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EDITORIAL COMMENT

Fractional Flow Reserve in Nonculprit Vessel During ST-Segment Elevation Myocardial Infarction

Reliable or Prone to Error?*

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The incidence of multivessel coronary artery disease during acute myocardial infarction (MI) has been reported to be >50% (1). However, management of nonculprit vessels has been controversial. In a post hoc analysis of the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial, multivessel percutaneous coronary intervention (PCI) performed during the index procedure resulted in higher mortality than when PCI was performed as a staged procedure (2). By contrast, more recent clinical trials have suggested that revascularization of nonculprit coronary artery stenoses during the first month after primary PCI might result in a significant survival benefit. The PRAMI (Preventive Angioplasty in Myocardial Infarction) and CvLPRIT (Complete Versus Lesion-Only Primary PCI) trials both showed angiographically guided complete revascularization in patients undergoing primary PCI for ST-segment elevation myocardial infarction (STEMI) led to better outcomes driven primarily by a later reduction of urgent revascularization (3,4). More mechanistic trials such as the DANAMI-3 PRIMULTI (Primary PCI in Patients With ST-Elevation Myocardial Infarction and Multivessel Disease: Treatment of Culprit Lesion Only or Complete Revascularization) and Compare-Acute (Comparison Between FFR Guided Revascularization Versus Conventional Strategy in Acute STEMI Patients With MVD) trials both also studied complete revascularization but used fractional flow reserve (FFR) guidance of the nonculprit vessel and demonstrated fewer nonculprit lesions to be revascularized compared with an angiographic-guided approach (5,6). The percentage of angiographically significant, non-infarct-related lesions with FFR >0.80 was 31% in the DANAMI-3 PRIMUTI trial and 50% in the Compare-Acute trial. Still, the primary composite outcome showed statistically significant improvement that was also driven mostly by reduced urgent revascularization of the noninfarct vessel. Finally, Ntalianis et al. (7) also investigated the stability of FFR results overtime in nonculprit lesions, including 75 STEMI patients and 26 non-ST-segment myocardial infarction (NSTEMI) patients immediately post-PCI and later after 35 ± 4 days. They found the FFR values in nonculprit lesions did not change between the acute and follow-up period. In only 2 patients, the FFR value was >0.80 in acute and lower than 0.75 at follow-up. Index of microcirculatory resistance (IMR) was measured in 14 nonculprit lesions and was normal in 79% of cases. Improved outcomes have also been reported for FFR guidance in multivessel revascularization in the setting of unstable angina or NSTEMI in the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) substudy (8) and FAMOUS-NSTEMI (Fractional Flow Reserve Versus Angiographically Guided Management to Optimise Outcomes in Unstable Coronary Syndromes) randomized trial (9). On the basis of these trials (8,9), the recent focused update of the American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions guideline for acute STEMI has changed the

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recommendations regarding nonculprit revascularization in acute MI patients from Class III to Class IIb.

However, the accuracy of FFR as a modality in a nonculprit lesion setting of acute MI has been questioned in the past. Microvascular dysfunction in the culprit territory may lead to impaired hyperemic flow in the nonculprit myocardium, causing FFR to be higher in the acute setting. Whether microvascular dysfunction involves the nonculprit territory, and if so, when does it resolve, are once again clinically relevant questions. Answers to these questions will help ensure the accuracy of FFR performed in nonculprit arteries at the time of index procedure or later during admission.

Two studies in the past have examined this question using positron-emission tomography and Doppler flow, and concluded that the noninfarcted myocardium is impacted during myocardial infarction of a remote territory. Uren et al. (10) studied 13 patients with single-vessel STEMI 8 ± 3 days post-fibrinolysis with positron-emission tomography for myocardial blood flow in infarcted and remote regions under basal, as well as hyperemic, conditions after giving dipyridamole and later after 6 ± 2 months in 9 of 13 patients. They compared the myocardial blood flow in remote regions to that in 10 control patients. The results showed that coronary vasodilator response was depressed in both infarcted and remote regions. In 6 months, the vasodilator response remained depressed in the infarcted region, but in the remote region improved, although remaining lower compared with normal control patients.

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de Waard et al. (11) studied 40 patients presenting with STEMI immediately post-revascularization in culprit and nonculprit arteries without epicardial disease with intracoronary Doppler flow velocities to calculate coronary flow reserve (CFR). Similar measurements were also made in 11 AMI porcine models both before and immediately after 75-min balloon occlusion of the left circumflex coronary artery. They found that CFR was reduced 36% in the culprit territory due to increased baseline flow and reduced hyperemic flow. Similar findings were found in the nonculprit arteries except in patients with a large infarction involving more than 15% myocardium, where culprit vessels showed lower CFR than nonculprit vessels. They proposed the microvascular dysfunction was wide spread and involved both infarct and noninfarct territories. Due to recent interest in microvascular function in the remote noninfarcted bed, Lee et al. (12) in this issue of *JACC: Cardiovascular Interventions* examine this question using a porcine MI model induced with microspheres. Coronary stenoses were created in both the left anterior descending (LAD) and the left circumflex coronary arteries followed by intracoronary injection of microspheres into the LAD to create the culprit territory. FFR and IMR were subsequently measured with successive microsphere injections in both the infarction and remote myocardial beds. Even though both arteries had similar stenoses with successive injections, IMR and FFR increased in the LAD territory; however, measurements in the circumflex remained unaffected. Increases in IMR in the LAD correlated with hyperemic mean transit time. The current study (12) thus demonstrates no evidence of involvement of the microcirculation in the remote noninfarcted myocardium.

Why is there a discrepancy with the older published reports? There were weaknesses in prior studies. The study by Uren et al. (10) was conducted in the fibrinolysis era in subjects more than a week after infarct and is not reflective of current practice. de Waard et al (11) used an intracoronary Doppler wire for their study, which introduces variability in measurements due to the unpredictable location of the Doppler crystal in the coronary lumen, resulting in inconsistent signal acquisition. As a result, only two-thirds of measurements could be used in their final analysis. This may have led to underestimation of hyperemic flows and will cause overestimation of FFR.

The current study by Lee et al. (12) and the study by Ntalianis et al. (7) both measured IMR in culprit and nonculprit vessels, demonstrating that IMR is low and does not change in nonculprit vessels. FFR calculation for hemodynamic significance of epicardial stenosis assumes distal microvascular resistance is negligible, and these studies prove FFR can be reliably calculated in nonculprit territory even in the acute setting because IMR remains low. Both the DANAMI-3 PRIMULTI trial, which assessed FFR 2 days after PCI, and the Compare-Acute trial, which assessed FFR at time of the index procedure in a much larger number of subjects, had also reached similar conclusions. In view of the work by Lee et al. (12), interventionists should feel confident of the accuracy of their measurement of FFR in the nonculprit vessel.

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