Finding an effective treatment for microvascular obstruction in STEMI: a road to perdition?

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This editorial refers to ‘Strategies to attenuate microvascular obstruction during P-PCI: the randomized reperfusion facilitated by local adjunctive therapy in ST-elevation myocardial infarction trial†, by S.A. Nazir et al., on page 1910.

Perdition is derived from the Latin word ‘perdere’, which literally means ‘to destroy’, and the ‘road to perdition’ refers to a course or path that is destined for failure and damnation. The search for effective therapies for the no-reflow phenomenon, an important and common complication after primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI), has in many ways been a road to perdition for the Interventional Cardiology community. No-reflow, which is caused by microvascular obstruction (MVO), is associated with larger infarct size, poor recovery of ventricular function, and reduced survival.1,2

There is a veritable graveyard of agents that appeared promising in bench and animal studies for prevention or treatment of no-reflow, only to fail in randomized clinical trials. The authors of the REFLO-STEMI trial, reported in this issue of the journal,3 therefore deserve credit for trying to tackle this recalcitrant problem.

In this important trial, 247 patients undergoing primary PCI for STEMI were randomized in a 1:1:1 fashion to either intracoronary adenosine, sodium nitroprusside (SNP), or neither. Cardiac magnetic resonance (CMR) imaging was performed 24–96 h following primary PCI, to determine infarct size and the extent of MVO. Neither early nor late MVO was improved in either experimental arm. Intraprocedural atrioventricular block was more common in patients receiving SNP.3

Why did yet another potentially promising trial fail in preventing no-reflow? Several possibilities should be considered (Figure 1).

One potential problem is the heterogeneity of the pathophysiology contributing to MVO and no-reflow, each of which may require a unique therapeutic approach. Although many of these overlap, broadly speaking there are three essential pathogenic components for MVO: (i) ischaemic injury; (ii) reperfusion injury; and (iii) distal atherothrombotic embolization.4,5 Myocardial ischaemia–reperfusion injury and endothelial damage are central to the development of no-reflow in the setting of primary PCI for STEMI. Endothelial damage is due to a combination of an acute inflammatory response, generation of reactive oxygen species, intracellular calcium overload, and opening of the mitochondrial permeability transition pore.6 This leads to endothelial cell swelling and protrusions, followed by myocyte swelling and interstitial tissue oedema, which can occlude the microvasculature. Microvascular spasm and downstream embolization from epicardial coronary thrombus and atherosclerotic debris during primary PCI compound MVO by plugging the microcirculation.7 Patients with diabetes have pre-existing microvascular disease, which can hasten the onset of MVO.4,5

Adenosine is an endogenous nucleoside mainly produced by the degradation of ATP, which antagonizes platelets and neutrophils, reduces calcium overload and oxygen free radicals, and induces vasodilation.9 Adenosine causes vasodilation by endothelium-independent but receptor-dependent mechanisms, mediated largely via A2 receptors. A2 receptors activate adenylate cyclase through G protein stimulation (Gs subfamily), while A1 receptors inhibit adenylate cyclase by stimulating Gi/Go.4 Much higher concentrations of adenosine are required (up to 1000-fold greater) to activate A2 receptors compared with A1 receptors.10 The relatively low sensitivity of the A2 receptor, plus the short half-life of adenosine, may therefore require high dosages of adenosine to be delivered locally to achieve the desired vasodilatory effect. Nitroprusside and nitroglycerin are nitric oxide donors that help vasodilate resistance arterioles. Microvessels are unable to metabolize nitroglycerin to nitric oxide, but nitroprusside does not require metabolism, a feature that makes this agent preferred to nitroglycerin for MVO.4,5,11 Clearly, this heterogeneity in pathophysiology creates...
challenges for identifying a unified approach for preventing or treating MVO. A detailed understanding of the prevailing pathogenic mechanism(s) leading to no-reflow in the individual patient is thus critical for selecting the most appropriate therapeutic approach, and a combination of approaches that synergistically target multiple pathways may eventually prove to be more beneficial.

Another important issue is that the optimal dose and method of drug delivery are unclear: in the current study, adenosine was administered through an intracoronary catheter initially and then through the guide (total 2–3 mg, two administrations). Earlier studies have assessed different doses (range 0.24–60 mg) and different routes (intracoronary vs. intravenous) and found disparate results. Even among studies utilizing the same route of delivery, the duration of infusion has not been standardized; intracoronary infusions have ranged from bolus push to slow infusion over 5–10 min, which may be particularly relevant due to the short half-life (<15 s) of adenosine. In animal studies, high dose (50 μg/kg/min) prolonged intracoronary infusions appear to be superior to a single low dose bolus in reducing no-reflow and limiting infarct size. The dose-dependent affinity of A2 and A1 receptors for adenosine described above may be a potential explanation for this observation. For SNP, the dosing and delivery have been more consistent. Yet, while benefit on surrogate reperfusion markers has been reported, the clinical benefit is less clear. The current study suggests no benefit of SNP on MVO or clinical outcomes.

Heterogeneity of study populations and adjunctive therapies should also be considered when interpreting results of studies in this field. For example, the current study was restricted to patients with ischaemic time of <6 h, while others have included a window of up to 12 h. Important differences also exist in utilization of adjunctive pharmacotherapy, including heparin vs. bivalirudin, clopidogrel vs. prasugrel or ticagrelor, and mechanical thrombus aspiration.

The methods of assessment of MVO have differed across studies, ranging from ST-segment resolution on ECG at 60–90 min, TIMI perfusion or blush grades, cardiac biomarkers, and various imaging modalities such as echocardiography, SPECT (single-photon emission computed tomography), and CMR. Although CMR is increasingly considered the gold standard for assessing infarct size and MVO in STEMI trials (including in the current trial), there remain some important limitations. Infarct size estimation with delayed enhancement CMR can be performed by visual assessment, semi-automated methods (such as full-width at half-maximum (FWHM), employed here) and other intricate algorithmic approaches. FWHM improves reproducibility but may be inaccurate for patchy or multiple infarcts, and when the infarct appears homogeneously grey rather than as a bright infarct core. Although good correlations have been reported between readers for individual studies, there may be significant interstudy variations. Currently used delayed enhancement CMR imaging techniques may also not have the optimal spatial resolution to detect small infarcts. From a practical standpoint, the data set for CMR is frequently incomplete. In the current trial, >20% of patients randomized did not undergo CMR imaging, due to a combination of in-hospital mortality and inability to complete the CMR protocol. Lastly, the optimal timing for assessment of MVO and infarct size post-STEMI is hotly debated. CMR estimation of infarct size has been shown to double during the first few days after coronary artery occlusion due to myocardial oedema, and then shrink by as much as 75% over 4–8 weeks as necrotic muscle is replaced by scar.

Figure 1 Key reasons for failure of microvascular obstruction (MVO) prevention therapies in clinical trials.
ejection fraction assessments also tend to be more reliable after 4 weeks.\textsuperscript{15,17}

Where does this leave us with regard to the use of intracoronary adenosine and SNP for prevention of no-reflow? Both US and European STEMI guidelines recognize the importance of MVO and no-reflow post-primary PCI, but, given the paucity of data, do not provide recommendations for or against the use of adenosine or SNP for preventing or treating MVO.\textsuperscript{18,19} Data from this study indicate that SNP may not be beneficial, while adenosine may be potentially harmful when administered routinely to patients with STEMI.\textsuperscript{3}

One could posit that future studies with adenosine may thus be unethical given potential harm observed with adenosine. However, this would be specious since this is one of the first studies to show a harmful effect of adenosine on cardiovascular outcomes other than atrioventricular block, with other studies showing favourable trends in clinical outcomes.\textsuperscript{12} Importantly, this study also does not address the administration of adenosine or SNP as ‘rescue’ therapies when no-reflow occurs after primary PCI. Thus, larger well-powered studies on this topic are still needed to exclude definitively a role of adenosine in this clinical scenario.

In conclusion, the well conducted REFLO-STEMI trial probably adds adenosine and nitroprusside to the graveyard of failed therapies for prevention of MVO and reduction of infarct size, and cardiologists remain stranded on a road to perdition for this difficult clinical problem. Moving forward, it will be critical to identify well-phenotyped subpopulations for future studies who may be more responsive to treatment, perhaps by focusing on early presentations of high-risk individuals, and by targeting the most prevalent or even multiple complementary mechanisms simultaneously, including intracellular cardioprotective signalling pathways. Clinically relevant endpoints for future trials also need to be assiduously selected, assessed, and followed-up, with special attention to minimizing drop-outs. It is now clear that there will be no silver bullet for success in this field. Hopefully, careful consideration of these important mechanistic and study design features in future trials will lead us to an exit from this road to perdition.

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References