EDITORIAL COMMENT

Baseline Fractional Flow Reserve and Stent Diameter Predict Event Rates After Stenting

A Further Step, But Still Much to Learn*

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Angiography with its inherent limitations might not reliably predict whether a stenosis induces ischemia. It is well-documented that the angiographic assessment of a coronary stenosis correlates poorly with its physiologic significance. Fractional flow reserve (FFR) is an index of the physiologic significance of a coronary stenosis and is defined as the ratio of maximal blood flow in a stenotic artery to normal maximal flow. The measurement of FFR by a sensor wire has been validated as a technique for the functional assessment of coronary stenoses. Validation studies of FFR measurements have demonstrated a strong correlation between the FFR and stress tests. The information provided by FFR is similar to that obtained with myocardial perfusion studies but is more specific, and FFR has a better spatial resolution, because every artery or segment is analyzed separately. The recommended diagnostic approach in patients with a coronary stenosis includes a number of noninvasive cardiac stress imaging techniques; however, it is well-known that, in patients with multivessel disease, such techniques are limited in their ability to allocate wall motion or perfusion defects to a “culprit” stenosis.

Pijls et al. (1) demonstrated that 5-year outcome after deferral of percutaneous coronary intervention of intermediate coronary stenoses, on the basis of an FFR cut-point of 0.75, was excellent. In addition, they demonstrated that the risk of cardiac death or myocardial infarction was not decreased by stenting. These findings are further substantiated by the fact that deferral of revascularization of angiographically severe but physiologically insignificant stenoses was associated with a favorable outcome and spontaneous resolution of symptoms. Deferring percutaneous coronary intervention in nonischemic stenotic lesions as assessed by FFR is associated with an annual rate of death or myocardial infarction of approximately 1% in patients with single-vessel coronary artery disease, which is lower than the rate after routine stenting. It is worth noting that, even in the era of drug-eluting stents (DES), stenting of a nonsignificant coronary artery stenosis has no prognostic advantage.

Normal epicardial coronary arteries provide no resistance to blood flow, not even during maximum hyperemia. Therefore, optimum coronary stenting should at least result in the disappearance of any hyperemic pressure drop within the respective coronary segment. The measurement of FFR has been proposed as a technique for optimizing the stent results. Indeed, the elimination of any trans-stenotic hyperemic gradient after stenting correlates well with optimal stent deployment on the basis of intravascular ultrasound (IVUS) criteria. Abnormal FFR identifies both residual hyperemic pressure gradient and abnormal resistance across the stented segment and in the adjacent parts of the vessel. In this respect, Pijls et al. (2) conducted a multicenter bare-metal stent (BMS) FFR registry in 750 patients to investigate the correlation between FFR measured after stent implantation and major adverse cardiac events, including the need for target vessel revascularization during the 6 months after implantation. This study demonstrated that measurement of FFR immediately after stent implantation is a strong independent predictor of the event rates such as death, myocardial infarction, or need for repeat revascularization of the target vessel within 6 months. Likewise, the study demonstrated that the higher the FFR, the lower the event rate such that, in 36% of the patients that FFR was normalized (FFR >0.95), event rate was 4.9%. In 32% of the patients, post-stent FFR was between 0.90 and 0.95, and event rate was 6.2%. In 32% of patients, post-stent FFR was <0.90, and event rate was 20.3%. In 6% of the patients, FFR was <0.80, and event rate was 29.5% (p < 0.001).

The study reported by Samady et al. (3) in this issue of JACC: Cardiovascular Interventions, is a post hoc analysis of 586 patients derived from the BMS FFR registry that was originally reported in 750 patients (2). Because the BMS registry demonstrated that an FFR >0.90 after stenting was associated with a low event rate of 6%, Samady et al. (3) sought to determine whether variables such as baseline FFR, stent diameter, and stent length would predict a post-stent FFR of ≥0.90. In this context, Samady et al. (3) demonstrated that a baseline FFR >0.70 compared with a baseline FFR <0.70, after deployment of a 3.0-mm-diameter stent in patients with a coronary artery stenosis, would yield a higher likelihood of achieving an FFR ≥0.90 (77% vs. 63%, respectively; p < 0.05). Likewise, Samady et al. (3) reported that a baseline FFR <0.50 compared with a baseline FFR...
ranging from 0.50 to 0.70 and a baseline FFR $>0.70$, after deployment of a stent with a diameter $<3.0$ mm, was associated with a higher event rate (40% vs. 15%, and 13%, respectively; $p < 0.05$). Furthermore, Samady et al. reported that event rates in patients with a stent diameter $>3.0$ mm, regardless of baseline FFR, were $<10\%$ with a BMS.

The authors are to be commended for their vigilance in identifying the predictors of post-stent FFR cut-point of 0.90. Notably, the study is a post hoc analysis of a large registry with all its inherent limitations and requires further validation, but the data have important clinical implications. In this respect, the results suggest that baseline FFR and stent diameter would usher in a decision-making strategy with respect to judicious use of a BMS versus a DES. In particular, the aforementioned data indicate that, among patients with a stent diameter $>3.0$ mm, event rates were $<10\%$ with a BMS, which is similar to that of DES; thus, this would potentially circumvent the need for a DES. In addition, the data indicate that patients with a stent diameter of 3.0 mm and baseline FFR $>0.70$ would have a significant likelihood of achieving an optimal post-stent FFR of $\geq 0.90$ with a BMS. Along the same line, patients with a stent diameter of $<3.0$ mm and FFR $>0.70$ would have an acceptable event rate of 13% with a BMS. In contrast, patients with a stent diameter $<3.0$ mm and FFR $<0.50$ would have a high event rate with a BMS.

In recent years, there has been an explosion in the use of DES, but concerns have been raised about the possible increased incidence of stent thrombosis with DES. A meta-analysis of all randomized trials comparing DES with BMS demonstrated similar mortality rates (4). One trial even showed an incidence of late stent thrombosis of 1.4% in the DES group versus 0.8% in the BMS group (5). Nevertheless, certain patient subsets might be well-served with the use of a BMS, if frequency of restenosis can be predicted to be low by FFR or stent diameter. In addition, multiple studies have shown that the single most important predictor of stent thrombosis is the premature discontinuation of antiplatelet therapy, with a dramatic increase in stent thrombosis seen in patients taken off therapy (6). It is of paramount importance that before stent implantation, all patients be evaluated for their ability to continuously receive and tolerate dual antiplatelet therapy.

There are several potential clinical implications for measurements of FFR before and after stenting. First, it is well known that angiography is limited in defining the significance of stenosis; therefore, the measurement of FFR might potentially obviate the need for stenting. Second, it is tempting to speculate that patients with a baseline FFR $>0.70$, stent diameter of 3.0 mm, and short lesion length might achieve an optimal post-stent FFR of 0.90, and thus DES might not be needed. Furthermore, if such a patient would require biopsy or noncardiac surgery, clopidogrel therapy could be discontinued within 4 weeks of stenting. Third, angiography is a rather inaccurate tool for evaluating the result of stenting, as stratified by IVUS. In this respect, incomplete stent deployment, protruding struts, or plaque shift at the entry or exit of the stent is often not recognized by angiography but might result in early in-stent restenosis (7). Such abnormalities can often be detected by the persistence of a hyperemic pressure gradient across the stented segment (8). Therefore, it is likely that several patients with restenosis in fact had suboptimal stent deployment not detected by angiography. Finally, coronary pressure measurement not only reveals an abnormal conductance within the stented segment but also indicates increased plaque accumulation in the remaining part of the coronary artery, contributing to decreased FFR and worst outcome (9).

The results of the aforementioned studies underscore the need for further prospective studies to assess the impact of baseline FFR, stent diameter, and stent length in predicting final FFR after stenting and to address whether additional strategies, such as performing IVUS or high-pressure balloon inflation after stenting in the setting of suboptimal FFR, would translate into improved outcome.

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