No-reflow: the next challenge in treatment of ST-elevation acute myocardial infarction

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This editorial refers to ‘Plasma levels of thromboxane A2 on admission are associated with no-reflow after primary percutaneous coronary intervention’ by G. Niccoli et al., on page 1843

Coronary revascularization is not synonymous with myocardial reperfusion. DeWood et al.1 almost three decades ago showed that ~90% of patients with transmural myocardial infarction had total coronary occlusion at angiography associated with acute thrombosis. This and other studies have paved the way for the use of fibrinolytics in the treatment of transmural or ST-segment elevation myocardial infarction (STEMI). Despite the clear benefits observed with fibrinolysis, a significant proportion of patients failed to achieve adequate reperfusion as witnessed by persistence of total coronary occlusion, slow epicardial flow at angiography, or failure of regression of other signs of ischaemia such as ST-segment elevation. The advances of percutaneous coronary intervention (PCI) led to the use of balloon angioplasty as a treatment modality for STEMI. Angioplasty was associated with improved epicardial flow, greater reperfusion rates, and improved survival. When readily available, angioplasty (with or without use of coronary stenting) has indeed become the standard of care for STEMI. As experience accumulated with primary angioplasty, it also became evident that there was a group of patients who seemed not to benefit fully from prompt restoration of antegrade flow as they failed to show resolution of indirect signs of ischaemia such as electrocardiographic changes, and improvements in perfusion abnormalities.2–3 These patients also presented peculiar angiographic phenomena characterized by evidence of ‘slow flow’ in the affected vessel and lack of contrast uptake (‘blush’) by the subtended myocardium. This condition is referred to as no-reflow.2–3 The clinical consequences of the no-reflow phenomenon have been rapidly recognized, and highlighted the potential dissociation between coronary revascularization and myocardial reperfusion in STEMI.2–3

Pathophysiology of no-reflow

The cause(s) of no-reflow are, however, still the topic of great debate. In 1974, Kloner et al. described that in dogs 90 min of ischaemia was associated with incomplete reperfusion due to extensive capillary damage.4 Kloner et al.5 went on to demonstrate that changes in the capillary bed followed extensive myocardial damage due to ischaemia. The paradigm of prolonged ischaemia leading to microvasculature damage and secondary thrombosis has been challenged, however, by clinical observations in the cardiac catheterization laboratory.6 Patients with no-reflow after PCI for acute myocardial infarction are often found to have a significantly greater amount of embolic material deriving from platelet–fibrin complexes as well as cholesterol crystals and macrophages trapped in the distal protection device vs patients without no-reflow.6 This led to the generation of an expanded paradigm in which plaque/thrombus embolization during balloon inflation was at least in part responsible for the no-reflow (Figure 1). These premises have led to a large series of experimental studies testing microvascular vasodilators, anti-inflammatory and antithrombotic agents, and thrombectomy/distal protection devices to prevent no-reflow in patients with AMI.3 Review of the individual studies is beyond the scope of this editorial, and no single agent has been shown consistently to improve coronary and myocardial flow, infarct size, and outcome. Much indeed remains unknown about the exact mechanisms leading to no-reflow and the best preventive and therapeutic intervention. The study by Niccoli et al.7 adds knowledge to this field by identifying a potential central role for thromboxane A2 (TxA2) in no-reflow. TxA2 was an independent predictor of no-reflow. Almost half of the patients had no-reflow after PCI and those patients had ~5-fold higher TxA2 levels. Of note, the study included a relatively small number of patients enrolled at a single centre, predominantly male, with first STEMI who had not been...
on aspirin and had received an aspirin load only shortly before intervention. Whether these findings apply to the whole group of patients with no-reflow is therefore unknown.

Interestingly in the dialogue between platelets and microvascularity, TxA2 represents a likely culprit. TxA2 is a powerful platelet agonist while also being a potent coronary vasoconstrictor. In 1989, Grover and Schumaker demonstrated that after 90 min of coronary occlusion in dogs the administration of a TxA2 receptor antagonist was associated with improved myocardial flow and flow reserve, and reduced infarct size compared with a saline solution or aspirin (40 mg/kg). Whether TxA2 levels may be reduced by higher doses or prolonged use of aspirin or if targeted anti-TxA2 treatment is necessary remains unclear. Promising results from novel TxA2 receptor blockers have been reported.

The pathophysiology of no-reflow is, however, very likely to be multifactorial, and no single agent may prove capable of preventing or treating no-reflow. For example, Niccoli et al. had shown in 2006 that patients with no-reflow had higher endothelin-1 (ET-1) circulating levels. ET-1 is a powerful vasoconstrictor agent with a potential causative role in no-reflow. Whether blockade of both TxA-2 and ET-1 is necessary to prevent or treat no-reflow is unknown.

**Clinical perspective**

While waiting for much needed research in this area, every attempt should be made to reduce ischaemic time and optimize pre-intervention therapy, including a timely administration of aspirin (≥325 mg) and clopidogrel (≥600 mg). Early use of high-dose statins (i.e. atorvastatin 80 mg) is also indicated pre-procedurally as they may reduce infarct size. Elective use of abciximab in the catheterization laboratory is encouraged in all cases, and the use of thrombectomy devices in selected patients may be appropriate. The use of a specific intervention to prevent/treat no-reflow cannot be advocated at this time, but investigational use in the setting of controlled clinical trials is encouraged. Assessment of PCI success should include the description of final TIMI (thrombolysis in myocardial infarction) flow and myocardial blush grade, paired with a non-invasive determination of myocardial reperfusion by means of ECG resolution or myocardial contrast echocardiography. Patients with no-reflow should be identified early and considered as at intermediate risk of adverse remodelling and heart failure, and are more likely to benefit from early heart failure treatment.

In conclusion, no-reflow remains a significant challenge for STEMI treatment. Patients who experience no-reflow are denied the benefits of early reperfusion treatment and remain at higher risk for short- and long-term mortality. Widespread use of primary PCI should be paired with an intensive search for the cause(s) and treatment of no-reflow. The study by Niccoli et al. is most welcome as it suggests that TxA2 may represent a novel target for intervention.

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Molecular Insights, and Biosite. G.G.L.B.-Z. has consulted for Boston Scientific, Cordis, Genae, Invatec, and Mediolanum Cardio Research, and has also received lecture fees from Brystol-Myers Squibb.

References

The above article uses a new reference style being piloted by the EHJ that shall soon be used for all articles.