

Defining Left Main Stenosis Severity With IVUS and FFR

Two complementary modalities provide doctors with data on when to intervene.

BY FILIPPO FIGINI, MD, AND AZEEM LATIB, MD, FACC

Fractional flow reserve (FFR) and intravascular ultrasound (IVUS) are useful tools for the assessment of intermediate coronary lesions. As these two tests provide different information about the examined plaque by assessing the functional significance and anatomical characteristics of the lesion, respectively, it is not surprising that on some occasions, they may provide a different answer when used to establish whether or not a certain lesion has to be treated.

This issue is particularly relevant in the assessment of left main (LM) coronary artery stenosis. Given the high mortality rate of LM disease, it is widely accepted that patients with significant LM disease should undergo revascularization independently of the presence of symptoms.^{1,2} On the other hand, revascularization of a lesion in the LM that is not functionally relevant exposes the patient to an unnecessary procedure and can lead to in-stent restenosis or thrombosis or to premature closure of a bypass graft.

FULFILLING AN UNADDRESSED NEED

Angiographic assessment of LM lesion severity is often unreliable,³ with a large inter- and intraobserver variability.⁴ This is particularly true for the ostium,⁴ distal bifurcation, and diffusely diseased segments, or in the presence of dense calcium or eccentric disease;⁵ even quantitative angiographic analysis of minimal luminal diameter does not correlate well with clinical events.⁶ Thus, the indication for revascularization often depends mainly on FFR and IVUS results, particularly in stable patients who are

asymptomatic and/or have not undergone testing for inducible ischemia prior to angiography.

Handling the discrepancy between visual estimation and functional significance of a stenosis is a frequent issue in daily practice. Park et al have sought to determine the factors related to this “visual-functional mismatch,” both in LM and non-LM lesions, using quantitative angiography, IVUS, and FFR. For 63 LM stenoses, angiography underestimated the functional significance of the lesion (stenosis < 50%; FFR < 0.8) in 16 cases (25%), whereas overestimation (stenosis > 50%; FFR > 0.8) occurred in eight patients (13%). Underestimation was more frequent in smokers and in the presence of a large plaque burden and plaque rupture.⁷

CLINICAL STUDIES OF IVUS AND FFR

Several clinical studies have demonstrated that if IVUS or FFR findings are negative, it is safe to defer myocardial revascularization.^{6,8-10} In 2001, Briguori et al compared IVUS measurements to FFR findings and found that a minimal luminal area < 4 mm², lesion length > 10 mm, and a stenosis > 70% could predict an FFR value of < 0.75 with optimal sensitivity and good specificity.¹¹ No left main stenoses were included in this study. The study by Jasti et al is the most widely cited regarding the evaluation of LM lesion severity with IVUS. Jasti and colleagues studied 55 ambiguous LM stenoses with IVUS as well as FFR and found that an IVUS MLA of 5.9 mm² or a minimal luminal diameter of 2.8 mm were predictive of FFR < 0.75 with 93% sensitivity and 95% specificity.¹⁰

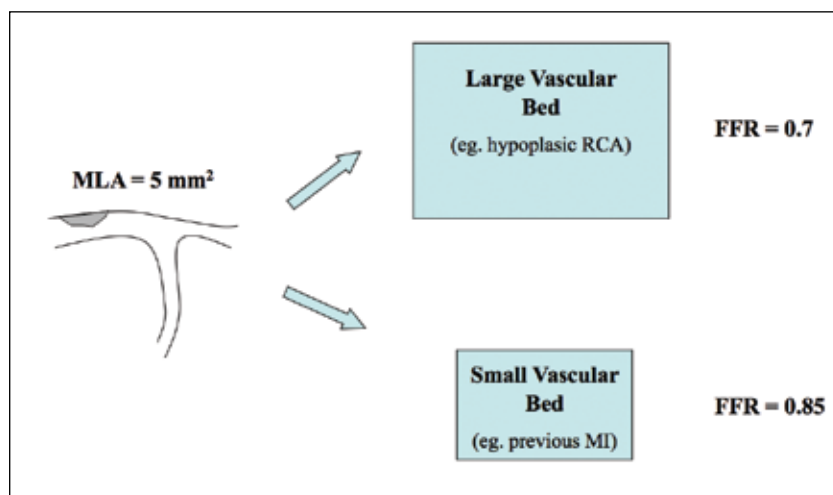


Figure 1. An example of how a given LM stenosis can be hemodynamically significant or not according to the extent of the subtended vascular bed.

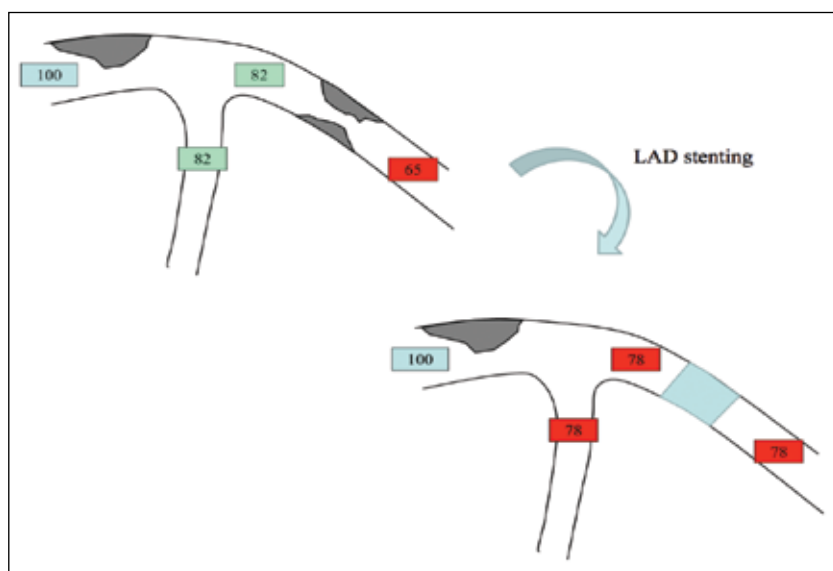


Figure 2. The effect of a secondary stenosis downstream of the LM; the numbers represent blood pressure recorded in various segments of the left coronary artery. In this example, with a tight proximal left anterior descending (LAD) artery stenosis, FFR in the mid-LAD is 0.65 and represents the sum of the effect of both LM and LAD lesions. If the FFR is measured in the proximal LAD before the secondary lesion, there is a false-negative result (0.82), as pressure is elevated upstream of the LAD stenosis. In the same way, the FFR measurement could be overestimated in the circumflex artery. After LAD stenting, the FFR is 0.78 in both the LAD and circumflex arteries and represents the real hemodynamic significance of the LM lesion.

The prognosis was excellent in patients with $\text{FFR} \geq 0.75$ who were treated medically. These results were prospectively validated in the LITRO study, which enrolled 354 patients with intermediate LM lesions and showed excellent event-free survival with medical therapy

and deferring revascularization in patients with an LM MLA $> 6 \text{ mm}^2$.^{2,12,13}

According to Kang et al, an IVUS MLA of 4.8 and 4.1 mm^2 were predictive of an FFR value < 0.8 and < 0.75 , respectively; however, no clinical follow-up was performed in this study. All patients with an MLA $> 6 \text{ mm}^2$ had a negative FFR; 82% of patients with an MLA $< 4.8 \text{ mm}^2$ had an FFR < 0.8 .¹⁴ The authors found a high incidence of plaque rupture by IVUS (33%), and ruptured plaques had a lower FFR value than nonruptured ones, even if the average MLA was not significantly different.^{7,14} It can be hypothesized that ruptured plaques, having an irregular surface, pose a greater resistance to blood flow than smooth lesions. This exemplifies how factors that are not detectable by angiography may influence the hemodynamic significance of a stenosis; the residual cross-sectional area is not the sole determinant of a pressure drop across the lesion.

A CLOSER LOOK AT IVUS

Even if IVUS does not directly assess the functional significance of the stenosis, it can provide important details about plaque morphology, such as the presence of calcium, fibrosis, or rupture. When virtual histology is performed, IVUS can provide information on plaque composition. Several IVUS studies have suggested that plaques with a different location in the LM may have different pathological features: lesions in the distal part or at the bifurcation often present a higher degree of plaque burden and are more frequently ruptured

and calcified, whereas ostial stenoses are frequently fibrotic with a smaller plaque burden and often show a recoil phenomenon after balloon angioplasty due to the presence of elastic fibers.^{4,15,16} Compared with the LAD artery, the relative frequency of thin-cap fibrofatty

atheroma in the LM is lower.¹⁷ It has not been demonstrated that treating a lesion just because of its “vulnerable” aspect alters a patient’s prognosis; plaque burden has instead been identified as an important predictor of events in patients with intermediate LM disease when revascularization is deferred.¹⁸

Evaluation of the circumflex origin is frequently challenging due to its angulation: IVUS parameters may not be completely reliable in predicting the functional significance of lesions at the ostium of side branches, retaining a good value in excluding significant stenoses but with a poor positive predictive value.¹⁹ IVUS evaluation of LM MLA may vary if the measurement is performed from the LAD artery or from the circumflex. Because MLA can be overestimated by artifact (but not underestimated), it is recommended to consider the smaller area measured.

A CLOSER LOOK AT FFR

FFR is being increasingly validated and utilized in interventional cardiology.²⁰⁻²² In studies that compare FFR and IVUS, FFR is generally regarded as the gold standard, as the functional relevance of a stenosis is considered the most important parameter indicating that revascularization is beneficial. On the other hand, acute coronary syndromes also occur with nonhemodynamically significant lesions, so the occurrence of an event during the subsequent follow-up period does not necessarily imply that the significance of the stenosis was underestimated at the time of evaluation.

Several caveats must be taken into account when using FFR for LM assessment. The method is indeed critically dependent not only on the anatomical characteristics of the lesion itself, but also on the vascular bed supplied by the LM (Figure 1). If there is an area of scarring due to a previous infarct in the territory of the left coronary artery, the quantity of viable myocardium subtended by the LM will be reduced, and the FFR result will be higher. This does not mean that FFR is underestimating the severity of the stenosis: it indicates that the lumen is adequate to supply the residual subtended vascular bed. On the other hand, if the right coronary artery is severely diseased or occluded and contralateral collateral flow is present, the vascular bed supplied by the LM is increased. In this case, FFR may be reduced with a stenosis that would not be significant in the absence of the occluded vessel.²³

Furthermore, the presence of additional stenoses in one of the branches of the LM can alter the pressure gradient across the examined lesion (Figure 2). When tandem lesions are present (eg, on LM and proximal LAD artery), it is often difficult to assess the individual contribution of single plaques to the overall FFR value.

If the transducer is positioned after the second stenosis, the FFR value will represent the sum of the pressure drop generated by the two lesions. Conversely, if the transducer is between the two plaques, then the FFR can be overestimated. A pullback of the pressure wire during continuous intravenous adenosine infusion may help in identifying the site of greatest gradient. The presence of a tight stenosis in one of the branches of the LM can also alter the pressure gradient across the LM, causing an overestimation of FFR if measured on the other branch;²⁴ this effect is more pronounced when the myocardial mass subtended by the secondary stenosis is large.

In the presence of isolated LM disease, FFR is a simple and reliable tool to assess the functional significance of intermediate lesions; however, results must be interpreted with caution when other lesions are present. In these cases of nonisolated LM lesions, IVUS is strongly preferred. Furthermore, FFR results must be interpreted with caution in patients with hypertrophic cardiomyopathy and other forms of microvascular dysfunction, in which maximal hyperemia cannot be reached.²⁵

We utilize continuous intravenous adenosine infusion to intracoronary administration because of greater stability of the hyperemic state, less artifacts due to drug administration, and the ability to perform pullback. Theoretically, a central intravenous line provides the best accuracy, but the difference in FFR between central and peripheral infusion, although statistically significant, is clinically irrelevant, with a mean value of 0.013.²⁶ In our practice, peripheral infusion (at a rate of 140 µg/kg/min) appears reliable, is more practical, and has the advantage of a reduced risk of vascular complications. Another important technical aspect to be remembered when FFR is used for the assessment of ostial LM lesions is to disengage the guiding catheter during pressure measurement.

There is debate regarding the optimal FFR cutoff value, as some studies used 0.75 and others use 0.8 as a threshold for treatment, so that a gray zone exists in evaluating the functional significance of a stenosis. However, FFR should not be considered only as a “yes or no” test, as it measures a physiologically continuous parameter. As a general rule, we use an FFR < 0.8 or an MLA < 5.9 mm² as our threshold to revascularize the LM.

CONCLUSION

In summary, IVUS and FFR are two complementary modalities: if clinicians want to know whether the lesion is causing ischemia, as is generally the case, then FFR is the test of choice provided that the aforementioned technical issues regarding the vascular bed and maximal hyperemia have been considered. If multiple lesions are



Figure 3. Left coronary angiography of a 73-year-old patient presenting with intermediate LM stenosis. IVUS showed an MLA of 4.3 mm²; however, FFR in the mid-LAD during adenosine infusion was 0.93. Based on this functional information, the LM stenosis was left untreated. After 2 years, the patient is asymptomatic and performing regular physical activity.

present, or if information is needed regarding plaque morphology, extent of calcification, and, after the procedure, about correct stent expansion and positioning, then IVUS is the most appropriate method.

Therefore, IVUS can be a good choice if the likelihood of performing percutaneous coronary intervention is high. When both methods are used, the results will not always be concordant. In these cases, the choice to treat or not relies on the experience and clinical judgment of the physician, as well as a thorough and objective assessment of the patient's history and symptoms (Figure 3). ■

Filippo Figni, MD, is with the San Raffaele Scientific Institute and EMO-GVM Centro Cuore Columbus in Milan, Italy. He has disclosed that he has no financial interests related to this article.

Azeem Latib, MD, FACC, is with the San Raffaele Scientific Institute and EMO-GVM Centro Cuore Columbus in Milan, Italy. He has disclosed that he serves on a Medtronic Advisory Board. Dr. Latib may be reached at info@emocolumbus.it.

1. Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization. *Eur Heart J*. 2010;31:2501-2555.
2. Kern MJ. Conversations in cardiology: using new media to transmit timely medical knowledge. How do you assess the left main stenosis with FFR and IVUS in a patient with multivessel CAD? *Catheter Cardiovasc Interv*. 2012;80:465-471.
3. Cameron A, Kemp HG Jr, Fisher LD, et al. Left main coronary artery stenosis: angiographic determination. *Circulation*. 1983;68:484-489.
4. Sano K, Mintz GS, Carlier SG, et al. Assessing intermediate left main coronary lesions using intravascular ultrasound. *Am Heart J*. 2007;154:983-988.
5. Ragosta M. The complexity involved in assessment of left main coronary artery disease. *JACC Cardiovasc Interv*. 2012;5:1026-1028.
6. Abizaid AS, Mintz GS, Abizaid A, et al. One-year follow-up after intravascular ultrasound assessment of moderate left main coronary artery disease in patients with ambiguous angiograms. *J Am Coll Cardiol*. 1999;34:707-715.
7. Park SJ, Kang SJ, Ahn JM, et al. Visual-functional mismatch between coronary angiography and fractional flow reserve. *JACC Cardiovasc Interv*. 2012;5:1029-1036.
8. Bech GJ, Droste H, Pijls NH, et al. Value of fractional flow reserve in making decisions about bypass surgery for equivocal left main coronary artery disease. *Heart*. 2001;86:547-552.
9. Hamilos M, Muller O, Cuisset T, et al. Long-term clinical outcome after fractional flow reserve-guided treatment in patients with angiographically equivocal left main coronary artery stenosis. *Circulation*. 2009;120:1505-1512.
10. Jasti V, Ivan E, Yalamanchili V, et al. Correlations between fractional flow reserve and intravascular ultrasound in patients with an ambiguous left main coronary artery stenosis. *Circulation*. 2004;110:2831-2836.
11. Briguori C, Anzuini A, Airolidi F, et al. Intravascular ultrasound criteria for the assessment of the functional significance of intermediate coronary artery stenoses and comparison with fractional flow reserve. *Am J Cardiol*. 2001;87:136-141.
12. de la Torre Hernandez JM, Hernandez Hernandez F, Alfonso F, et al. Prospective application of pre-defined intravascular ultrasound criteria for assessment of intermediate left main coronary artery lesions results from the multicenter LITRO study. *J Am Coll Cardiol*. 2011;58:351-358.
13. de la Torre Hernandez JM, Ruiz-Lera M, Fernandez-Friera L, et al. Prospective use of an intravascular ultrasound-derived minimum lumen area cut-off value in the assessment of intermediate left main coronary artery lesions [in Spanish]. *Rev Esp Cardiol*. 2007;60:811-816.
14. Kang SJ, Lee JY, Ahn JM, et al. Intravascular ultrasound-derived predictors for fractional flow reserve in intermediate left main disease. *JACC Cardiovasc Interv*. 2011;4:1168-1174.
15. Maehara A, Mintz GS, Castagna MT, et al. Intravascular ultrasound assessment of the stenoses location and morphology in the left main coronary artery in relation to anatomic left main length. *Am J Cardiol*. 2001;88:1-4.
16. Tyczyński P, Pregowski J, Mintz GS, et al. Intravascular ultrasound assessment of ruptured atherosclerotic plaques in left main coronary arteries. *Am J Cardiol*. 2005;96:794-798.
17. Mercado N, Moe TG, Pieper M, et al. Tissue characterisation of atherosclerotic plaque in the left main: an in vivo intravascular ultrasound radiofrequency data analysis. *EuroIntervention*. 2011;7:347-352.
18. Okabe T, Mintz GS, Lee SY, et al. Five-year outcomes of moderate or ambiguous left main coronary artery disease and the intravascular ultrasound predictors of events. *J Invasive Cardiol*. 2008;20:635-639.
19. Koh JS, Koo BK, Kim JH, et al. Relationship between fractional flow reserve and angiographic and intravascular ultrasound parameters in ostial lesions: major epicardial vessel versus side branch ostial lesions. *JACC Cardiovasc Interv*. 2012;5:409-415.
20. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med*. 2009;360:213-224.
21. De Bruyne B, Pijls NH, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med*. 2012;367:991-1001.
22. Misaki T, Kunii H, Mizukami H, et al. Long-term clinical outcomes after deferral of percutaneous coronary intervention of intermediate coronary stenoses based on coronary pressure-derived fractional flow reserve. *J Cardiol*. 2011;58:32-37.
23. Iqbal MB, Shah N, Khan M, et al. Reduction in myocardial perfusion territory and its effect on the physiological severity of a coronary stenosis. *Circ Cardiovasc Interv*. 2010;3:89-90.
24. Daniels DV, Van't Veer M, Pijls NH, et al. The impact of downstream coronary stenoses on fractional flow reserve assessment of intermediate left main disease. *JACC Cardiovasc Interv*. 2012;5:1021-1025.
25. Magni V, Chieffo A, Colombo A. Evaluation of intermediate coronary stenosis with intravascular ultrasound and fractional flow reserve: its use and abuse. *Catheter Cardiovasc Interv*. 2009;73:441-448.
26. Lindstaedt M, Bojara W, Holland-Letz T, et al. Adenosine-induced maximal coronary hyperemia for myocardial fractional flow reserve measurements: comparison of administration by femoral venous versus antecubital venous access. *Clin Res Cardiol*. 2009;98:717-723.