EDITORIAL COMMENT

Advances in the Assessment of No-Reflow After Successful Primary Percutaneous Coronary Intervention for Acute ST-Segment Elevation Myocardial Infarction

Now That We Can Diagnose It, What Do We Do About It?*

Paul A. Grayburn, MD, FACC, James W. Choi, MD, FACC
Dallas, Texas

The current standard of care for acute ST-segment elevation myocardial infarction (STEMI) is primary percutaneous coronary intervention (PCI), provided that it is available and can be performed soon enough after the onset of symptoms. However, successful restoration of antegrade coronary flow with PCI of the “culprit” lesion does not always result in myocardial salvage because of the known disparity between epicardial coronary flow and microvascular perfusion in the acute myocardial infarction (MI) setting.

See pages 552 and 560

Kloner et al. (1) first described the no-reflow phenomenon in dogs with experimental MI. Ito et al. (2) demonstrated the presence of no-reflow in humans by using intracoronary myocardial contrast echocardiography (MCE) to show absence of microvascular perfusion despite successful PCI with Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 in roughly 25% of patients. No-reflow is associated with microvascular plugging by neutrophils and/or microemboli, perivascular edema, platelet activation, and inflammation and may be aggravated by reperfusion injury. Ischemic preconditioning is known to protect against the no-reflow phenomenon. In clinical studies, no-reflow is associated with worse outcomes, including left ventricular (LV) dysfunction and death (3,4). Accordingly, the American College of Cardiology/American Heart Association guidelines for management of STEMI have stressed the importance of evaluating the no-reflow phenomenon: “A high priority exists for the development of simple, accurate, readily available noninvasive techniques to assess the success of pharmacological reperfusion early, i.e., 60 to 90 minutes after administration of therapy” (5). In this issue of the Journal, 2 papers (6,7) have attempted to measure the extent of microvascular damage associated with the no-reflow phenomenon after successful primary PCI for acute STEMI.

Index of Microcirculatory Resistance (IMR)

Fearon et al. (6) report the results of IMR in 29 patients who underwent successful PCI of the infarct artery after STEMI (primary PCI in 26 and rescue after failed thrombolysis in 3). Using a pressure/thermistor wire placed distally in the culprit vessel after PCI, IMR was calculated as the product of distal coronary pressure and hyperemic transit time (derived by thermodilution during intracoronary papaverine or intravenous adenosine). They found that IMR correlated much better with peak creatine kinase (CK) and 3-month echocardiographic wall motion score than TIMI frame count, myocardial blush grade, coronary flow reserve ratio, or ST-segment resolution. An IMR lower than the median value of 32 U was deemed reasonably good to identify patients whose wall motion score improved at 3 months. The authors concluded that IMR is an independent predictor of acute microvascular damage and late (3-month) LV functional recovery. The study has obvious limitations, such as small numbers, use of peak CK to assess infarct size, potential differences between intracoronary papaverine and intravenous adenosine. They found that IMR correlated much better with peak creatine kinase (CK) and 3-month echocardiographic wall motion score than TIMI frame count, myocardial blush grade, coronary flow reserve ratio, or ST-segment resolution. An IMR lower than the median value of 32 U was deemed reasonably good to identify patients whose wall motion score improved at 3 months. The authors concluded that IMR is an independent predictor of acute microvascular damage and late (3-month) LV functional recovery. The study has obvious limitations, such as small numbers, use of peak CK to assess infarct size, potential differences between intracoronary papaverine and intravenous adenosine, and absence of outcomes. However, the strength of this approach is that it can be performed in the catheterization laboratory immediately after primary PCI and thus give the earliest possible estimate of the effect of primary PCI on microvascular function. In addition, IMR provides a direct quantitative measure of microvascular function, which is an advantage over TIMI frame counts, blush score, or ST-segment resolution.

The AMICI Trial

The authors of the AMICI (Acute Myocardial Infarction Contrast Imaging) trial (7) studied myocardial perfusion by using MCE in 110 consecutive patients who underwent successful primary or rescue PCI within 6 h of STEMI. They performed MCE within 1 day of PCI and compared it with TIMI flow grade, myocardial blush grade, peak CK, ST-segment resolution, and echocardiographic wall motion score. The end point was LV remodeling, which occurred in 25% of patients and was defined as a 20% increase in LV end-diastolic volume at the 6-month follow-up echocardi-
oography. With the use of multivariate analysis, these researchers found only the endocardial length of the myocardial perfusion defect on MCE and a TIMI score <3 to predict LV remodeling. In the subset of patients with a TIMI score of 3, only the endocardial length of MCE perfusion defect predicted LV remodeling. The study could have been stronger had more patients been enrolled, had outcomes been analyzed, and had a more accurate measurement of LV remodeling and infarct size, specifically if cine magnetic resonance with delayed hyperenhancement, been used (8). Moreover, the authors did not take advantage of the ability of MCE to provide quantitative information about myocardial blood volume and microvascular flow (9,10). Nevertheless, the study confirms that MCE, a direct noninvasive measure of microvascular damage after STEMI, is superior to subjective and indirect measures (TIMI score, myocardial blush grade, and ST-segment resolution).

**Implications for Treatment**

Although these 2 studies demonstrate the ability to detect no-reflow early after PCI for STEMI, what do we do with the information? Unfortunately, the answer is not clear. Although several clinical trials have evaluated adjunctive therapy to address microvascular dysfunction accompanying STEMI, no therapy has yet been proven to reverse no-reflow. The EMERALD (European and Australian Multicenter Evaluative Research on Atrial Fibrillation–Dofetilide) trial (11) showed that distal protection devices successfully remove atheroembolic debris during primary PCI but do not improve survival, microvascular flow, reperfusion, infarct size, or LV function. The CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) trial (12) showed primary stent placement to be superior to primary balloon angioplasty, but adjunctive therapy with abciximab did not improve outcome. In contrast, the ADMIRAL (Platelet Glycoprotein IIIb/IIIa Inhibition With Coronary Stenting for Acute Myocardial Infarction) trial (13) showed that abciximab given to patients before primary PCI improved TIMI score, LV function, and a composite end point of death, nonfatal MI, and target vessel revascularization. However, there is no evidence that abciximab can salvage established no-reflow. Small studies of intracoronary vasodilators, such as verapamil, nicardipine, and nitroprusside, have shown improved TIMI scores, but outcomes data are lacking (14–17). The AMISTAD II trial (18) failed to show improved clinical outcomes in 21,118 patients with STEMI undergoing reperfusion therapy with adenosine as an adjunctive therapy. Nicorandil, a mitochondrial potassium–channel opener, has been shown to improve microvascular perfusion in patients with STEMI when given before reperfusion (19,20). Sodium–hydrogen pump inhibitors block intracellular calcium overload; however, large multicenter trials have not shown clinical benefit as adjunctive therapy to primary PCI (21,22).

**Implications for Future Research**

Could the trials of treatment for no-reflow have been wrong? It is possible that failure of therapeutic benefits in no-reflow patients is related to inclusion of all STEMI patients, the majority (70% to 75%) of which do not have no-reflow phenomenon. Thus, the use of IMR or MCE to identify no-reflow patients, who are optimal candidates for adjunctive therapies, could affect future trial design. Patients with documented no-reflow by these methods could be randomized to treatment or placebo, using cine magnetic resonance to assess infarct size and MCE to quantitate perfusion. In the meantime, we are left to wonder what to do when we find no-reflow in our patients.

Reprint requests and correspondence: Dr. Paul A. Grayburn, Baylor Heart and Vascular Institute, 621 N. Hall Street, Suite H030, Dallas, Texas 75226. E-mail: paulgr@baylorhealth.edu.

**REFERENCES**

7. Galilto L, Garramone B, Scarà A, et al., on behalf of the AMICI Investigators. The extent of microvascular damage at myocardial contrast echocardiography is superior to other known indexes of post-infarct reperfusion in predicting left ventricular remodeling: results of the AMICI study. J Am Coll Cardiol 2008;51:552–9.