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REVIEW TOPIC OF THE WEEK

Clinical Utility of Intravascular Imaging and Physiology in Coronary Artery Disease

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ABSTRACT

Intravascular imaging and physiology techniques and technologies are moving beyond the framework of research to inform clinical decision making. Currently available technologies and techniques include fractional flow reserve; grayscale intravascular ultrasound (IVUS); IVUS radiofrequency tissue characterization; optical coherence tomography, the light analogue of IVUS; and near-infrared spectroscopy that detects lipid within the vessel wall and that has recently been combined with grayscale IVUS in a single catheter as the first combined imaging device. These tools can be used to answer questions that occur during daily practice, including: Is this stenosis significant? Where is the culprit lesion? Is this a vulnerable plaque? What is the likelihood of distal embolization or periprocedural myocardial infarction during stent implantation? How do I optimize acute stent results? Why did thrombosis or restenosis occur in this stent? One of the legacies of coronary angiography is to presume that one technique will answer all of these questions; however, that often has been proved inaccurate in contemporary practice. (J Am Coll Cardiol 2014;64:207–22) © 2014 by the American College of Cardiology Foundation

More than 2 decades have passed since Drs. Nico Pijls and Bernard DeBruyne introduced fractional flow reserve (FFR) as a method of assessing coronary stenosis severity and since Dr. Paul Yock invented grayscale intravascular ultrasound (IVUS) that spawned second-generation intravascular imaging techniques such as: 1) IVUS radiofrequency tissue characterization, including virtual histology (VH)-IVUS, integrated backscatter IVUS, and iMap; 2) optical coherence tomography (OCT), the light analogue of IVUS; and 3) near-infrared spectroscopy that detects lipid within the vessel wall and that has recently been combined with grayscale IVUS in a single catheter as the first combined imaging device. These tools have moved beyond the research setting. They are useful for answering questions that occur during daily practice including: Is this stenosis significant? Where is the culprit lesion? Is this a vulnerable plaque? What is the likelihood of distal embolization or periprocedural myocardial infarction (MI) during stent implantation? How do I optimize acute stent results? Why did thrombosis or restenosis occur in this stent?

The subspecialty of interventional cardiology is data driven. Although correlations with histopathology are important, the ultimate benefit will be determined if these techniques improve clinical diagnosis, treatment, outcomes, and whether patients benefit, irrespective of technical or histopathological accuracy.

IS THIS STENOSIS SIGNIFICANT?

Three randomized trials (DEFER [Deferral Versus Performance of PTCA in Patients Without Documented Ischemia], FAME [Fractional Flow Reserve Versus Angiography for Multivessel Evaluation]-I, and FAME-II) established FFR (the ratio of distal to proximal pressure at maximum hyperemia) as the

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ABBREVIATIONS AND ACRONYMS

DES = drug-eluting stent(s)

FFR = fractional flow reserve

ISR = in-stent restenosis

IVUS = intravascular ultrasound

LMCA = left main coronary artery

MI = myocardial infarction

MLA = minimum lumen area

OCT = optical coherence tomography

TCFA = thin-cap fibroatheroma

VH = virtual histology

gold standard for assessing the significance of a non-left main coronary artery (LMCA) lesion. DEFER showed it was safe to defer percutaneous coronary intervention of lesions with an FFR >0.75 (1,2). The FAME-I trial found that treating lesions with an FFR >0.80 by using mostly first-generation drug-eluting stents (DES) was harmful, whereas not treating such lesions was cost-saving (3,4). The FAME-II trial found that treating lesions with an FFR <0.80 with the use of optimal medical therapy alone was deleterious compared with optimal medical therapy plus DES implantation (5). Although initially more expensive, the increased cost of "optimal medical therapy plus DES implantation" was decreased by one-half 1 year later (6).

Its predecessor, coronary flow reserve (CFR), measures the relative increase in coronary flow *velocity* during maximal hyperemia, reflecting both epicardial stenoses and the microcirculation, and is influenced by many factors affecting the microcirculation, such as diabetes, ventricular hypertrophy, and prior myocardial infarction. Unlike CFR, FFR is able to measure the actual volume of blood flow through a stenotic coronary artery as a percentage of normal hyperemic flow, because at maximum hyperemia, flow into a myocardial territory is proportional to pressure since the resistance is minimal and constant. FFR is independent of pressure, heart rate, contractility, and the status of the microcirculation and takes into account both antegrade and retrograde collateral blood flow, as well as the amount of viable myocardium.

There has been a recent renewal of interest in resting indices, such as iFR (instantaneous wave free ratio) or a hybrid approach combining iFR and FFR. However, the validity of these alternative physiologic approaches will depend on the clinical outcomes of randomized iFR vs. FFR trials, such as DEFINE-FLAIR or SwedeHeart.

Many studies have attempted to identify invasive imaging criteria that are equivalent to FFR or noninvasive testing. Although the IVUS minimum lumen area (MLA) in non-LMCA lesions is the parameter that best correlates with physiology, reported IVUS MLA cutoff thresholds range from 2.1 to 4.4 mm^2 (**Table 1**) (7–25) and are smaller in Asian patients than in studies of Western populations, the "most common" cutoff is approximately 3.0 mm^2. Most IVUS studies show a relatively high negative predictive value but a low positive predictive value, indicating that using IVUS to justify the need for percutaneous intervention is wrong approximately one-half of the time. There have been no randomized IVUS trials comparable to DEFER, FAME-I, or FAME-II or randomized trials of IVUS deferral compared with FFR deferral. However, a recent propensity-matched study by de la Torre Hernandez et al. (26) suggests that clinical outcomes are similar whether IVUS or FFR is used to decide which lesions to stent or which to leave alone, although a greater number of lesions are stented with IVUS compared with FFR (72% vs. 51.2%; $p < 0.0001$).

Anatomic assessment of lesion severity is not improved with OCT, although OCT-derived MLA cutoffs are smaller than with IVUS (19,27–29). Some studies have "corrected" for vessel size (12,13,16,17), but none has factored in subtended viable myocardium.

In a recent substudy from the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) Study, nonfibroatheromas were associated with very few events at 3 years of follow-up, suggesting that tissue characterization and plaque composition may be an alternate method to predict lesion stability and defer intervention (30).

LMCA LESIONS

Four angiographic studies (2 historic [31,32] and 2 contemporary [33,34]) indicated that agreement among experts regarding the significance of an LMCA lesion can be as low as 30% (**Fig. 1**). There have been 2 equivalent FFR and IVUS registry studies in patients with intermediate LMCA lesions in which an FFR >0.80 or an IVUS MLA >6.0 mm^2 was used to defer revascularization, with similar long-term results compared with patients with an FFR <0.80 or an MLA <6.0 mm^2 treated with revascularization (33,35). A study by Jasti et al. (36) in Western patients indicated that an IVUS MLA <6 mm^2 in the LMCA best correlated with an FFR <0.80, while a study in Korean patients suggested that 4.8 mm^2 was the preferred IVUS MLA cutoff (37), which is again consistent with the smaller MLA cutoffs found in Asian patients compared with Western patients.

Both IVUS and FFR have limitations in assessing LMCA disease. Ideally, when clinically indicated, IVUS should be performed from both the left anterior descending and left circumflex coronary arteries to define the MLA within the LMCA and to accurately assess disease at the left anterior descending and left circumflex ostia (38,39). Patients with LMCA disease have not typically been included in the many FFR