

Using Fractional Flow Reserve in Complex Lesions

FFR overcomes other technologies' shortcomings to fine-tune clinical decisions for challenging cases.

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Complex coronary lesions are characterized by a higher rate of interobserver and intraobserver variability for assessment of stenoses significance. The use of a coronary angiogram for assessing the significance of a stenosis is limited because it is merely a "luminogram" and does not provide much insight into the hemodynamic significance of a stenosis. Fractional flow reserve (FFR) provides a physiologic method for assessing the significance of a coronary stenosis at maximal hyperemia.¹ The utility of FFR is established in multiple settings of complex lesions, including discerning the hemodynamic significance of equivocal left main coronary artery (LMCA) lesions and multivessel disease (MVD).²⁻⁵ FFR reliably interrogates any individual stenosis and can be used to immediately decide in the catheterization laboratory whether to stent. FFR has been validated to correlate strongly with clinical outcomes in the short term²⁻⁵ and long term (up to 5 years) in the DEFER trial.⁶ This review outlines the utility of FFR for a decision-making strategy among patients with LMCA stenosis, MVD, and coronary bifurcation lesions (CBL).

FFR FOR LEFT MAIN CORONARY STENOSIS ASSESSMENT

The American College of Cardiology and American Heart Association recommend coronary artery bypass grafting (CABG) as a class 1A indication for a significant LMCA stenosis.⁷ Angiographic assessment of the LMCA stenosis, visually or by quantitative coronary angiography

(QCA), is challenging, and autopsy studies suggest that most mild stenoses in the LMCA are reported as significant by angiography.^{8,9} It is well known that bypass surgery of a noninsignificant stenosis can lead to a higher rate of graft failure.¹⁰ A significant LMCA stenosis has been traditionally defined as stenosis > 50% luminal diameter and is a class 1A recommendation for surgical revascularization. It is also well known that grafting an insignificant lesion would lead to a higher rate of disease progression in the grafted native artery and a high rate of graft failure.¹¹ Given the inherent limitations with luminography and intraobserver variability for the assessment of the LMCA stenosis, a more reliable form of evaluation is essential in determining the hemodynamic significance of the LMCA stenosis.

We reported a strong correlation between FFR and intravascular ultrasound (IVUS) minimum lumen area in patients with an LMCA stenosis.¹² In addition, we demonstrated that among patients with an LMCA stenosis, an FFR of > 0.75 is a strong predictor of survival and event-free survival. Courtis et al¹³ performed FFR evaluation after intracoronary adenosine administration in patients with angiographically intermediate lesions. Revascularization with CABG or left main stenting was subsequently performed in patients with FFR < 0.75, but medical therapy was recommended for patients with FFR > 0.80. The management strategy was individualized for patients with an FFR between 0.75 and 0.80. This study showed a similar incidence of major adverse cardiac events (MACE), as defined by death, myocardial infarction, or revascularization, when

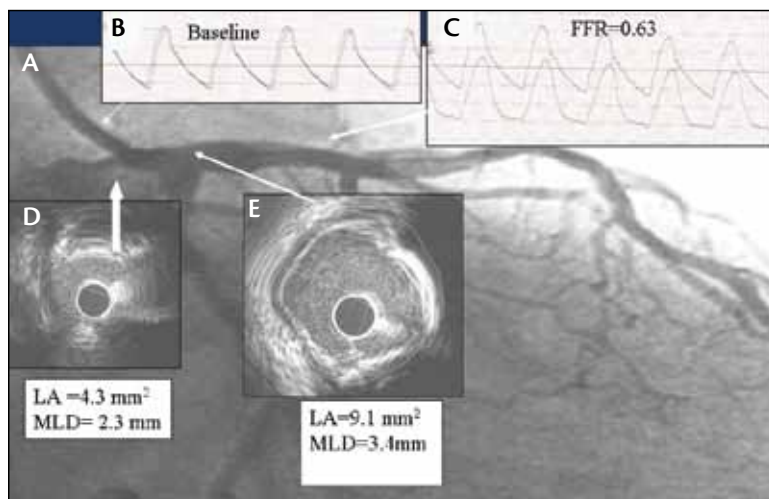


Figure 1. Coronary angiogram demonstrating a borderline stenosis of the LMCA (A). Pressure transducer is in the aorta (B). FFR = 0.63, after the pressure transducer crossed the left main stenosis (C). IVUS of the left main ostium indicates a significant stenosis (MLA = 4.3 mm²) (D). IVUS of the distal left main (area = 9.1 mm²) (E).

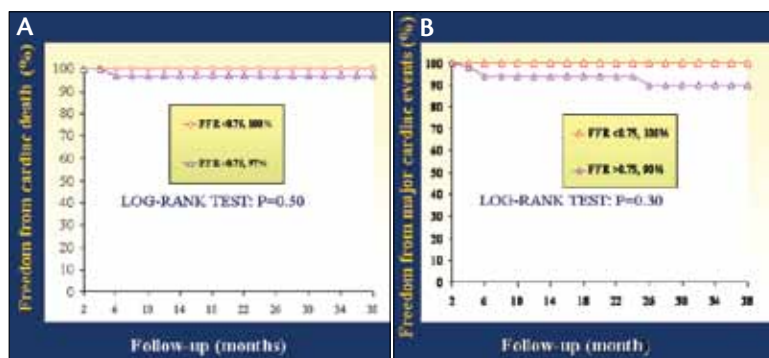


Figure 2. Thirty-eight month Kaplan-Meier freedom from cardiac death estimate in patients with LMCA stenosis and FFR < 0.75 who underwent revascularization versus those with FFR > 0.75 who were continued on medical therapy (A). Thirty-eight month Kaplan-Meier freedom from major cardiac events estimate in patients with FFR < 0.75 versus those with FFR > 0.75 (B).

comparing the two groups at 14-month follow-up, which supported the safety of deferring revascularization based on FFR evaluation of an intermediate or equivocal LMCA stenosis. A major limitation of the study was the low dose of intracoronary adenosine (< 90 µg) used to evaluate the significance of the LMCA stenosis. Contemporary data have shown that higher doses of intracoronary adenosine are safe and may lead to fewer false-negative FFR results.¹⁴ Hamilos et al¹⁵ performed FFR in 213 patients with an equivocal LMCA stenosis. Patients with FFR < 0.80 underwent surgical revascularization. There was poor correlation between coronary diameter stenosis and FFR; 23% of patients with < 50% diameter stenosis by angiography had FFR < 0.80. The

5-year survival estimates were 89.8% in the nonsurgical group treated medically (FFR > 0.80) and 85.4% in the surgical group ($P = 0.48$). Figure 1 shows a representative case of the LMCA stenosis. There is a borderline stenosis at the ostium of the LMCA by angiography; the FFR of the LM stenosis was 0.63, and the IVUS of the LM demonstrates that the ostium of the LM is significant. Figure 2 shows that FFR of > 0.75 is a strong predictor of survival and event-free survival among patients with an LMCA stenosis.

FFR FOR MULTIVESSEL DISEASE ASSESSMENT

FFR outperformed myocardial perfusion imaging (MPI) in patients with MVD. MPI is the most commonly used noninvasive modality for evaluating coronary artery disease (CAD). It is based on the principle of differential flow in the vascular bed. In a recent study by Melikian et al,¹⁶ the performance of MPI was assessed against FFR in 67 patients. In 42% of patients, MPI and FFR detected identical ischemic territories; 36% of MPI underestimated and 22% overestimated the number of ischemic territories in comparison with FFR. As a functional index of epicardial vessel stenosis, FFR is unique to each vessel and not influenced by the presence and/or absence of stenoses in adjacent vessels. The authors concluded that FFR is ideally suited to the functional assessment of coronary stenoses in patients with multivessel CAD.

The FAME (Fractional Flow Reserve Versus Angiography in Multivessel Evaluation) trial¹⁷ is the largest randomized, prospective, multicenter clinical trial that compared stenting guided by FFR with

stenting guided by angiography alone in 1,005 patients with two or more diseased coronary arteries. The primary endpoint (a composite of death, myocardial infarction, and repeat revascularization) occurred in 91 patients (18.3%) in the angiography group and in 67 patients (13.2%) in the FFR group ($P = .02$). Myocardial infarction occurred in 43 patients (8.7%) in the angiography group and in 29 patients (5.7%) in the FFR group ($P = .07$). There was no significant difference in the all-cause mortality. A total of 47 patients (9.5%) in the angiography group and 33 patients (6.5%) in the FFR group required repeat revascularization ($P = .08$). Additionally, an FFR-guided strategy reduced the number of stents used, decreased the amount

of contrast agent used, and resulted in a similar functional status with no decrease in health-related quality of life. Furthermore, the procedure-related costs were significantly lower with the FFR-guided strategy. The 2-year follow-up of the FAME trial demonstrated sustained benefit in that 22.2% of patients randomized to angiography-guided PCI had a primary endpoint compared with 17.7% in the FFR-guided treatment arm, an absolute reduction of 4.5%.

Tonino et al¹⁸ examined the relationship between angiographic severity and FFR in the FFR cohort of the FAME study. In the FFR group, 44.1% had stenoses of 50% to 70% by the visual estimate, 37.5% had stenoses of 71% to 90%, 14.3% had stenoses of 91% to 99%, and in 10.6%, stenoses were totally occluded. In the overall FFR arm of the FAME trial, the subgroup with angiographic lesion severity of 50% to 70% by visual estimation had an FFR < 0.80 in only 35%, which increased to 80% in the group with angiographic lesion severity of 71% to 90% and to 96% in the group with angiographic severity of 91% to 99%. The authors concluded that even in patients with a borderline stenosis (a 50% to 70% stenosis), FFR was useful in determining the significance of the stenosis. Figure 3 shows a representative patient with multivessel disease. Although both the stenoses of the left anterior descending (LAD) artery and right coronary artery (RCA) were significant by angiography, neither FFR of the LAD nor the RCA was significant, and stenting was deferred. Because FFR of the left circumflex artery (LCX) was 0.66, only the LCX underwent stenting.

The use of FFR influences the decision-making strategy for revascularization. Lindstaedt et al¹⁹ demonstrated that in 25 patients with multivessel disease, the recommendation between CABG to PCI was changed in nine (36%) of the patients. Based on FFR evaluation after angiography, four patients were switched from CABG to PCI, and five patients were switched from PCI to CABG.

SYNTAX score is a useful index to risk-stratify patients with MVD before PCI. In a substudy of the FAME trial,²⁰ a functional SYNTAX score was calculated by counting only ischemia-producing lesions with FFR < 0.80. The functional SYNTAX score was compared to the angiographic SYNTAX score in predicting events. The functional SYNTAX score, compared with SYNTAX score, moved 32% of the patients to a lower-risk group and had higher predictive accuracy for predicting events than SYNTAX score.

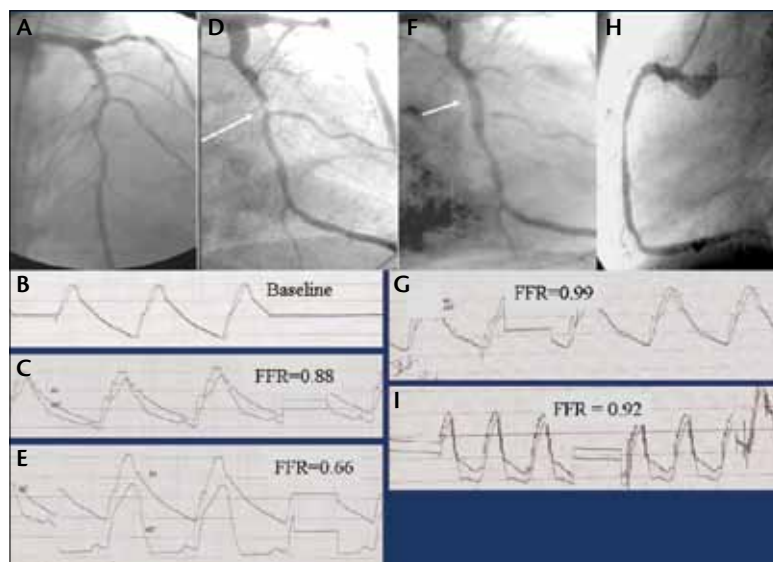


Figure 3. Coronary angiogram demonstrating a 70% diffuse stenosis in the mid-LAD (A). At baseline, identical pressures were recorded by guiding catheter and pressure transducer (B). FFR was 0.88 with pressure transducer positioned distal to the stenosis in the LAD (C). Angiogram of the LCX shows critical stenosis in the proximal LCX (D); FFR of the LCX was 0.66 (E). Angiogram of the LCX after deployment of a 3.5 X 18-mm stent shows significant improvement of lumen diameter (F). FFR was 0.99 after stenting (G). Angiogram of the RCA shows 60% to 70% stenosis of the proximal RCA (H). FFR of the RCA was 0.92 (I). Because FFR was < 0.75 in the LCX, PCI was performed only in the LCX, and PCI of other vessels was deferred.

FFR IN PATIENTS WITH BIFURCATION LESIONS

CBLs remain a challenging coronary artery disease subset, comprising 15% to 20% of all PCIs.²¹ The heterogeneity and differences within CBL, such as severity of the disease in the main vessel and side branch, vessel diameter, and side branch angulations, are some of the technical challenges of bifurcation lesions. Moreover, these lesions frequently limit blood supply to large areas of the myocardium and have higher rates of restenosis and stent thrombosis. A number of bifurcation lesion classification schemes have been proposed to help determine the best stent strategy that would provide successful procedural and long-term outcomes.^{22,23} However, most of these classification schemes are confusing and difficult to remember, which render their application in clinical practice less useful.

Conventional approaches for the treatment of CBL include the simple strategy (single-stent placement) versus complex strategy (upfront two-stent placement). Currently, there is no evidence to support the superiority of routine upfront two-stent strategy compared to single-vessel stent strategy. Recent randomized trials, however, have enhanced our understanding of bifurcation lesion management.²⁴⁻²⁹



Figure 4. RAO view: Coronary angiogram shows a significant stenosis of the LAD and diagonal at the bifurcation (A). LAO view: LAD and diagonal stenosis at the bifurcation (B). FFR of the LAD was 0.84 (C). FFR of the diagonal was 0.85 (D).

These studies have shown that the use of a complex strategy does not reduce the rate of MACE and has been associated with longer procedure and fluoroscopy times, higher contrast volume, and procedure-related myocardial infarction. Moreover, a recent meta-analysis of six randomized trials comparing these two strategies demonstrated no significant differences in rate of death or target lesion revascularization yet, the rate of myocardial infarction was significantly higher in the complex strategy.³⁰ One major difference between all the randomized studies was the definition of *residual side branch stenosis* used by each trial.

The challenge of assessing side branch lesion severity begins by recognizing the limitations of coronary angiography as purely a luminogram. It has been known that coronary angiography often leads to overestimation of the functional significance of the ostial side branch moreso than lesions in other segments of the coronary circulation.

There are currently no randomized studies to demonstrate the use of FFR-guided strategy for CBL. Initial data by Koo et al^{31,32} showed that only 27% of the side branch lesions with > 75% stenosis by QCA were functionally significant when assessed by FFR. Additionally, no lesions with < 75% stenosis by visual assessment had FFR < 0.75. The study showed that visual assessment of a jailed side branch tends to overestimate the significance of a stenosis and highlights the importance of physiologic assessment of these lesions. Koo et al³² have also demonstrated that the functional severity of jailed side branch lesions after PCI did not change at 6-month follow-up

when assessed by FFR. Therefore, these data may support the concept that an aggressive two-stent strategy in the management of CBL does not ensure better clinical outcomes.

We investigated the impact of FFR-guided strategy compared with angiography-guided strategy for the assessment of stenoses in patients with MVD and bifurcation lesions.⁴ The study demonstrated that the event rate was significantly lower when an FFR-guided strategy was used. A large randomized study is needed to compare the impact of FFR-guided strategy compared with final kissing-balloon inflation after stenting of the main vessel in patients with bifurcation lesions. The coronary angiogram in Figure 4 demonstrates significant stenoses of the LAD and diagonal at the bifurcation. Before considering revascularization, FFR of the LAD and diagonal were 0.84 and 0.85, respectively. FFR of > 0.75 is a strong predictor of survival and event-free survival

among patients with an LMCA stenosis, and the patient continued medical therapy.

CONCLUSION

FFR, an invasive pressure-derived index of stenosis severity, can be performed easily, rapidly, and safely in patients with coronary artery disease as a surrogate of noninvasive detection of ischemia. In particular, measurements of FFR in a subset of patients with complex lesions including left main coronary artery stenosis, multivessel disease, and bifurcation lesions are of prime importance because there is no robust correlation between stress test and FFR. Furthermore, FFR provides a more refined individualized assessment of the true severity of coronary artery disease and a more appropriate selection of the epicardial lesions to be treated. ■

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