EDITORIAL

Myocardial perfusion imaging prior to coronary revascularization: From risk stratification to procedure guidance

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According to the 2016 American Heart Association Heart Disease and Stroke statistics update, 16.5 million people in the United States ≥ 20 years of age have coronary artery disease (CAD).[1] A large study of all veterans undergoing elective coronary angiography in the Veterans Affairs health care system between 2007 and 2012 demonstrated that the 1-year risk of death or myocardial infarction for patients with obstructive CAD ranges from twice (for 1-vessel disease) to more than quadruple (for 3-vessel or left main disease) that of patients without visible CAD.[2] Furthermore, obstructive CAD is a frequent cause of angina which may limit quality of life.[3] In patients with stable CAD, coronary revascularization may be pursued to (1) decrease angina and improve quality of life, and/or (2) to prolong life and prevent downstream hard cardiovascular events such as myocardial infarction. The role of coronary revascularization in patients with obstructive but stable CAD, and how best to perform it, is a topic of ongoing debate and research.

Large clinical trials have conclusively shown that both optimal medical therapy and revascularization can achieve improvement in myocardial ischemic burden, as assessed by myocardial perfusion imaging (MPI), and symptom burden.[4–7] For example, in the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, both the PCI and medical therapy groups experienced an approximately sixfold reduction in angina prevalence, with 74% of the PCI group and 72% of the medical therapy group free of angina at 5-year follow-up. A substudy of COURAGE using nuclear myocardial perfusion stress testing revealed that patients in both arms also exhibited improvement in myocardial perfusion; at a mean follow-up of 12 months, at least 5% absolute reduction in ischemic myocardium was seen in 33% of patients in PCI group and 19% of patients in medical therapy group.[8] Another substudy of COURAGE used the Seattle Angina Questionnaire to evaluate five domains of patient-reported health status, including physical limitation, angina frequency, and quality of life, over 3 years of follow-up after randomization. A clinically significant improvement in each of these measures at 3 years was seen in a large proportion of patients with no significant difference between the two arms.[9] The recently presented Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina (ORBITA) trial cast some doubt on the effectiveness of PCI on symptom burden in stable CAD when assessed in a blinded, randomized placebo-controlled fashion.[10] There is abundance of literature on the prognostic value of MPI in patients with stable CAD which allows for its use in risk stratification.[11–13] While the COURAGE trial did not demonstrate a benefit of coronary revascularization on hard cardiovascular events in patients with stable CAD,[5] a seminal retrospective study suggested that MPI may be useful to guide coronary revascularization.[14] In that study, patients with moderate or severe ischemia had

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lower cardiac death with revascularization while those with no or mild ischemia did better with medical therapy without revascularization. These data have been reproduced in multiple independent retrospective studies[15–17] but not in all.[18] It is important to emphasize that we still lack prospective studies validating the role of MPI in guiding coronary revascularization.

An important question in clinical management of patients with stable CAD is whether a non-invasive technique can reliably predict improvement in blood flow and ischemia to a specific region of myocardium after revascularization. Bober et al.[19] used positron emission tomography (PET) stress testing before and after coronary revascularization in a small series of 19 patients to show that myocardial regions with perfusion defects on initial imaging achieved a significant improvement in blood flow after revascularization. The study was not powered to detect differences in clinical outcomes, but the data suggest that MPI may be useful for determining if a myocardial region will or will not benefit from revascularization. A logical next step would be to evaluate whether patients with ischemia on MPI who receive revascularization of the specific ischemic territory have better clinical outcomes than those who do not, either because the revascularization failed to include all of the ischemic territory, or no intervention was performed at all.

In this issue of the Journal, Li et al.[20] report on a retrospective study of 286 consecutive patients who underwent stress and rest SPECT MPI prior to treatment by complete coronary revascularization (CCR), incomplete coronary revascularization (ICR), or no coronary revascularization (NCR) within 3 months of MPI. All patients had significant CAD by angiography defined as $\geq$ 70% diameter stenosis of at least one major epicardial artery or one of its major branches. Uniquely, the completeness of coronary revascularization was defined by ischemia on MPI rather than by anatomic obstruction on angiography[21]—i.e., if a patient had ischemia in the LAD territory and significant stenoses in both the LAD and LCX territories, revascularization of the LAD lesion alone would suffice to consider this CCR. Conversely, if the same patient had only LCX stenosis that underwent revascularization but an LAD that had diffuse disease not amenable to revascularization, it would be considered ICR. The aim of the study was to compare the outcomes of each treatment group and determine how those outcomes differ between patients with vs without moderate-severe baseline ischemia. Among all patients over a mean follow-up of 46 months, there were 30 deaths and 65 major adverse cardiovascular events (MACE—defined as all-cause death, non-fatal myocardial infarction, or unplanned repeat revascularization).

In this study, 39% of patients received CCR, 32% ICR, and 29% NCR. Coronary revascularization (CCR and ICR combine) was associated with lower MACE (22.1% vs 36.4%, $P < .001$) but similar mortality (15.5% vs 15.5%, $P = .163$) compared to NCR. CCR was associated with significantly lower mortality and MACE in both the overall cohort (death HR 1.88, $P = .018$; MACE HR 2.10, $P < .001$ as compared to ICR/NCR) and among patients with $\geq$ 10% ischemic myocardium on baseline MPI (death HR 1.71, $P = .017$; MACE HR 2.08, $P < .001$ as compared to ICR/NCR), but not among those with less ischemia. In multivariate Cox regression, CCR was independently associated with lower mortality (hazard ratio 0.31, $P = .017$) and MACE (hazard ratio 0.30, $P < .001$). The authors conclude that CCR is associated with superior outcomes compared with ICR or NCR in patients with obstructive CAD and detectable ischemia on MPI, especially in patients with $\geq$ 10% ischemic myocardium.

One very important aspect of the present study is the use of MPI, rather than coronary angiography, for defining complete and incomplete revascularization. As the authors point out in their discussion, revascularization is often incomplete even when done in the controlled setting of clinical trials. For example, in the COURAGE nuclear substudy, nearly half of patients had $\geq$ 5% ischemic myocardium *after* PCI, and 16% had $\geq$ 10% ischemic myocardium.[8] A key limitation is the absence of follow-up imaging to determine the effect of revascularization and/or medical therapy on the perfusion abnormality. We are therefore uncertain whether revascularization, even if complete by this definition, resulted in resolution of ischemia. By the same token, it is possible that ICR or even NCR may have resulted in comparable favorable effects on myocardial perfusion.[22] Nevertheless, prior studies using serial MPI have demonstrated that coronary revascularization is more effective at reducing myocardial ischemia than medical therapy,[7,8,23,24] and that changes in myocardial perfusion on serial imaging provide useful prognostic information that associates with cardiovascular events even after accounting for baseline perfusion defect size, left ventricular ejection fraction, and clinical characteristics.[25] In the study by El-Hajj et al.[25] of 698 patients who underwent serial regadenoson MPI, the worst outcomes were seen in patients who had worsening perfusion pattern over time irrespective of whether or not they had coronary revascularization in the interim. Another limitation involves the determination of coronary territories by myocardial perfusion which is not an exact science and may be misleading on occasions due to the well-known overlap of these territories. This may have led to misclassification of the completeness of revascularization. An important limitation in this study, similar to any other retrospective study, is that the decision for coronary revascularization and its completeness is not randomized and therefore may have been due to a number of characteristics that were not accounted for, and these in turn may have affected the clinical outcome. The small sample size and the relatively small number of events during follow-up are other limitations. Finally, in the ICR arm it is unclear whether CCR was feasible but not performed or not feasible at all, and therefore could not have been performed.

The study by Li et al.[20] adds to the literature on how MPI can be used to guide management of patients with stable CAD and help in the decision making of when coronary revascularization is useful. The ongoing International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial will provide prospective randomized controlled data on this subject in the near future.[26] It is certain that MPI has a key role in the management of patients with stable CAD at every level from diagnosis, to risk stratification, and ultimately to decision making.

Disclosures

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