EDITORIAL

Physiology-Based Revascularization Decisions and Improved Clinical Outcomes Following Percutaneous Coronary Interventions

Richard G. Bach, MD

The introduction of coronary angiography more than 50 years ago led to a major shift in the diagnosis and management of coronary artery disease. As the first technique to visualize the severity and location of obstructive lesions in the coronary arteries of living patients, coronary angiography enabled the development of coronary revascularization by coronary artery bypass graft (CABG) surgery and percutaneous coronary intervention (PCI), arguably 2 of the most important advances in cardiovascular medicine.

Related article

Despite its central role in the management of coronary syndromes, as a 2-dimensional contrast "luminogram," a coronary angiogram has well-recognized and important limitations. Coronary angiograms may overestimate or underestimate lesion severity, and as early as the 1980s, it was recognized that coronary angiography has a limited ability to predict the physiologic significance of individual lesions, especially for intermediate narrowing in the 40% to 70% diameter stenosis range.[1] Yet, not unlike in the first years after it was introduced, visual interpretation of a coronary angiogram has remained the most commonly used tool for making clinical decisions regarding revascularization for a patient with obstructive lesions of the coronary arteries. Because patients' symptoms and outcomes are more related to the physiologic consequence (myocardial ischemia) from a coronary artery lesion than to its mere presence, and the magnitude of benefit of revascularization appears directly related to the baseline extent of ischemia,[2] there remains a problematic disconnect between an approach to decision-making for revascularization based on imprecise visual estimation of anatomy and the expectation of a physiologic benefit of PCI.

Advances in guidewire sensor technology in the 1990s allowed for the direct measurement of lesion-related coronary physiology in patients undergoing cardiac catheterization. These advances included the incorporation of a pressure sensor into a 0.014-inch guidewire and the development of the concept of fractional flow reserve (FFR), a pressure-derived measure of maximal myocardial blood flow beyond a stenosis divided by the theoretical normal maximal flow in the absence of a stenosis, such that FFR in a vessel with no obstruction is 1.0.[3] FFR can be simplified as the ratio of pressure measured distal to a lesion over the aortic pressure at peak hyperemia (blood flow at maximal vasodilation). It is measured by advancing the guidewire pressure sensor adequately beyond the stenosis in question and maximally vasodilating the resistance vessels by administering a potent vasodilator, usually adenosine. FFR has been validated as a reproducible, lesion-specific measure of stenosis severity that strongly correlates with rigorously determined ischemia by noninvasive testing.[3,4]

However, the result of lesion assessment by FFR, and therefore potentially the decision to perform revascularization, may be discordant with visual impression of the angiogram about 65% of the time when assessing intermediate coronary artery lesions of 50% to 70% diameter stenosis and about 20% of the time when assessing lesions of 70% to 90% diameter stenosis, traditionally judged by visual estimation to be unequivocally severe.[5] Clinical trials have shown that measurement of FFR can allow safe deferral of PCI for lesions judged angiographically severe that are found to have a nonischemic FFR value of greater than 0.75[6]; that among patients with multivessel disease referred for PCI, when compared with angiographic guidance, selection of lesions for revascularization based on an FFR threshold of 0.80 or less provided improved clinical outcomes[7]; and that among patients with stable ischemic heart disease, FFR-guided PCI improved outcomes when compared with medical therapy alone.[8]

A large body of evidence, therefore, shows that by enabling an objective measure of clinically relevant lesion physiologic significance, measurement of FFR can overcome many of the limitations of angiography for diagnosing and treating coronary artery disease. On the strength of randomized trial data, use of FFR received a class IIa recommendation in the most recent 2011 PCI guideline from the American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography and Interventions[9] and a class I recommendation in the 2018 revascularization guidelines from the European Society of Cardiology/European Association for Cardiothoracic Surgery,[10] for assessing angiographically intermediate coronary lesions to guide revascularization decisions in patients with stable ischemic heart disease. More recently, an index of physiologic lesion significance using resting translesional hemodynamics that obviates some of the difficulties and cost associated with inducing coronary hyperemia with adenosine, the instantaneous wave-free ratio (a ratio of mean pressure distal to the stenosis over aortic pressure measured during the "wave-free" period of diastole under resting conditions), has also been validated as a method for objectively determining lesion physiology for selection of lesions for revascularization,[11] potentially increasing accessibility to and ease of use for physiologic lesion assessment to more laboratories and operators.

Given the improvements in diagnostic lesion assessment over the past 25 years documented for invasive physiologic testing, what is the current state of decision-making for coronary

revascularization for patients with coronary artery disease? In 2014, Toth et al[12] reported a web-based survey of 495 interventional cardiologists who were provided 5 angiograms that contained 12 focal intermediate stenoses for which FFR values were known but not disclosed and were asked to decide on revascularization or, if felt necessary, to choose FFR, quantitative coronary angiography, or imaging by intravascular ultrasound or optical coherence tomography to further assess lesion significance. Among these cardiologists, 3158 (71%) of the 4421 revascularization decisions were based on visual interpretation of the angiogram only, and of those decisions, 47% were discordant from the known functional significance of the lesion by FFR. In 2019, the investigators repeated their survey of 411 additional interventional cardiologists, who were again asked to make decisions on management of 5 angiograms with focal intermediate lesions. The results showed that among these cardiologists, 2237 (60%) of 3749 decisions were again made solely on the basis of angiographic appearance, and of those, 39% were discordant with the known functional significance of the coronary stenosis by FFR.[13]

Likewise, in a nationwide survey in Italy conducted in 2017 designed to assess reasons for use and nonuse of invasive coronary physiology assessment in practice among consecutive cases performed by 140 invasive cardiologists in 76 catheterization laboratories, most decisions (608 of 1178 [52%]) regarding intermediate stenosis management were made based on visual assessment only. Further, the most common reason for not performing physiologic lesion assessment was the cardiologist's confidence that the clinical and angiographic data were sufficient to achieve the correct decision for the patient.[14]

The reasons interventional cardiologists have not embraced more widespread use of invasive physiologic lesion assessment are unknown, but may include misplaced confidence in visual estimation by angiography, costs, lack of familiarity or experience with the technology, confusion regarding the optimal thresholds for the definition of ischemia, and possibly uncertainty that the results of randomized clinical trials and their selected study populations can be generalized to routine practice. Relevant to the last 2 of these concerns, in this issue of *JAMA*, Sud and colleagues[15] report a new contribution that examined the association between physiologic guidance of percutaneous revascularization decisions and outcomes in patients with coronary artery disease.

The authors analyzed a large provincial registry in Ontario, Canada, over a 5-year period from 2013 to 2018. From nearly 500 000 coronary angiograms available for analysis, 17 004 had measurements of FFR. After appropriate exclusions, 9106 patients with single-vessel FFR measured served as the study population, most of whom presented with stable coronary artery disease. Of the 2693 patients who had an ischemic FFR of 0.80 or less, 2029 (75.3%) underwent PCI and 664 (24.7%) did not undergo PCI and were treated with medical therapy, whereas of the 6413 patients who had a nonischemic FFR of greater than 0.80, 810 (12.6%) underwent PCI. The primary outcome was a major adverse cardiac event (MACE), which included all-cause death, hospitalization for myocardial infarction, hospitalization for unstable angina, or urgent coronary revascularization, assessed at 30 days, 1 year, and 5 years. The association between PCI and outcomes was estimated for each FFR cohort after adjustment by propensity score inverse probability of treatment weighting.

The authors reported that among patients with lesions with an ischemic FFR of 0.80 or less, PCI, compared with no PCI, was associated with a significantly lower incidence of MACE at 30 days, 1 year, and 5 years, with rates of 2.8% vs 6.0% (hazard ratio [HR], 0.47 [95% CI, 0.30-0.75]), 11.9% vs 15.2% (HR, 0.76 [95% CI, 0.58-0.99]), and 31.5% vs 39.1% (HR, 0.77 [95% CI, 0.63-0.94]), respectively. Among patients with lesions with a nonischemic FFR of greater than 0.80, PCI, compared with no PCI, was associated with a significantly higher incidence of MACE at 30 days, 1 year, and 5 years, with rates of 3.1% vs 1.5% (HR, 2.11 [95% CI, 1.26- 3.54]), 10.6% vs 6.5% (HR, 1.67 [95% CI, 1.27-2.21]), and 33.3% vs 24.4% (HR, 1.37 [95% CI, 1.14-1.65]), respectively. The results were consistent in sensitivity analyses after excluding patients who presented with an acute myocardial infarction, when examining variable timing of CABG in follow-up, and when stratifying by numbers of diseased vessels.

These results provide validation of the added value of invasive physiologic testing to guide decision-making in clinical practice settings. The findings confirm a significant early and sustained benefit of revascularization for lesions found by invasive physiologic assessment to have an FFR of 0.80 or less, and significant harm associated with PCI of lesions found nonischemic by an FFR of greater than 0.80. The results further validate the FFR ischemic threshold of 0.80 or less as an objective criterion associated with improved outcome with PCI in everyday practice, as had been observed in randomized clinical trials.[7,8]

Several limitations should be considered in the evaluation of the results of the study by Sud et al.[15] First, as with most observational studies, selection bias and residual confounding may affect outcome comparisons. Second, the study was restricted to single-vessel FFR assessment and intervention, and the findings may not be generalizable to more complex multivessel physiologic assessment to guide PCI decisions. Third, the incidence of periprocedural myocardial infarction was not reported, and this may have failed to capture events that might have theoretically diminished the benefit of PCI for patients with ischemic FFR or increased the hazard of PCI for patients with nonischemic FFR. Fourth, the reasons PCI was not performed despite an ischemic FFR or that PCI was performed despite a nonischemic FFR were not collected and are unknown. Physiologic testing by FFR is only 1 variable in a complex multifaceted decision process for or against revascularization of any given lesion; there are many valid reasons that such decisions may have been reasonable and justified.

Nevertheless, as one of the largest population-based, multicenter studies of invasive physiologic lesion assessment by FFR and its relationship to outcomes across multiple clinical centers, this study serves as an affirmation that the application of invasive physiologic testing into routine clinical practice accompanied by adherence to recommended

thresholds for deciding to proceed with or defer revascularization is associated with improved outcomes. More broadly, the findings provide support that a physiologically based approach to decision-making for coronary revascularization using validated and widely available pressure wire–based techniques has advantages compared with visually interpreted angiography. Conversely, it follows that failure to incorporate such physiologic assessment into the routine practice of diagnostic cardiac catheterization and clinical decision-making for managing coronary artery disease represents a missed opportunity to provide better outcomes for patients with coronary artery disease. The results observed in the study by Sud et al[15] should be welcome news to clinicians who were awaiting further evidence that in everyday practice physiologic guidance can help optimize the outcomes of revascularization by objectively selecting patients who will benefit from PCI and to avoid the risks of revascularization by better identifying those who will not.

ARTICLE INFORMATION

Author Affiliation: Cardiovascular Division, Washington University Medical Center in St Louis, St Louis, Missouri.

Corresponding Author: Richard G. Bach, MD, Cardiovascular Division, Washington University School of Medicine in St Louis, 660 S Euclid Ave, St Louis, MO 63110 (rgbach@wustl.edu).

Published Online: November 13, 2020. doi:10.1001/jama.2020.22998

Conflict of Interest Disclosures: None reported.

REFERENCES

1. White CW, Wright CB, Doty DB, et al. Does visual interpretation of the coronary arteriogram predict the physiologic importance of a coronary stenosis? *N Engl J Med*. 1984;310(13):819-824. doi:10.1056/NEJM198403293101304

2. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation*. 2003;107(23):2900-2907. doi:10.1161/01.CIR.0000072790.23090.41

3. Pijls NH, Van Gelder B, Van der Voort P, et al. Fractional flow reserve: a useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. *Circulation*. 1995;92(11):3183-3193. doi:10.1161/01.CIR.92.11.3183

4. Pijls NH, De Bruyne B, Peels K, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med*. 1996;334(26):1703-1708. doi:10.1056/NEJM199606273342604

5. Tonino PA, Fearon WF, De Bruyne B, et al. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. *J Am Coll Cardiol*. 2010;55(25):2816-2821. doi:10.1016/j.jacc.2009.11.096

6. Bech GJ, De Bruyne B, Pijls NH, et al. Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: a randomized trial. *Circulation*. 2001;103(24):2928-2934. doi:10.1161/01.CIR.103.24.2928

7. Tonino PA, De Bruyne B, Pijls NH, et al; FAME Study Investigators. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med*. 2009;360(3):213-224. doi:10.1056/NEJMoa0807611

8. De Bruyne B, Fearon WF, Pijls NH, et al; FAME 2 Trial Investigators. Fractional flow reserve-guided PCI for stable coronary artery disease. *N Engl J Med*. 2014;371(13):1208-1217. doi:10.1056/NEJMoa1408758

9. Levine GN, Bates ER, Blankenship JC, et al; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; Society for Cardiovascular Angiography and Interventions. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol*. 2011;58(24):e44-e122. doi:10.1016/j.jacc.2011.08.007

10. Neumann FJ, Sousa-Uva M, Ahlsson A, et al; ESC Scientific Document Group. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J*. 2019;40(2):87-165. doi:10.1093/eurheartj/ehy394

11. Davies JE, Sen S, Dehbi HM, et al. Use of the instantaneous wave-free ratio or fractional flow reserve in PCI. *N Engl J Med*. 2017;376(19):1824-1834. doi:10.1056/NEJMoa1700445

12. Toth GG, Toth B, Johnson NP, et al. Revascularization decisions in patients with stable angina and intermediate lesions: results of the international survey on interventional strategy. *Circ Cardiovasc Interv*. 2014;7(6):751-759. doi:10.1161/CIRCINTERVENTIONS.114.001608

13. Toth G WW, Fournier S, Toth B, Johnson N, Barbato E. Revascularization decisions in patients with stable angina and intermediate lesions: results of the second International Survey on Interventional Strategy (ISIS-2). Paper presented at: European Society of Cardiology Congress; August 30, 2020; Amsterdam, the Netherlands.

14. Tebaldi M, Biscaglia S, Fineschi M, et al. Evolving routine standards in invasive hemodynamic assessment of coronary stenosis: the Nationwide Italian SICI-GISE Cross-Sectional ERIS Study. *JACC Cardiovasc Interv*. 2018;11(15):1482-1491. doi:10.1016/j.jcin.2018.04.037

15. Sud M, Han L, Koh M, et al. Association between adherence to fractional flow reserve treatment thresholds and major adverse cardiac events in patients with coronary artery disease. *JAMA*. Published online November 13, 2020. doi:10.1001/jama.2020.22708