by LOcal adjunctive therapy in ST-Elevation Myocardial Infarction) trial: a randomised controlled trial comparing intracoronary administration of adenosine or sodium nitroprusside with control for attenuation of microvascular obstruction during primary percutaneous coronary intervention. Southampton (United Kingdom): NIHR Journals Library; 2016.
62. Zhao S, Qi G, Tian W, et al. Effect of intracoronary nitroprusside in preventing no-reflow phenomenon during primary percutaneous coronary intervention: a meta-analysis. J Interv Cardiol 2014;27:356–64.
63. Iwakura J, Ito H, Okamura A, et al. Nicorandil treatment in patients with acute myocardial infarction: a meta-analysis. Circ J 2009;73:925–31.
64. Cung TT, Morel O, Cayla G, et al. Cyclosporine before PCI in patients with acute myocardial infarction. N Engl J Med 2015;373:1021–31.
65. Hale SL, Kloner RA. Dabigatran treatment: effects on infarct size and the no-reflow phenomenon in a model of acute myocardial ischemia/reperfusion. J Thromb Thrombolysis 2015;39:50–4.
66. Chen WR, Tian F, Chen YD, et al. Effects of liraglutide on no-reflow in patients with acute ST-segment elevation myocardial infarction. Int J Cardiol 2016; 208:109–14.
67. Navarese EP, Frediani L, Kandzari DE, et al. Efficacy and safety of intracoronary epinephrine versus conventional treatments alone in STEMI patients with refractory coronary no-reflow during primary PCI: The RESTORE observational study. Catheter Cardiovasc Interv 2020. [Epub ahead of print].