No Reflow and the Quest to Achieve Optimal Perfusion During the Acute Phase of Myocardial Infarction*

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Improved survival in the acute phase of myocardial infarction (MI) is directly related to the speed at which the occluded infarct-related epicardial artery can be recanalized after symptom onset, the degree of patency achieved, and the quality of restoration of blood flow to the microcirculation and myocardium at risk. Three decades ago, Kloner et al. (1) reported important capillary damage associated with interstitial and myocardial cellular edema after 90 min of coronary occlusion in an experimental canine model with electron microscopy. More prolonged periods of coronary occlusion resulted in severe inflammation and disruption of the capillary network. Similar processes occur in the clinical setting of acute MI. However, in addition to the microcirculatory damage caused by the ischemia-reperfusion injury, placement of a stent into a previously thrombosed vessel may result in distal embolization, spasm, and release of vasoactive mediators. When the pathophysiologic response is severe, the slow or no reflow phenomenon occurs, defined as adequate restoration of epicardial flow but poor or no distal tissue-level perfusion (2).

Several years ago, the Stent Primary Angioplasty in Myocardial Infarction Study (STENT-PAMI) trial tested percutaneous transluminal coronary angioplasty with and without stent placement and observed a non-significant higher mortality rate in the stent group, perhaps accounted for by a trend toward lower rates of Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 or myocardial blush grade (MBG) in the stent group (3). This led to an intense effort to optimally restore coronary blood flow, not only at the epicardial level, but also at the microcirculatory level in patients who received stents on the premise that amelioration of the no-reflow phenomenon might improve survival (4–8). The Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) was a multicenter clinical trial of 2,082 patients with acute MI (primarily, ST-elevation myocardial infarction [STEMI]) that presented within 12 h of symptom onset; patients were randomized to primary balloon angioplasty ± abciximab versus primary stenting (Multilink) ± abciximab, typically started minutes before the procedure. Recurrent ischemia and subacute thrombotic events were significantly reduced with abciximab treatment, although there were no differences in one-year mortality rates (4.1% for abciximab vs. 4.4% for placebo) (5).

In this issue of the Journal, Costantini et al. (6) examine a subset of 1,301 patients in a retrospective review of the CADILLAC coronary angiograms and report improved one-year survival in patients who achieved greater tissue-level perfusion after therapy. De Luca et al. (10) reported similar findings after percutaneous coronary intervention (PCI) for STEMI in patients with heart failure. In the Costantini et al. (9) study, tissue-level perfusion was assessed angiographically at the time of cardiac catheterization by MBG; most patients did not achieve optimal blush grade. Most patients did not achieve optimal blush grade. Despite TIMI flow grade 3 restoration in 96.1% of patients, blush grade was normal in only 17.4% of subjects; 33.9% had reduced flow, and 48.7% had no-reflow. The one-year mortality rates were 1.4%, 4.1%, and 6.2%, respectively (p = 0.01). The worse the blush grade, the worse the left ventricular function at seven-month follow-up angiography. Abciximab was not associated with better tissue-level perfusion, nor was there an association between tissue-level perfusion and the use of coronary stents compared with balloon angioplasty alone. In other words, coronary stenting, which requires deployment of a bulky stent at high inflation pressures into a vessel with an acute thrombotic process during acute MI, was not associated with worse tissue-level perfusion, an important observation because many acute MI patients receive stents during their PCI procedure to prevent subacute closure and restenosis.

The reader should be cautious before extrapolating the Costantini results to all patients who present with STEMI. The CADILLAC trial excluded patients with cardiogenic shock, saphenous vein graft lesions, relatively small infarct vessels, and longer lesions as well as patients requiring urgent coronary bypass surgery; ~12% of patients did not have STEMI or left bundle-branch block, and ~45% of patients had inferior MI. Thus, CADILLAC did not test abciximab in a higher risk MI group, which, along with other protocol differences, may explain the discordant negative results of the CADILLAC trial with other earlier smaller, positive abciximab studies that included higher risk subjects (4,6).

A key issue in evaluating the efficacy of glycoprotein IIb/IIIa blockade in improving tissue-level perfusion after recanalization of the infarct-related artery is the timing of its administration (11). In the Costantini study, the longer it took to achieve recanalization (i.e., later average time from symptom onset to balloon), the more likely it was that...
MBG 0/1 was observed. Early treatment after symptom onset before the patient presents to the catheterization laboratory for PCI would allow more time for abciximab to work, thus potentially reducing thrombus burden, allow for better visualization of the culprit lesion (which may facilitate stent selection or identification of the infarct-related vessel in a difficult patient with multivessel disease), improve microcirculatory flow, and facilitate the PCI procedure. In CADILLAC, facilitated PCI with early pretreatment was not used, and abciximab was given minutes before the PCI procedure was performed, similar to other smaller trials (6,8). Large ongoing acute STEMI trials such as the Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events (FINESSE) may provide more definitive answers regarding the relationship between improved coronary flow reserve (tissue-level perfusion) resulting from early pretreatment with abciximab before PCI and whether or not this has an impact on long-term outcome (12).

Epicardial blood flow as assessed by MBG, as used in CADILLAC, is a semi-quantitative method to assess the microcirculation. Direct assessment of coronary flow reserve (CFR) using a Doppler guide-wire technique provides a more direct method to assess microvascular reserve. In a recent study of patients with anterior MI undergoing PCI, a CFR >2 rather than MBG predicted recovery of left ventricular function (13). Angiographic techniques are limited to the timing of the procedure and are not well suited for serial observations. Thus, a drug might well improve coronary vascular reserve in the acute MI setting, but the improvement may occur just after the angiographic procedure was terminated; later improvement in the microcirculation may not be captured. Non-invasive imaging, for example, serial myocardial contrast echocardiograms or perhaps serial electrocardiograms (e.g., resolution of ST-segment elevation) may be better suited to indirectly measure tissue-level perfusion than angiographic methods and should be considered in the planning of future trials to assess the microcirculation (8,14–16).

It is difficult to test the efficacy of drug therapy to improve slow or no-reflow and then prove that the improved survival with treatment is directly related to the change in flow patterns at the microcirculatory level. Associations in a retrospective analysis, as shown in the Costantini et al. (9) study, are not the same as prospective serial observations in individual patients with a prespecified hypothesis. To truly answer the question of whether improved tissue-level perfusion is the right target for the assessment of the efficacy of glycoprotein IIb/IIIa blockade, serial changes in the microcirculation of individual patients would need to be measured, and improvement in tissue-level perfusion shown to be directly related to long-term outcome after adjustment for other variables known to affect outcome. For example, one could hypothesize that abciximab might improve survival by reducing early recurrent ischemic-thrombotic events or reducing the inflammatory process and that the survival benefit with the drug has little to do with tissue-level perfusion. Tissue-level perfusion might simply be a marker of the duration of the ischemia/injury process (ischemia-reperfusion injury), and an inappropriate target for the assessment of the benefits of abciximab therapy.

The era of placebo-controlled trials in acute STEMI to assess glycoprotein IIb/IIIa receptor blockade on restoration of microcirculatory flow has probably passed because many clinicians would think it is unethical to withhold therapy simply to test whether or not glycoprotein IIb/IIIa receptor blockers improve tissue-level perfusion, given the reduction in recurrent ischemic-thrombotic events and improved survival in higher risk patients observed with therapy. The Costantini et al. (9) and De Luca et al. (10) studies demonstrate the importance of considering the quality of microcirculatory reperfusion to estimate one-year survival. Clearly, more research into methods to more rapidly restore microcirculatory flow, prevent distal emboli, and reduce ischemia-reperfusion injury is needed. In the meantime, the quest to improve tissue-level perfusion and reduce the no-reflow phenomenon, a frustrating experience to the interventional cardiologist who has just performed a wonderful recanalization result, might be better achieved by a continued intense national effort to reduce the time from a patient’s symptom onset to successful recanalization of the infarct-related vessel.

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