REVIEW ARTICLE

Coronary microvascular reperfusion injury and no-reflow in acute myocardial infarction

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Abstract

Purpose: To review (1) the mechanisms of coronary microvascular reperfusion injury, particularly in the relationships between microvascular endothelium dysfunction, microstructure damage, microemboli and no-reflow phenomena; (2) the no-reflow presentation and management at ischemia-reperfusion to suggest future direction for no-reflow therapy in acute myocardial infarction.

Sources: Original articles and reviews published between 1997 and 2007 and focusing on the no-reflow phenomenon in MEDLINE and PubMed. The search terms used were “no-reflow”, “microvascular injury”, “acute myocardial infarction” and “reperfusion injury”. All papers identified were English-language, full text papers. In addition, the reference lists of identified relevant articles were also searched.

Conclusions: The no-reflow phenomenon is characterised by damage to microvascular function and microstructure at ischaemia-reperfusion. Microemboli contribute to no-reflow. Clinical myocardial contrast echocardiography (MCE), scintigraphic and magnetic resonance imaging (MRI) have shown evidence of microvascular damage, eg, perfusion defects are closely related to lack of contractile recovery and irreversible myocyte damage. Clinical agents and devices targeting microvascular injury (especially protection of endothelium and reduction of microemboli) after acute myocardial infarction may be key points to improve no-reflow.

Keywords: microvascular reperfusion injury, acute myocardial infarction, no-reflow

Acute myocardial infarction (AMI) is the leading cause of morbidity and mortality in the western world. By the year 2020, it will be the major cause of death in the world.¹ Currently, thrombolysis, percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) have become standard treatments in AMI. Despite complete restoration of epicardial coronary artery patency, progressive flow impairment and tissue hypoperfusion persists within the inner half of the infarct following reperfusion.²

The term “no-reflow” describes the compromised myocardial blood flow at the microvascular level after coronary artery occlusion and reperfusion. Major determinants of the amount of no-reflow are the duration of occlusion, infarct size and, also, the duration of reperfusion. Rapid expansion of perfusion defects occurs during reperfusion. No-reflow detected at 24 hrs may persist or may reverse spontaneously at one month, a time when major steps of infarct healing are taking place.³

Pathological mechanism of microvascular injury at ischemia-reperfusion

Nicklas et al first proposed the concept of vascular stunning in 1989.⁴ Bolli et al found that a reversible ischemic insult (15 min) caused a prolonged increase in resting vascular resistance and prolonged impairment in vasodilator responsiveness, which was not related to the severity of contractile depression. They suggested that reversible ischemia also caused microvascular "stunning".⁵ In canine experiments, 40 min ischemia did not lead to perfusion defects after 20 min reperfusion, but substantial areas of no-reflow were visualized after 90 min ischemia with reperfusion for 10 sec - 20 min. Thus, the extent of microvascular damage was worsened with longer durations of ischemia.^{6,7}

In the last 10 yrs, the cumulative evidence of studies suggested that microvascular dysfunction and integral damage might be crucial for the occurrence of no-reflow.

1. Microvascular dysfunction

Endothelial injury may result from various risks, eg, reintroduction of abundant oxygen after the first few minutes of reperfusion evokes a burst of potent free radical and peroxynitrite at ischemia-reperfusion. The endothelium becomes dysfunctional and nitric oxide (NO) formation decreases within 2.5 - 5 min of reperfusion. By 20 min, neutrophils adhere to the endothelium and migrate across the endothelium into reper-fused tissue. Endothelial dysfunction is present from 4 - 12 wks, and ischaemic preconditioning may preserve microvascular functional vasodilation and integrity.^{8,9} Postconditioning, the application of short periods of re-occlusion after ischemia and reopening of the epicardial arteries reduces infarct size.^{10,11} Vascular functioning can be improved by postconditioning, along with reduced leukocyte accumulation and greater maximal vasodilatory responses.¹²

Risks of microvascular endothelial injury at ischemia-reperfusion:

(i) Oxygen-free radicals

Oxygen free radicals (OFR) peak at 2–10 min reperfusion after coronary artery occlusion. They are derived from the xanthine oxidase reaction, mitochondria and polymorphonuclear cells. Purine precursors are degraded to hypoxanthine at ischemia, and OFR are produced via xanthine oxidase at reperfusion.¹³ The superoxide dismutase pathway, normally responsible for the clearance of superoxide anions, may be altered after an ischemic insult.⁸ Severe damage to endothelium by OFR induces loss of endothelium derived relaxing factor (EDRF), impairs EDRF relaxation of vascular smooth muscle and prevention of platelet aggregation and neutrophil adherence. In addition, OFR can damage microvascular permeability and endothelial membrane function via lipid peroxidation, and cause intracellular calcium overload. Angiographic no-reflow after successful primary or rescue PCI can be predicted from ET-1 plasma levels¹⁴ suggesting that ET-1 antagonists might be beneficial in the management of no-reflow.

(ii) Sympatho-adrenal activation

Activation of the sympathoadrenal system and myocardium angiotensin II increase intracellular calcium levels at acute reperfusion. This induces positive inotropism, impairment of diastolic function, and extensive coronary spasm (including small, 100-300 μ m, and microvascular, <100 μ m, arteries).¹⁵ In addition, oxidized catecholamines become free radicals which exacerbate lipid peroxidation, endothelium dysfunction and tissue damage.¹⁶

(iii) Fluids and calcium flux

The increased OFR, decreased ATP and Na⁺/K⁺ transport function in myocardium and microvessels induce intracellular fluid shift and calcium overload at reperfusion. This leads to hemoconcentration and endothelial swelling, and H₂O and Na⁺ enter endothelium.¹⁶⁻¹⁸ Simulated ischemia severely depresses cGMP synthesis in microvascular endothelium through ATP depletion and acidosis, thereby reducing NO production.¹⁹

Hypoxic ischemia induces a combination of hyperosmolarity and lactic acidosis which modify red blood cells. The erythrocyte membrane becomes more rigid with time, which contributes to the decreased erythrocyte deformability after AMI.²⁰

Coronary artery spasm occurs when the KATP channel is inhibited at reperfusion. Activation of the KATP channel may prevent endothelial injury, expand smaller arteries and improve coronary circulation.²¹

(iv) *Inflammation*

The cardiac inflammatory reaction arises largely from the reperfused area. Deposition of the C3a, C5a, C5b-9 and cytokines (eg, P-selectin, IL-6) increase polymorphonuclear permeability in the risk region and further release OFR and platelet activating factor.^{16,22} OFR induce lipid peroxidation of cellular membrane (eg, polymorphonuclear, platelet), and release of leukotriene B4 and thromboxane A2 that cause platelet aggregation, neutrophil activation and a neutrophil plug.²³

Activated neutrophils can exacerbate reperfusion injury: (a) neutrophils adhere to the endothelium and cause capillary plugging in infarcted myocardium; (b) neutrophils produce free radicals and oxidant stress (eg, superoxide, hydroxyl radicals) that directly injure endothelium, deactivate EDRF and alter vascular tone; (c) polymorphonuclear cells release reactive oxygen metabolites, proteolytic enzymes, and lipoxygenase products (eg, lysosomal proteolytic enzymes, myeloperoxidase) that affect platelet and endothelial function.

Endothelium can modulate leucocyte, platelet and microvascular function by release of adhesion molecules (intercellular adhesion molecule-1 or P-selectin) and soluble factors (NO, prostacyclin, endothelin and platelet activating factor).^{24,25} Similarly, platelets may affect polymorphonuclear cell activation by release of thromboxane A2, platelet derived growth factor, serotonin, lipoxygenase products, proteases and adenosine. Finally, interaction between endothelium, platelets and polymorphonuclear cells can induce no-reflow, even if no thrombosis occurred.⁸

(v) *The Plaque chip and micro-thrombus*

When thrombolysis therapy and PCI are performed, an atheromatous plaque chip (cholesterol crystal) may follow reperfusion reflow and obstruct the distal microvascular circulation. Directional and rotational atherectomy has a higher risk of no-reflow than balloon angioplasty.²⁶

Thrombolytic drugs can activate the complement and kinin systems, and increase the concentration of IL-6 and thrombin. Endothelium damage results in collagen exposure. Collagen-induced activation of platelets, through FcR gamma, plays an important role in the extension of ischemia-reperfusion injury.²⁷ The interaction of circulating platelets with adherent platelets proceeds through activated $\alpha\text{IIb}\beta_3$ integrin receptors. The activated platelets release vasoconstrictive substances, eg, 5-HT, TXA2, ADP, thromboxane, serotonin and thrombin, which induce vascular smooth muscle cell migration, microvascular spasm, local platelet aggregation and deposition.²⁸ On the other hand, tissue factor, a membrane bound glycoprotein that activates the extrinsic coagulation pathway (via activating factor VII) when exposed to blood, contributes to no-reflow.²⁹ Thus, microemboli may contribute to the no-reflow, leading to micro- and potentially macro-infarcts.

(vi) *Myocardial injury at ischemia-reperfusion*

Myocardial injury at ischemia-reperfusion also occurs. OFR can induce cell membranes and microsomal lipid peroxidation, which damage cell membranes and sarcoplasmic reticulum function including inactive ATPase pumps. Acidosis ($\text{pH} \leq 7.0$) protects against myocyte death at ischemia. However, the return of pH to normal after reperfusion leads to loss of myocyte viability. This worsening injury is a 'pH paradox' and is mediated by changes of intracellular pH (pH(i)). Cytosolic [calcium] is increased during prolonged ischemia. At reperfusion, energy supply in the presence of high $[\text{Ca}^{2+}]$ causes hypercontractility. Once a cell has developed calcium overload, it is communicated to adjacent cells, and induces contraction band necrosis.¹⁷ Reperfusion has been shown to accelerate myocardium apoptosis.

In the complicated risks of ischemia-reperfusion myocardium injury, microvascular dysfunction plays an important role in myocardium injury, and severe microvascular damage can develop no-reflow phenomena.

2. Microstructure integrity damage

Endothelial cells might be more prone to ischemia/reperfusion-induced damage than cardiomyocytes.^{10,31} Local areas of endothelial swelling and endothelial protrusions (called "blebs") were the most common findings at reperfusion. Electron microscopy of no-reflow areas revealed swollen intraluminal endothelial protrusions and membrane bound intraluminal bodies. These protrusions occluded the capillary lumen, and caused regional perfusion defects. Endothelial cells showed decreased numbers of pinocytotic vesicles and nuclear chromatin margination. After 20 min reperfusion, capillaries contained tightly packed erythrocytes, endothelial gaps, sometimes plugged by platelet and fibrin thrombi, with numerous extravascular red blood cells. Occasionally, capillaries seemed to be compressed by subsarcolemmal blebs of neighbouring swollen myocytes.⁸ Ultrastructural investigations after different durations of occlusion (20–180 min) in a dog model of coronary ligation and reperfusion demonstrated that microvascular damage (first observed after 60 min) always lagged behind myocardial cell injury (first apparent after 20 min) and that microvascular alterations were always located in zones of irreversibly damaged myocytes.

Sudden myocardial cell swelling with prominent intracellular and interstitial oedema is one of the very early morphological changes induced by reperfusion. As tissue oedema might compress the microvascular bed, no-reflow may, in part, be attributed to changes in total cross sectional vascular area.⁸

In summary, neutrophil infiltration and activation, OFR, adhesion molecules, complement system and platelet activation at ischemia-reperfusion jointly damage microvascular function and microvasculature (eg, ATP decrease, pH change, swelling of endothelium and bleb formation). The microvascular endothelium may then lose modulation for vasodilation, anti-

inflammation, anti-platelet adhesion & activation and antioxidation. Moreover, the microvascular dysfunction induces microvascular spasm, thromboembolism, and develops irreversible damage of microstructure integrity.^{17,32} Simultaneously, microvascular perfusion may also be impaired by microvascular embolization with increased plaque rupture debris, erythrocytes and neutrophils plugs, microvascular spasm and distal vascular resistance in the infarcted zone. Finally, the development of the infarcted core, microvascular obstruction and intramyocardial hemorrhage³³ may predict clinical complications including myocardial cell death (necrosis and apoptosis), ventricular remodeling, reperfusion arrhythmia, cardiac rupture (Figure 1).

Clinical presentation of no-reflow phenomena

The size of myocardial infarction is closely correlated with the amount of anatomical no-reflow visualized by perfusion staining with thioflavin S along with a high spatial concordance.³⁴ In an experimental series, the no-reflow zone was confined to the zone of infarction and tended to be slightly smaller in size in the majority of hearts. Infarct size seemed to be the major determinant of the amount of no-reflow irrespective of the duration of coronary occlusion.³⁵⁻³⁷ Moreover, the observation that a longer duration of occlusion tended to result in bigger no-reflow zones may be explained by bigger infarcts after longer ischemia. Thus, infarct size is a major determinant of the size of anatomical no-reflow.

Angiographic no-reflow is a strong predictor of major cardiac complications, including congestive heart failure, malignant arrhythmias and cardiac death after AMI.³⁸ Furthermore, patients with both normal epicardial flow (TIMI grade 3 flow) and normal tissue level perfusion (TMP grade 3) had an extremely low risk of mortality (Figure 2).³⁹ TIMI frame count indicates the number of angiographic frames required for the contrast medium to reach standardised distal landmarks of the coronary artery. The corrected TIMI frame count was developed to quantify distal coronary flow and the angiographic "blush" score has been used to assess myocardial tissue perfusion. An increase in

FIGURE 1. Pathogenesis of microvascular injury, no-reflow presentation at ischemia-reperfusion.

FIGURE 2. The relationship of TMP grade and mortality in impaired perfusion of the myocardium.

corrected TIMI frame count following successful IRA opening in AMI is an early angiographic indicator of coronary microvascular injury.³⁹⁻⁴¹ In addition, coronary doppler flow wires can be used to measure coronary flow velocity and coronary flow reserve following epicardial reperfusion to estimate the degree of microvascular dysfunction in the infarct zone.^{42,43} This detects no-reflow after anterior infarction better than other angiographic, electrocardiographic and enzymatic modalities.⁴⁴

Using gas-filled microbubble agents, direct injections delineate myocardial perfusion territories by myocardial contrast echocardiography (MCE). MCE can be used to assess microvascular perfusion and, hence, it has become the gold standard to investigate the no-reflow phenomenon. Ito et al found that patients with TIMI grade 2 flow after PCI showed substantial no-reflow on MCE, defined as contrast defects after angioplasty of more than 25% of the risk

zone. Even with TIMI grade 3 flow, 16% of the patients showed no-reflow. Improvement of left ventricular function was only observed in patients with reflow. Thus, microvascular integrity, as assessed by MCE, is closely related to myocyte viability.⁴⁵ Currently, MCE has profoundly extended our understanding of microvascular perfusion after AMI. Intravenous contrast application with bedside imaging is now feasible.

Evidence for progressive impairment of tissue reperfusion is provided by ⁸²rubidium positron emission.⁸ Intracoronary injection of macroaggregated ^{99m}technetium albumin after successful percutaneous recanalisation demonstrated substantial perfusion defects. Infarct size measurement with ^{99m}Tc-sestamibi SPECT can be used to determine the degree of left ventricular damage and the amount of myocardial salvage following reperfusion.⁴⁶

MRI hypoenhancement 1–2 min after contrast injection is assumed to represent zones of no-reflow, and may be a promising technique to evaluate microvascular dysfunction, since it can be used to assess distal coronary flow, myocardial tissue perfusion, and regional and global left ventricular function. Even after correction for the predictive value of infarct size, microvascular obstruction in MRI has prognostic implications for clinical outcome.³³ A recent study validated the amount of hypoenhancement *vs.* anatomical no-reflow assessed by injection of thioflavin S and regional myocardial blood flow in a canine model of reperfused AMI.⁴⁸

Resolution of ST segment elevation after reperfusion correlates with the amount of myocardial perfusion visualised by MCE and appears to reflect restoration of myocardial tissue perfusion. Rapid ST-segment resolution following successful recanalization of the infarct related artery (IRA) during primary angioplasty predicts reduced infarct size and improved survival compared with delayed ST-segment resolution.^{48,49} In the individual patient, residual ST segment deviation after reperfusion in a single lead with maximum ST segment deviation is at least as good as summed ST elevation in predicting final myocardial damage.⁵⁰

Serial measurements of serum biochemical markers including myoglobin, creatine kinase-MB or troponin I (or T) at baseline and 60 (or 90) min after reperfusion have been useful for the assessment of IRA patency. Elevation of serum troponin T is a sensitive marker of myocardial injury, reflecting microvascular injury caused by distal coronary embolisation.⁸ The pattern of cardiac marker release can be used to estimate infarct size in a similar fashion as ^{99m}Tc-sestamibi SPECT imaging.⁵¹ Thus, the amount of tissue perfusion might, in part, be estimated by biochemical markers even without invasive procedures or sophisticated and expensive technical equipment.

Management of microvascular injury

The degree of regional functional recovery is related to the extent of microvascular damage.⁵² Therapy tar-

TABLE 1. Reperfusion therapeutic targets and agents from the infarct-related artery to the myocardium

<i>Reperfusion therapeutic targets</i>		
Epicardial Coronary Artery	Microcirculation	Myocardial Salvage
Combination pharmacotherapy PCI and antithrombotics CABG	Calcium antagonists	Aqueous O ₂
	GP IIb/IIIa inhibitor	Cold
	ACEI & ATII blockade	GIK
	HMG-CoA inhibitor	Adenosine
	Adenosine	Nicorandil
	Nicorandil	Na ⁺ /H ⁺ pump inhibitor
	Complement inhibitor	GP IIb/IIIa inhibitor
	Inflammatory inhibitor	
	Nitroprusside	
	Filter	
	Intra-Aortic Balloon	
	Counterpulsation	

Note: Reperfusion therapeutic agents are listed below target.

Abbreviations: PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; ACEI, angiotensin converting enzyme inhibitors; GIK, Glucose-Insulin-Potassium.

geting microvascular injury may improve clinical outcomes after AMI. (Table 1)

1. Drug therapy

Calcium antagonists can prevent endothelial injury by scavenging free radicals, improving reflow, decreasing neutrophil accumulation, preserving sarcoplasmic reticulum function and high energy phosphates. They improve TIMI grade flow and reduce reperfusion-induced ventricular fibrillation, stunning and overall infarct size.⁵³ Early administration of intracoronary verapamil during direct PCI improves post-procedural myocardial perfusion, as evaluated by myocardial perfusion grade.⁵⁴

GP IIb/IIIa inhibitors reduce recurrent ischemic events in reperfused AMI.⁵⁵ Because sigmaSTR determines microvascular perfusion, GP IIb/IIIa inhibitors may improve endothelial function at reperfusion to reduce no-reflow.⁵⁶⁻⁵⁸

Fibrinolytics and GP IIb/IIIa inhibitors accelerate global tissue reperfusion compared with fibrinolytic monotherapy.⁵⁹ Abciximab increased tissue reperfusion by improving peak flow velocity in the recanalized IRA. It also improves wall motion index, and left ventricular function and reduces Tc-99m sestamibi scintigraphic perfusion defects after rotational atherectomy.⁸ However, GP IIb/IIIa blockade can stabilize the culprit lesion but it neither reduces microvascular platelet accumulation or infarct size after transient coronary occlusion in swine⁶⁰ nor protects against platelet-mediated injury isolated reperfused rat hearts.⁶¹ The discrepancy in the reports needs further investigation.

Thiol/sulphydryl agents have antioxidant activity that protects ischemic myocardium. Ramipril stimulates the release of prostaglandins and NO from the endothelium, mediated by kinins,⁶² Clinical ACE inhibitors have short- and long-term benefits in the prevention of myocardial stunning, infarct size and reperfusion arrhythmias in AMI.⁶³ However, ATII blockade has different results in reperfusion injury. Jugdutt et al suggested that AT1R blockade combined with up-regulation of AT2R protein expression could contribute to the cardioprotective effects of ATII blockade during reperfused myocardial infarction.⁶⁴ However, Ryckwaert et al indicated that only blockade of both AT1 and AT2 receptors improved ventricle function from ischaemia reperfusion.⁶⁵ The beneficial mechanism of ATII blockade at ischemia-reperfusion needs further exploration.

Statins maintain steady-state eNOS mRNA, and increase eNOS expression in human endothelial cells by prolongation of the already-long mRNA half-life from 28 to 46 hrs and by post-translational phosphorylation of eNOS protein. Thus, statins may improve coronary flow reserve and reduce platelet deposition, neutrophil infiltration and the extent of necrosis in reperfused myocardium.^{66,67} Chronic pre-treatment with statins could preserve the microvascular integrity after AMI independent of lipid lowering, leading to better functional recovery.⁶⁸

ATP or adenosine may prevent endothelial dysfunction and neutrophil-mediated endothelium injury and myocardial stunning at reperfusion. Adenosine

has an anti-ischemic effect by opening of mitochondrial KATP-channels, and adenosine therapy produced better TIMI 3 flow and less no-reflow than in controls.⁶⁹ However, in another study, adenosine reduced infarct size when it was administered with fibrinolytics, but clinical outcomes were not improved.⁷⁰ The inconsistent benefits need further investigation. Intracoronary administration of adenosine combined with nicorandil may improve both the occurrence of no-reflow in patients during PCI for AMI and short-term clinical outcome, compared with adenosine alone.⁷¹

Nicorandil has KATP channel opener-like and nitrate-like properties at ischemia-reperfusion. In addition to its direct beneficial effect on improving hemodynamics, scavenging free radicals and inhibiting neutrophil activation, nicorandil induces an early reduction of the ischemic preconditioning (PC) threshold to reduce infarct size.⁷² Furthermore, it has a delayed cardioprotective effect by a reduction in infarct size 24 hrs later. This late PC effect may be the result of a direct action of nicorandil associated with up-regulation of COX-2 and Bcl-2.⁷³ K(ATP) channel activation, but not NO, may be a major mechanism of protection against microvascular injury, causing the no-reflow phenomenon in the heart.⁷⁴ During primary angioplasty, intravenous nicorandil enhances tissue perfusion in the infarct region measured with MCE.⁷⁵ Combined intravenous and intracoronary administration of nicorandil reduces reperfusion injury and improves the myocardial infarction frame count and ST resolution in AMI.⁷⁶

Inhibition of C1 esterase reduces infarct size at ischemia-reperfusion.¹⁶ CLB54 monoclonal antibodies administrated, >10mg/kg, directed against CD11/CD18 reduced infarct size in an ischemia-reperfusion baboon model. Fucoidan, a P-selectin inhibitor, improved coronary flow reserve and reduced platelet deposition, neutrophil infiltration and the extent of necrosis at early after reflow. However, in a randomized controlled trial, fucoidan had no positive benefit on inhibition of neutrophil recruitment in AMI.⁷⁷ Pre-treatment with carvedilol preserves endothelial junctions and reduces myocardial no-reflow after AMI reperfusion.⁷⁸ DeltaPKC activation, by protein kinase

C, impairs blood flow in the infarcted tissue after restoring flow in the occluded artery. Therefore, AMI patients with no-reflow may benefit from treatment with a deltaPKC inhibitor given in conjunction with removal of the coronary occlusion.⁷⁹

Intracoronary administration of nitroprusside (NTP) is safe and superior to nitroglycerin (NTG) in improving final epicardial blood flow and microvascular circulation in patients with AMI undergoing primary PCI. Combination therapy of a PercuSurge device and NTP provided additional benefit to NTP alone for improving microvascular circulation.^{80,81}

Further study is needed to determine the relative benefits of these therapies and the proper timing of therapy at the onset of reperfusion.

2. Distal embolization prevention and intra-aortic balloon counterpulsation

Although the use of GuardWire during primary PCI in AMI does not improve microvascular flow or function, reduce infarct size, or enhance long-term event-free survival,^{82,83} most studies confirm that distal protection devices may prevent many unfavourable events by limiting embolization and improving outcomes. Distal embolization may be successfully minimized by using the AngioGuard Emboli Capture Guidewire (Cordis).⁸⁴ The benefits of Filter protection devices are seen especially in patients with higher embolic potential including older patients and those with unstable angina.⁸⁵⁻⁸⁷ However, the benefits of distal protection device need to be supported by a larger population study.

Intra-aortic balloon counterpulsation augmentation performed after reperfusion improves myocardial perfusion at the tissue level, and reduces the extent of no-reflow caused by microvascular obstruction.⁸⁸ This may be a promising approach for prevention of no-reflow.

Conclusion

The no-reflow phenomenon is characterised by damage to microvascular function and microstructure at ischaemia-reperfusion. Microembolisation contributes to no-reflow. Clinical TMP, MCE, scintigraphic and

MRI have shown evidence of microvascular damage. Perfusion defects are closely related to lack of contractile recovery and irreversible myocyte damage. The key to improve no-reflow after AMI may be the development of a new integrated no-reflow treatment approach. This would include agents and devices targeting microvascular injury especially those that protect endothelium and reduce microembolisation.

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