The 'no-reflow' phenomenon

LUCY BLOWS, DIVAKA PERERA, SIMON REDWOOD

Abstract

Microvascular perfusion is considered a key factor with respect to preservation of left ventricular function and prognosis. No-reflow is recognised in the context of acute coronary syndromes and percutaneous intervention: myocardial blood flow at a tissue level remains impaired following restoration of epicardial flow. Once no-reflow is established, treatment is often ineffective and this phenomenon is associated with poor short- and long-term outcomes. A number of different pharmacological agents are used to prevent and treat this condition although data to support their use are limited. This article examines the pathophysiological aspects of this condition, its clinical correlates and proposed management strategies.

Key words: no-reflow, ischaemia, microvasculature, vasodilators.

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Introduction

Inadequate coronary flow, with resultant myocardial ischaemia, is frequently a consequence of epicardial obstruction to blood flow as a result of critical coronary stenoses, with or without focal spasm, thrombotic occlusion or vessel dissection. However, it has become increasingly clear that the epicardial circulation cannot be considered in isolation but must be considered together with the subtended microvasculature, as myocardial blood flow is also dependent on microvascular function and the extent of collateral recruitment.

Trials investigating the role of primary percutaneous intervention for acute myocardial infarction show that while early intervention has undoubted benefits over thrombolysis in terms of prognosis, the reduction in the rate of re-infarction, improvement in left ventricular function and reduction in mortality are modest.[1-3] This may in part be because epicardial vessel patency does not necessarily reflect perfusion at a microvascular level, which is critical to minimise myocardial damage.[4,5]

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The no-reflow phenomenon has been recognised for a number of years. It describes the position when, in the context of ischaemia, myocardial blood flow remains impaired following restoration of epicardial blood flow. This is demonstrated angiographically by sluggish clearance of contrast from unobstructed epicardial vessels.

No-reflow reflects an end point in a pathological process and by definition is associated with no antegrade coronary flow. However, less severe degrees of flow impairment are frequently observed angiographically and are likely to reflect similar pathophysiological mechanisms. It is clear that impaired flow (TIMI flow < 3) is also associated with adverse outcomes.[6-8] This article aims to discuss the mechanisms involved in these processes and their clinical consequences.

Prevalence and clinical importance of no-reflow

Estimates of the prevalence of no-reflow vary according to the precise definition and the technique used to diagnose the condition, for example, myocardial contrast echo (MCE)-defined no-reflow was found to be present in 16% of patients with angiographic TIMI 3 flow after percutaneous coronary intervention (PCI) in one study.[9] Such inconsistencies make data interpretation for this subject particularly difficult.

No-reflow is most commonly recognised during PCI: estimates of its occurrence vary from 2% in elective PCI of stable patients[10] to 30% in the context of acute myocardial infarction (defined by MCE).[9] Patients with no-reflow tend to be older and to have suffered less pre-infarct angina.[11] There is no gender difference or difference in the presence or conventional atherosclerotic risk factors.[12]

Thrombus-containing lesions predispose to this phenomenon and thus it is more frequently seen during intervention to saphenous vein grafts (occurring in up to 20%).[13] In addition, it is encountered more often in the context of intervention on chronic total occlusions[12] and during rotational atherectomy.[14] In the latter scenario this may be related to creation of an increased burden of atherosclerotic debris and to 'un-roofing' of endothelial lipid pools with resultant increased platelet aggregation.

The no-reflow phenomenon has also been observed following coronary artery bypass grafting, although its incidence in this setting has fallen with modern improvements in cardioplegia, reduced bypass time and off-pump surgery.[15]

No-reflow is a clinically important phenomenon because insufficient myocardial blood flow leads to impaired healing and

collateral development. It is associated with a ten-fold increase in the incidence of in-hospital death and acute myocardial infarction, left ventricular dysfunction, ventricular arrhythmias, early congestive cardiac failure and even cardiac rupture.[12,13,16,17]

Pathophysiology

The pathophysiological mechanisms leading to the no-reflow state are incompletely understood. It appears to occur as a result of the interaction between a number of factors that cause damage to the microvasculature and prevent normal perfusion of the myocardium. However, many of the assumptions made regarding the development of no-reflow are based on animal models, which may incompletely reflect the mechanisms at play in human subjects. Animal models often involve vessel ligation and consequent myocyte necrosis (without the presence of thrombus). By contrast, in clinical scenarios of no-reflow the presence of thrombus appears to be a major contributing factor.

A number of classifications have been proposed for this phenomenon but none is entirely satisfactory because of clear overlap between different pathological aspects of the condition.[18]

When considering the microvasculature in the context of no-reflow, there are essentially two components influencing myocardial blood flow, namely a cellular component and the micro-vessel lumen.

Cellular aspects of no-reflow

Myocardial ischaemia provokes a cascade of pro-inflammatory reactions, including activation of the complement system, adherence of neutrophils to the coronary endothelium, leukocyte-mediated injury, and the production of cytokines such as interleukin-6 and interleukin-1.[19] Consequently, levels of intracellular degradation products such as AMP, ADP and adenosine hypoxanthine increase. The associated levels of calcium ions in turn activate xanthine oxidase, resulting in oxygen free radical production.[12,20] These compounds lead to the destruction of endothelial cell membranes and protein denaturation, with resulting loss of cellular integrity.[21] Depending on the severity and duration of the insult, these cellular changes may be irreversible.

Furthermore, in response to ischaemia there is an increase in anaerobic production of osmotically active substances such as lactate and this leads to an increase in intracellular water content by up to 20%. As a result, myocytes and endothelial cells become swollen with large intraluminal projections, which compromise blood flow.[22] During reperfusion the increased hydrostatic pressure exacerbates this cellular and interstitial oedema and may lead to diffuse capillary rupture with haemorrhage into ischaemic tissue.[18]

Luminal aspects of no-reflow

Vessel obstruction is a key contributor to the no-reflow phenomenon. Endothelial damage, as outlined previously, leads to impaired autoregulation and the release of potent vasoconstrictors such as serotonin, causing profound vascular spasm.[23]

Distal embolisation is also thought to have an important role in this condition. It is likely to play a particularly important role in the context of percutaneous intervention, where thrombotic material, activated leukocytes, platelet aggregates, plaque debris and fibrin deposits shower the microvasculature, leading to vascular sludging of intact, albeit dysfunctional, microvasculature. The resulting neuro-hormonal and inflammatory activation further exacerbates flow disruption as a result of additional vasoconstriction.

Clinical presentation

The presentation of these patients depends on the clinical context. In patients with acute myocardial infarction, manifestations include ongoing chest pain and persistent ST-elevation with or without haemodynamic instability. Following percutaneous intervention it may appear suddenly and dramatically with chest pain, gross ECG changes and haemodynamic decompensation following coronary angioplasty or stent deployment. In this setting abrupt reduction in blood flow is usually due to distal dissection or embolisation of thrombus; active exclusion of these conditions is necessary before a diagnosis of no-reflow can be made.

Diagnosis

Current methods for determining the status of the microcirculation include myocardial contrast echocardiography, nuclear imaging techniques such as positron emission tomography and contrast magnetic resonance imaging. Angiographic parameters are frequently used in clinical studies, although these are at best semi-quantitative. Such parameters include the TIMI frame count, defined as the number of frames required for the contrast medium to reach standardised distal coronary landmarks, and the myocardial blush score, which is a subjective assessment of contrast density and its subsequent washout.[24-26]

Angiographic methods provide only a crude assessment of tissue perfusion whilst non-invasive techniques such as myocardial contrast echo (MCE), nuclear and positron emission tomography (PET) imaging improve diagnostic accuracy but may be impractical in acute clinical situations, as they require complicated offline analysis separately from angiographic characterisation of the epicardial anatomy.

Regardless of the diagnostic limitations, impaired microvascular flow as determined by any of these techniques independently predicts impaired recovery of left ventricular function and a poor prognosis.[9,27]

Of the non-invasive techniques, myocardial contrast echo appears the most useful in a clinical setting, since it allows determination of myocardial blood volume and myocardial blood flow. Microvascular integrity, as measured by MCE, has been shown to be closely related to myocyte viability.

Invasive diagnosis of no-reflow has been made using the Doppler flow wire.[28] After restoration of vessel patency, the blood flow rapidly slows, with a characteristic pattern of deceleration of the diastolic velocity. However, interrogation of coronary flow in isolation is limited by the inability to distinguish between epicardial and microvascular compartments. The recently validated method of determining minimum microvascular resistance using

thermodilution techniques and a pressure wire may overcome some of these difficulties.[29,30]

Management

Effective approaches to target no-reflow are important in view of its adverse consequences. Unfortunately, there are few consistent data in this field, largely because its occurrence is somewhat unpredictable and the clinical consequences in individual patients make it a difficult subject for large-scale clinical trials of interventional and pharmacological strategies. Instead, recommendations regarding management are often based on data using examination of the effect of various interventions on end points such as myocardial flow and left ventricular function as surrogates for hard outcomes.

Treatment of no-reflow has not been shown to reduce infarct size because it is usually confined to areas that have already sustained significant damage. However, treatment may improve healing and left ventricular remodelling and may reduce infarct expansion. Furthermore, it may also affect collateral development.

Prevention of no-reflow

Cellular dysfunction

In order to reduce the incidence of structural no-reflow, early intervention for the treatment of ischaemic events should be employed where possible to abort the spiralling microvascular dysfunction. Abolition of ischaemia may restore calcium homeostasis and halt free radical production, thus preserving mitochondrial and cellular integrity. Addressing this phenomenon on a cellular level requires a reduction of myocardial oxygen demand, conventionally with the use of beta blockers and calcium channel blockers.[21] The potassium channel opener nicorandil not only serves to reduce preload and afterload as a result of its systemic actions but also reduces intracellular calcium and protects from free radical effects in tissue that has not been irreversibly damaged. In conjunction with calcium channel blockers it also appears to have a favourable effect on the inflammatory processes inherent to this condition.[31,32] Pre-treatment with these drugs in high-risk situations is a common strategy, although there is little evidence to support this approach directly.[33,34]

The use of compounds targeting intracellular oedema such as mannitol or dexamethasone is not associated with any clinical benefit.

Allopurinol has been investigated as a potential treatment option in view of its capacity to reduce free radical activity. However, *in vivo* studies have failed to show a benefit, as excessive doses prior to an ischaemic insult are required.[35]

Luminal obstruction

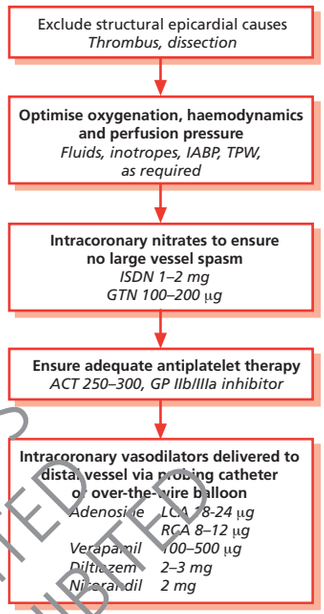
As discussed previously, micro-embolisation plays an important role in the development of no-reflow. It has been suggested that the use of distal protection devices in high-risk scenarios such as acute myocardial infarction or saphenous vein graft intervention might protect against this phenomenon.[36] For example, the Filter Wire–Ex, a distal embolic protection device, has been shown to have a beneficial effect on markers of myocardial reperfusion (corrected TIMI frame count, grade 3 myocardial blush, early ST segment elevation resolution, and peak creatine kinase release) and on left ventricular function.[37,38] However, data are conflicting and disappointingly: for example, the Emerald study failed to demonstrate a reduction in infarct size or an improvement in flow with distal protection devices.[39]

In high-risk situations such as acute myocardial infarction, there is some evidence that stenting is more likely to result in no-reflow than angioplasty alone, possibly because of greater plaque and thrombus disruption.[21] However, any benefits of a strategy of angioplasty alone rather than stenting in the short term would have to be offset against a higher rate of re-occlusion and repeat revascularisation in the medium and long term.

Targeting platelet aggregates with glycoprotein (GP) IIb/IIIa inhibitors has also been advocated as a management strategy for no-reflow. The GP IIb/IIIa inhibitor abciximab has been shown to improve capillary perfusion in animal studies. As yet there have been no large-scale trials specifically examining these drugs in the context of no-reflow, though data form the ADMIRAL trial examining TIMI flow with GP IIb/IIIa inhibitors in the context of primary PCI support their use prior to intervention.[40-42]

Likewise, prostaglandins, ibuprofen and heparinised saline have been shown experimentally to reduce platelet activation[43-45] although this has not been translated into clinical benefit.

Figure 1. Proposed management strategy for no-reflow



Key: IABP= intra-aortic balloon pump; TPW = temporary pacing wire; ISDN = isosorbide dinitrate; GTN = glycerine trinitrate; ACT = activated clotting time; GP IIb/IIIa inhibitor = glycoprotein IIb/IIIa inhibitor; LCA = left coronary artery, RCA = right coronary artery

Treatment of established no-reflow

A proposed management strategy is shown in figure 1 but interventions in the context of established no-reflow are disappointing. Once established, complete reversal of the situation is rare, although it is associated with an improved prognosis. A number of treatments have been tried and most have not been of proven benefit. Perfusion pressure should be maximised with fluid resuscitation, inotropes and intra-aortic balloon counter-pulsation and other supportive measures such as oxygen therapy should be employed.

In the event of abrupt cessation of flow, once an epicardial cause has been excluded, the most successful method of restoring flow is with the use of vasodilators to correct the microvascular spasm inherent in this situation. Anecdotally, these are best delivered through the central port of an over-the-wire balloon or via a transport catheter, for example, a Multifunctional Probing Catheter (Scimed/Boston Scientific), directly into the distal vessel to maximise drug delivery. In this context nicorandil appears promising: its use has been shown to be of clinical benefit in the context of acute myocardial infarction, with improved recovery of left ventricular function.[46] Nitrates are frequently used to treat epicardial spasm but have not been shown to be of benefit in no-reflow as their vasodilatory effects are restricted to arterioles greater than 100 µm in diameter.[10]

Calcium channel blockers act via their effects on vascular smooth muscle. They also influence endothelial function by stimulating the release of endothelium-derived relaxing factor and reducing calcium influx into ischaemic cells.[47,48] *In vitro* a favourable effect on platelet aggregation has been observed through attenuation of the effects of catecholamines. These drugs have been shown to improve no re-flow but not mortality, possibly because of the studies were underpowered. Verapamil is most commonly used in this context although diltiazem and nicardipine have been used and are well tolerated.[49]

Adenosine is the most powerful endogenous vasodilator in humans. It appears to have a number of potential benefits in no-reflow. It improves blood flow directly as a result of its vasoactive properties and appears to preserve endothelial integrity by replenishing high phosphate stores, inhibiting neutrophil function and reducing free radical formation.[50–52] It has also been suggested that adenosine has additional benefits via activation of preconditioning mechanisms. Clinically, its use in the setting of acute myocardial infarction has been associated with a reduced incidence of no-reflow, improved left ventricular function and a reduction in adverse events.[53]

Other vasoactive substances such as papaverine[54] and the nitric oxide donor nitroprusside[55] have been shown to be effective in improving microvascular flow but again not outcome measures. Intracoronary thrombolysis has no role in the treatment of this condition and likewise coronary artery bypass grafting is contraindicated in this context.

In summary, the lack of a definitive management strategy for no-reflow reflects the conflicting and limited data available. As outlined previously, prophylactic measures are not of conclusive benefit. Intra-coronary nitrates should be used to ensure that epicardial spasm is not contributing to impaired flow. It has been suggested that the vasodilators of choice in the situation are verapamil and adenosine; however, there are no large-scale comparative studies of these drugs to date.

Key messages

- No-reflow is estimated to occur in between 2–30% of patients undergoing percutaneous coronary intervention (PCI), depending on patient subsets
- Its occurrence is associated with poor short- and long-term prognosis
- Protective measures include early intervention, aggressive antiplatelet therapy and the use of distal protection devices. Once established, treatment is largely based on administration of intracoronary vasodilators

Conclusion

At present, treatment strategies for this phenomenon are limited and no single approach is likely to solve this difficult clinical problem, as its causes are multi-factorial and act synergistically. Recovery is crucially dependent on the degree of irreversible cellular damage, which in turn is affected by numerous variables, not least of which is collateral flow to the ischaemic territory. The increasing use of invasive physiological assessment and advances in bedside myocardial contrast echo will advance our understanding of the pathophysiology of microvascular function in this clinically challenging subject.

Conflict of interest

None declared.

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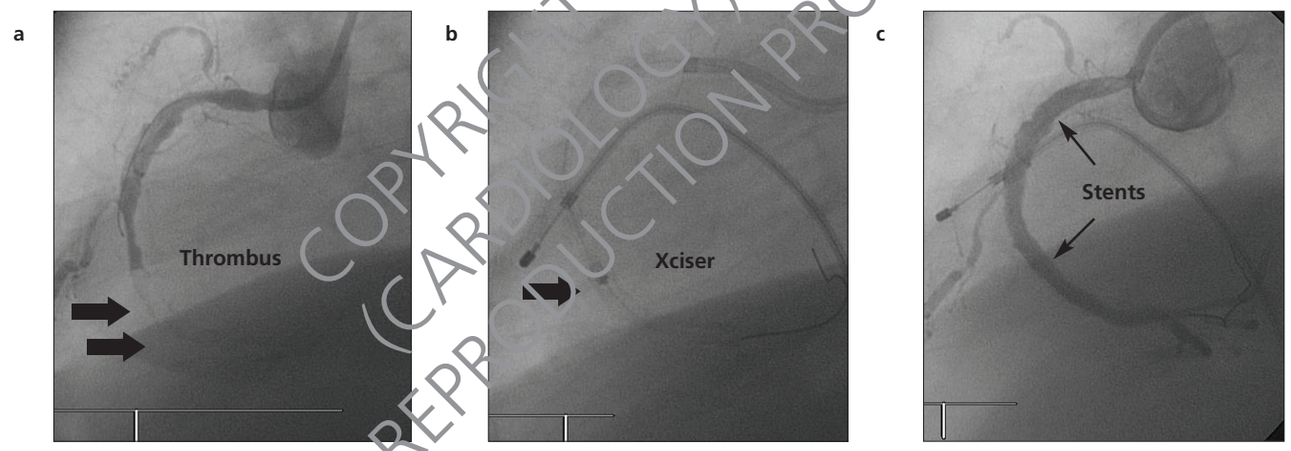
CASE REPORT

Intracoronary thrombectomy

JULIAN GUNN, TUSHAR RAINA

Figure 1. Coronary angiogram showing; **a**: occlusive thrombus in the right coronary artery, **b**: deployment of the Xciser thrombectomy catheter; **c**: the final result after insertion of the two stents



Case report

A 78-year-old man presented with an acute coronary syndrome two weeks following orthopaedic surgery. Coronary angiography revealed that the right coronary artery (RCA) contained a large occlusive thrombus (figure 1a).

After deployment of an 8F Amplatz left-1 guide catheter, an exchange length Balance Heavy Weight wire was advanced through the lesion and a 2 mm Xciser thrombectomy catheter advanced into the lesion. This device is suction-driven, and extracts the thrombus through a propeller-type macerator at the tip (figure 1b).

After balloon inflation and insertion of 4 x 15 mm and 3.5 x 32 mm stents, the final result is shown in figure 1c.

Conflict of interest

None declared.

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