Update on FFR, OCT, and IVUS

Expanded use of these modalities could overcome the limitations of coronary angiography.

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Coronary angiography remains the most commonly used imaging modality to describe the degree and extent of coronary atherosclerosis during diagnostic cardiac catheterization and percutaneous coronary intervention (PCI). Its accuracy is affected by technical limitations, important interobserver variability, and its poor visualization of the vessel wall. Furthermore, it provides limited information about the functional significance of the lesion. Today, intravascular ultrasound (IVUS), fractional flow reserve (FFR), and optical coherence tomography (OCT) are extensively used to overcome the aforementioned limitations. Despite the increasing published data validating their advantages, IVUS, FFR, and OCT remain largely underutilized.1

FRACTIONAL FLOW RESERVE

FFR is the ratio of the mean coronary arterial pressure measured distal to the lesion of interest to the mean aortic pressure with pharmacologically induced maximum coronary hyperemia. It is now widely accepted as the gold standard for the evaluation of functional myocardial ischemia and as a reference for other invasive (IVUS, OCT) and noninvasive (SPECT-MPI, dobutamine echocardiography, and CMP-MPI) modalities.2

The initial DEFER study aimed to assess the appropriateness of stenting functionally nonsignificant intermediate coronary stenosis, used a cutoff of FFR < 0.75 for positivity of the test, and demonstrated excellent 5-year results, with a risk of cardiac death or myocardial infarction < 1% for the deferred group (nonstatistically significant compared to the PCI group).3 After the FAME 1 and 2 trials, which investigated the outcomes of FFR-guided PCI in patients with multivessel coronary artery disease and stable coronary artery disease, respectively, a cutoff of < 0.8 is currently used for the positivity of the test, as recommended by the 2014 expert consensus statement by SCAI.4 In a more recent trial, Depta et al showed that borderline FFR (0.8—0.85) carries the same risk as gray-zone FFR (0.75—0.8) regarding number of deferred lesion interventions and risk significantly higher than nonborderline FFR (≥ 0.85), raising the question whether the cutoff of 0.8 needs to be reconsidered.5

Intravenous adenosine has been used in most randomized trials as the main hyperemic agent. Intracoronary nicorandil, or sodium nitroprusside and intravenous regadenoson, have been found to induce similar hyperemic response and similar FFR results to adenosine, and they may be safer in selected subgroups.6–9

The instantaneous wave-free ratio (iFR) was developed as an alternative to FFR without the need for hyperemia. Using a high-fidelity pressure wire, iFR takes advantage of the “wave-free period,” a specific period in diastole during which the pressure and flow are proportionally related (unlike different periods of the cardiac cycle). By averaging those measurements in three to five beats, the functional significance of coronary lesions may be assessed.

The ADVISE, VERIFY, CLARIFY, and RESOLVE trials showed variable correlation rates between iFR and FFR.10–13 Despite its ease of use, debate regarding its reproducibility, accuracy, and correlation with FFR persists. To date, iFR is not a widely accepted alternative to FFR.

The RIPCORD study, which attempted to assess the impact of routine FFR at the time of diagnostic coronary angiograms, showed that the routine addition of FFR to the coronary angiogram may change the initial managing plan in 26% of patients.14 Furthermore, FFR-guided coronary artery bypass grafting resulted in a lower number of graft anastomoses and on-pump surgeries, with similar event rates at 26-month follow-up compared to traditional coronary angiogram-guided PCI.15 A FAME substudy showed that similar angiographic lesions in women may be less ischemia-producing than in men, suggesting increased use of FFR in women to prevent unnecessary PCI.16 Furthermore, FFR use is cost effective and cost saving.17–19 The routine use of FFR is associated with fewer stent implantations but no improvement in mortality compared to angiography-guided PCI, as shown by a recent large cohort study.20

IMAGING
FFR has not been used in saphenous vein grafts due to the presumed limited response of the vein grafts to adenosine. Di Serafino et al demonstrated that FFR-guided PCI for moderate graft lesions resulted in improved major adverse cardiac and cerebrovascular event rates, with reduced cost compared to angiography-guided PCI.

In an effort to perform a completely noninvasive FFR, FFR(CT) was developed based on computational fluid dynamic techniques. A special software technique using physical laws of mass conservation and momentum balance has managed to estimate fluid pressure and velocity and achieve improved discrimination of hemodynamically significant lesions. FFR(CT) increased the accuracy of regular computed coronary angiography in the NXT, DEFACTO, and DISCOVER-FLOW trials.

Optical coherence tomography (OCT) technology uses near-infrared light to produce excellent in vivo imaging of the vessel wall, with an axial resolution of 10 to 15 μm. One of the limitations of OCT is penetration depth of 2 to 4 mm, as well as the requirement of a blood-free environment for optimal imaging.

Before percutaneous intervention, OCT allows accurate description of the vessel size and the extent of the atherosclerotic plaque; identification and characterization of lipid-rich plaques, thin-cap fibroatheroma, calcification, and fibrous cap thickness; distinction between white and red thrombus; and calculation of total thrombus burden. OCT ensures optimal sizing and complete stent coverage of the vulnerable plaque. In prospective, nonrandomized cohorts with serial OCT evaluations in patients with STEMI or acute coronary syndromes, it has been suggested that thrombectomy without angioplasty or stent placement may be sufficient.

After PCI, OCT provides detailed description of the stent strut coverage, edge dissections, stent protrusion or fracture, residual thrombus, restenosis, or thrombosis. Data about the long-term clinical consequences of those OCT findings are currently unavailable.

Recently, the use of OCT has been successfully evaluated in saphenous vein grafts, as well as carotid, renal, iliac, superficial femoral, and transplanted coronary arteries.

To date, there are no randomized trials supporting the use of OCT to guide PCI. An example of OCT-guided PCI is seen in Figure 1. The DOCTORS trial will assess the use of OCT to optimize results in patients with NSTEMI.

A novel OCT-derived FFR is under investigation, which combines OCT’s excellent resolution with FFR’s assessment of functional significance based on the calculation of blood flow resistance and hyperemic microvascular resistance.

OCT today has emerged as a user-friendly, fast, and safe imaging modality that offers instant, high-resolution 2D or 3D intravascular images. The main disadvantages are the inability to visualize ostial lesions because of the difficulty of clearing the blood in the coronary ostia and the absence of large randomized trials to assess the clinical significance of the numerous OCT findings. The previously reported OCT drawback of the inability to visualize larger vessels has been overcome with the use of novel OCT technology, and the need for contrast injections, which may be important in patients with kidney disease, can be overcome with use of dextran.
Intravascular Ultrasound

Stent underexpansion, smaller postprocedure lumen dimensions, residual reference segment stenosis, and the presence of thrombus or dissection have been reported to be the IVUS predictors of restenosis or stent thrombosis. A number of studies have demonstrated that IVUS-derived minimum stent area (MSA) after stent deployment is a predictor of in-stent restenosis. In this respect, in the SIRIUS IVUS substudy, an MSA of 5 mm$^2$ after deployment of sirolimus-eluting stents highly predicted stent patency, which was defined as an MSA > 4 mm by IVUS at follow-up. Likewise, a recent large study showed that poststenting MSA was the only independent predictor of angiographic in-stent restenosis in patients who underwent zotarolimus-eluting, everolimus-eluting, and sirolimus-eluting stent implantation. The best cutoff values of MSA for predicting ISR were 5.3 mm$^2$, 5.4 mm$^2$, and 5.5 mm$^2$ for zotarolimus-, everolimus-, and sirolimus-eluting stents, respectively.

A meta-analysis of randomized trials demonstrated that stenting with a bare-metal stent guided by IVUS, compared with angiography, significantly reduced major adverse cardiac events. Furthermore, another meta-analysis of 18,707 patients from three randomized studies comparing IVUS-guided stenting with angiography and other studies showed that IVUS guidance reduced the rates of mortality, myocardial infarction, and stent thrombosis, but not the rate of revascularization. Along the same lines, a recently published large-scale prospective, multicenter, nonrandomized ADAPT-DES study of 8,583 patients showed IVUS guidance compared to angiography reduced the risk of stent thrombosis, myocardial infarction, and major adverse cardiac events within 1 year after drug-eluting stent (DES) implantation. Although the ADAPT-DES study supports IVUS-guided DES implantation, large randomized trials are warranted to confirm the utility of IVUS for reduction of event rates because current randomized trials have been underpowered to definitively assess the clinical utility of IVUS guidance.

IVUS is a valuable tool for the assessment of the left main coronary artery (LMCA) stenosis. An example of IVUS-guided PCI is described in Figures 2 and 3. In an analysis of 55 patients, Jasti et al reported that an IVUS minimum lumen area (MLA) of 5.9 mm$^2$ and a minimum lumen diameter of 2.8 mm strongly predicted FFR < 0.75. The LITRO study, which enrolled 354 patients with intermediate LMCA lesions, reported that an IVUS MLA > 6 mm$^2$ was safe for deferring revascularization. In the 2-year follow-up period, there was no significant difference between the deferred and revascularized groups in terms of cardiac death-free survival and event-free survival. Recently, the Society of Cardiovascular Angiography and Interventions recommended using an IVUS MLA cutoff value of 6 mm$^2$ for a decision-making strategy regarding revascularization in patients with an LMCA stenosis. However, the use of IVUS should be discouraged when evaluating non-left main lesions, because the diagnostic performance of IVUS MLA to predict FFR is not high enough to reliably exclude lesions that are hemodynamically significant.

Conclusion

FFR has emerged as a valuable tool in the cath lab to determine the functional significance of intermediate coronary lesions and appropriately guide treatment strategies. For that reason, it has been upgraded to a class IA in the European guidelines for multivessel PCI and class Ila in the 2013 SCAI consensus document to assess angiographic...
intermediate coronary lesions (50%–70%). 4,45 Although registry studies and meta-analyses support IVUS-guided DES implantation, large randomized trials are warranted to confirm the utility of IVUS for reduction of event rates. The SCAI endorsed using an IVUS MLA cutoff value of 6 mm² for a decision-making strategy regarding revascularization in patients with an LMCA stenosis. OCT is a promising novel imaging technology that provides a large amount of data regarding the vessel wall and atherosclerotic plaque. Larger studies are needed to investigate the clinical value of this information.

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