

Assessing Intermediate Left Main Lesions With IVUS or FFR

How intravascular ultrasound and fractional flow reserve can be used in this challenging subset.

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Left main disease is found in approximately 5% of patients with stable angina and in approximately 7% of patients presenting with an acute myocardial infarction.¹ In a majority of patients, left main disease is associated with atherosclerosis in the other coronary arteries. Three-year survival in patients with > 50% left main stenosis is 50%. In the subgroup of patients with 50% to 70% stenosis, 3-year survival is 66%, but for patients with > 70% stenosis, survival is 41%.² Therefore, accurate assessment of the degree of left main stenosis has important prognostic and therapeutic implications.

Although angiography is the gold standard for assessing coronary stenoses, in the case of left main disease, it tends to underestimate the severity of stenosis when compared to findings at autopsy.³ This is due to a lack of a reference segment in cases of diffuse disease and, at times, due to a very ostial or very distal location of the left main stenosis. Angiography has significant intraobserver and interobserver variability.⁴ Therefore, particularly in intermediate left main disease, more detailed anatomic information obtained with intravascular ultrasound (IVUS) or physiologic assessment using fractional flow reserve (FFR) can provide useful clinical information to complement the angiographic assessment.

FFR CONSIDERATIONS IN LEFT MAIN DISEASE

FFR determination in the left main coronary artery is easily performed. Typically, the left main is intubated with a guiding catheter and, after appropriate antithrombin administration, a pressure sensor guidewire (St. Jude Medical, Inc., St. Paul, MN, or Volcano Corporation, Rancho Cordova, CA) is advanced into either the left anterior descending or left circumflex artery. Occasionally,

measurements may be obtained sequentially in both the left anterior descending and left circumflex arteries, depending on the exact lesion morphology that is present. Hyperemia is typically induced by intracoronary adenosine in bolus doses of 50 to 200 μ g. Higher doses are preferred for left main assessment, and doses in excess of 100 μ g should be utilized, if tolerated. In the presence of ostial lesions or any indication of catheter damping, the guide catheter is removed from the ostium and hyperemia is induced using intravenous adenosine (140–280 μ g/kg per minute).

It is important to recognize that while angiographic assessment of left main disease had guided therapy for more than 30 years, even experienced angiographers are unable to reliably assess lesion severity. Lindstaedt et al performed angiography and FFR in 51 patients with intermediate left main (40%–80% diameter narrowing) stenoses. Lesions were graded as significant or insignificant by four experienced interventional physicians blinded to the FFR results. Using FFR as the gold standard for significant lesions, the angiographers correctly classified the lesions in less than 50% of cases (regardless of FFR threshold of 0.75 or 0.8). Observer variability was high, resulting in only 29% of cases achieving unanimous appropriate classification.⁵ Similarly, Hamilos et al found a diagnostic accuracy of angiographic left main assessment for detecting physiologically significant stenoses (FFR < 0.8) of only 69%.⁶

FFR has previously been used to assist in treatment planning (Table 1). In a prospective study involving 54 patients with equivocal left main disease by coronary angiography, FFR measurement was performed with 140 μ g/kg per minute of intravenous adenosine. In slightly

more than half of the patients, FFR was < 0.75 , and coronary artery bypass was performed. The remainder of the patients with FFR > 0.75 were managed medically. At 3 years, survival was 97% and 100%, and event-free survival was 83% and 76%, respectively.⁷ An updated data set with 213 patients from this group with 73 bypass-treated and 136 medically treated patients had identical survival rates over 5 years of follow-up. In this population, a threshold of 0.8 was applied.⁶

Jimenez-Navarro et al studied 27 consecutive patients with intermediate (30%–50%) left main stenoses. Of these, 19 had FFR values > 0.75 and were treated medically. The average FFR in these patients was 0.88. During a mean follow-up of 26 ± 12 months, one patient was treated with surgery at another institution, despite the FFR results, and one required surgery due to progression of the left main lesion after 4 years. No patients died due to cardiac issues.⁸

In a very similar series, Legutko et al studied 38 consecutive patients with intermediate left main lesions ($44\% \pm 10\%$). Of these, 20 (53%) had an FFR > 0.75 and were treated medically. One patient had surgery due to progression of the left main stenosis, and one experienced a myocardial infarction unrelated to the left main lesion. Of note, two of the 18 patients with an FFR < 0.75 , in whom surgery was performed, died.⁹

Lindstaedt et al studied 51 patients with intermediate

left main lesions (40%–80% diameter stenosis). A threshold value of 0.8 was used for this study. Twenty-four patients had FFR above threshold and were managed medically. During a mean follow-up of 29 ± 16 months, survival was 100% in the medically treated group and 81% in the surgically treated group. Event-free survival was 66% and 69%, respectively. In the medical group, only one event was related to disease progression in the left main; all others were due to additional disease in branch vessels.¹⁰

A smaller study of 15 consecutive patients with indeterminate left main stenosis also showed that no patients with an FFR > 0.75 , who were treated with medical therapy, showed symptoms from left main disease during 32.5 months of follow-up.¹¹

Most recently, Courtis et al studied 142 patients with mean $42\% \pm 13\%$ left main stenosis. They used a threshold value of > 0.8 to assign a patient to medical therapy and < 0.75 to assign a patient to surgical therapy. Patients with an FFR between 0.75 and 0.8 were assigned based on FFR and other clinical findings. At 14 ± 11 months of follow-up, the 82 patients (58%) assigned to medical therapy had a major adverse cardiovascular event (MACE) rate of 13% and a cardiac death and infarction rate of 6%. In the 60 patients (42%) assigned to surgical therapy, MACE was 7% ($P = .27$) and cardiac death and infarction was 7% ($P = .70$). Importantly, these investigators found that in the medically treated group, the incidence of

TABLE 1. STUDIES USING FFR TO ASSESS TREATMENT STRATEGY FOR INTERMEDIATE LEFT MAIN CORONARY DISEASE

Study	FFR Threshold	Total Number	Medical Therapy			Surgical Therapy			Follow-Up Time (mo)
			n (%)	MACE	Death	n (%)	MACE	Death	
Hamilos (2009) ⁶	0.8	213	136 (65%)	26%	9 (6.5%)	73 (35%)	17%	7 (9.6%)	35 ± 25
Courtis (2009) ¹²	0.75 surg; 0.8 med	142	82 (58%)	13%	3 (3.6%)	60 (42%)	7%	3 (5%)	14 ± 11
Lindstaedt (2006) ¹⁰	0.75 surg; 0.8 med	51	24 (47%)	31%	0	27 (53%)	34%	5 (19%)	29 ± 16
Suamaru (2005) ¹¹	0.75	15	8 (53%)	0	0	7 (47%)	29%	0	33 ± 10
Legutko (2005) ⁹	0.75	38	20 (53%)	10%	0	18 (47%)	11%	2	24 mean
Jimenez-Navarro (2004) ⁸	0.75	27	20 (74%)	10%	0	7 (26%)	29%	2	26 ± 12
Bech (2001) ^{7*}	0.75	54	24 (44%)	24%	0	30 (56%)	17%	1	29 ± 15

*Represents a subset of Hamilos (2009).⁶

Abbreviations: FFR, fractional flow reserve; MACE, major adverse cardiac events (death, revascularization, infarction); med, medical therapy recommended above this level; surg, surgical therapy recommended below this level.

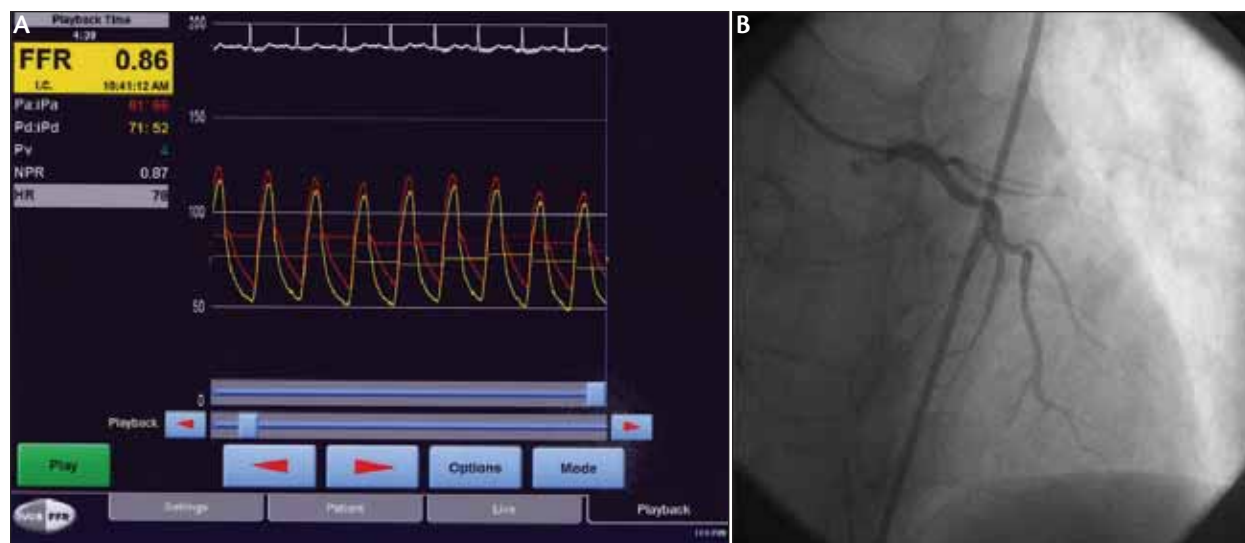


Figure 1. FFR recording with the pressure wire in the left anterior descending artery. Adenosine 200 μ g/kg per minute administered intravenously was utilized as the hyperemic stimulus. Based on these results, no left main intervention was suggested (A). Cranial projection of the left main coronary artery showing a possible ostial lesion (B).

MACE was higher in patients who had FFR measured using lower adenosine bolus doses ($86 \pm 57 \mu$ g) versus those in whom FFR was measured using higher adenosine doses ($176 \pm 102 \mu$ g). Patients with MACE more commonly had diabetes (55%) than those without MACE (21%).¹²

A study involving 52 patients found that there is a good correlation between intracoronary and intravenous adenosine in the majority of patients; however, in approximately 8% of patients, the FFR obtained by intravenous adenosine was 0.05 higher than that obtained by intracoronary adenosine. This finding is likely indicative of a suboptimal hyperemic response to intracoronary adenosine in some patients.¹³ Another study showed that FFR values decreased with incremental doses of intracoronary adenosine starting at 60 μ g. All FFR values with intracoronary adenosine were higher than those obtained with intravenous adenosine. However, no significant difference was noted between the two when 150 μ g of intracoronary adenosine was used.¹⁴

TAKE HOME MESSAGE

FFR values below 0.75 are considered indicative of significant ischemia-producing lesions, although more recently, some studies have been using a threshold of 0.8. In cases of FFR between 0.75 and 0.8, other clinical parameters should assist in choosing the proper treatment strategy. Patients with left main FFR > 0.8 have an excellent prognosis with medical management. High doses of either intracoronary or intravenous adenosine must be used to ensure accurate FFR determination.

Figure 1 displays a typical FFR determination for assisting in determining therapeutic strategy. Once FFR documented that the left main was not critical, percutaneous intervention of the right coronary was performed.

IVUS IN AMBIGUOUS LEFT MAIN DISEASE

IVUS has received considerable attention in assessing left main disease with respect to its severity and plaque composition, as well as to guide percutaneous therapies for left main disease. IVUS provides high-quality, cross-section images of the entire left main, including information about positive remodeling. The technique of left main IVUS imaging involves placement of a guidewire into either the left anterior descending or the left circumflex coronary artery. A slow, preferably motorized, pullback of the IVUS catheter is then performed from the branch artery into the sinus of Valsalva, ensuring that the guiding catheter does not obstruct views of the true ostium. Suter et al¹⁵ evaluated left main assessment using pullback runs from both branch arteries. The mean stenosis was $30\% \pm 8\%$. Minimal lumen area in the left main was not significantly different when assessed from either branch artery. There was, however, a nonsignificant tendency for higher areas when the pullback was from the left circumflex, suggesting some degree of eccentric catheter travel through the more acute circumflex takeoff (interclass correlation coefficient 0.74).

Standard criteria for IVUS measurements in indeterminate left main disease are lacking. Our best information comes from a study of 121 patients with angiographically and IVUS-assessed normal left main arteries. In this nor-

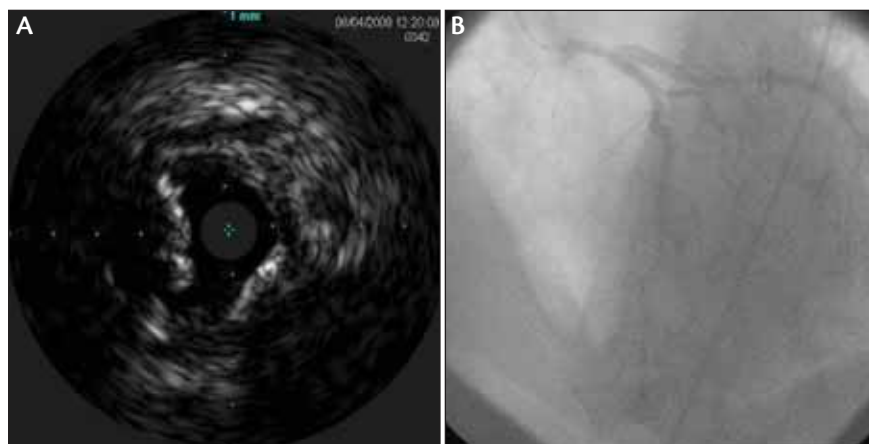


Figure 2. IVUS image of the left main lesion indicating an MLA of 3.9 mm² (A). Cranial projection showing a questionable mid left main lesion (B).

mal North American population, Fassa et al established that the mean minimal luminal area (MLA) for left main arteries was 16.25 ± 4.3 mm² and the lower range for normal left main area was 7.5 mm² (mean minus 2 SD).¹⁶

In a study of 197 patients, all 21 patients with > 50% left main stenosis on quantitative angiography had an IVUS minimum luminal diameter (MLD) of < 2 mm. All patients with < 30% stenosis on quantitative angiography had an IVUS MLA of > 9 mm². All patients with MLA < 6 mm² and an IVUS percent luminal stenosis > 50% had angina and a positive stress test. The study concluded that an MLD of < 2 mm by IVUS was highly suggestive of significant left main disease.¹⁷ Sano et al¹⁸ also studied the relationship between IVUS and angiographic assessment of left main lesions. Significant lesions were defined as > 50% stenosis by angiography or < 6 mm² MLA by IVUS. Lesions were assessed as significant by IVUS in 44.3% of cases, but by angiography in only 13% of cases. Less than half of the angiographically ambiguous left main lesions had significant stenosis, as determined by IVUS.

In another pivotal study, FFR was compared to IVUS. Jasti et al studied 44 patients with ambiguous left main coronary stenosis. Using FFR < 0.75 as a gold standard for ischemia, an MLD by IVUS of 2.8 mm had the highest sensitivity and specificity to predict an FFR < 0.75 (93% and 98%, respectively) followed by an MLA of 5.9 mm² (93% and 95%, respectively). An FFR threshold of 0.75 was used to triage patients to revascularization versus medical treatment. The event-free survival was similar in both arms.¹⁹

Dragu et al studied 20 patients with indeterminate left main disease and found excellent correlation between multidetector computed tomography and IVUS with regard to assessment of minimal lumen diameter and area, lumen area stenosis, plaque burden, and plaque characterization.²⁰

As with FFR, IVUS has been used to guide therapy. Fassa et al¹⁶ used IVUS MLA to study 214 patients with angiographically moderate left main artery stenoses. Left main revascularization was then performed in the majority (86%) of 83 patients with an MLA < 7.5 mm², and was deferred in the majority (87%) of the 131 patients with an MLA of ≥ 7.5 mm². At long-term follow-up (3.3 ± 2 years), there was no significant difference in MACE between the patients with an MLA < 7.5 mm² who underwent revascularization and patients

with an MLA ≥ 7.5 mm² in whom revascularization was deferred. The authors concluded that deferring revascularization with a left main MLA ≥ 7.5 mm² appeared to be safe. Of note, the MLA threshold of < 7.5 mm² used for assigning patients to revascularization in this study was derived from the lower limit of normal and was not correlated with a physiologic measurement, such as FFR. Additionally, these criteria were not strictly adhered to in the decision-making process. Patients in this study with an MLA < 7.5 mm², in whom revascularization was not performed (14.5%), had a worse outcome when compared to patients with an MLA < 7.5 mm² who were revascularized. However, the distribution of patients in these groups was very different, and advanced age and increased comorbidities may have contributed to the worse outcome in patients in whom revascularization was deferred.

Okabe et al²¹ followed 114 patients who had an angiographically determined left main stenosis of < 50% and in whom IVUS was performed. Follow-up was carried out for 5 years. Excluding the 11 patients who received immediate bypass surgery and three who subsequently died of noncardiac causes, clinical outcome in the remaining 100 patients, who were initially treated medically, was excellent. At a mean follow-up of 32 ± 17 months, there was a 6% mortality rate, a 2% bypass surgery rate, and no infarction or need for percutaneous intervention. The only multivariate predictor of events was the IVUS plaque burden at the lesion site (65% vs 49%; $P < .001$). Of note, the average MLA in the group incurring events was 7.2 ± 2.2 mm².

In a study involving 122 patients with left main disease who were treated medically, IVUS reference plaque burden and lesion lumen area, maximum and minimum lumen diameters, plaque area, and area stenosis were univariate predictors of outcomes. MLD, as determined by IVUS, diabetes, and an untreated stenosis > 50%, were

independent predictors of events, whereas parameters derived from quantitative coronary angiography were not. The MLA in the 18 patients who experienced events was $6.8 \pm 4.4 \text{ mm}^2$.²² Similar findings were also reported in a study of 102 patients with angiographically normal or mild left main disease, in which MLA determined by IVUS and diabetes were the only two multivariate predictors of late coronary events.²³

TAKE HOME MESSAGE

Angiographic assessment of intermediate left main lesions is unreliable. In patients with angiographically indeterminate disease, IVUS MLD $< 2.8 \text{ mm}$ or MLA $< 6 \text{ mm}^2$, suggest a physiologically significant lesion and identify patients who may benefit from revascularization. If the IVUS MLA is > 7.5 to 9 mm^2 , revascularization may be safely deferred. IVUS MLA values between 6 to 7.5 mm^2 should be interpreted in conjunction with the patient's clinical history, stress testing, or FFR results. Figure 2 demonstrates the use of IVUS to assist in the decision-making process.

PUTTING IVUS AND FFR RESULTS INTO CLINICAL CONTEXT

Although IVUS and FFR are important tools in determining the significance of indeterminate left main disease by angiography, they should not be used in isolation. Putting the results of these ancillary tools into clinical context on a case-by-case basis is critical. In other words, we have to treat the patient and not the numbers. For example, in a patient with angina, a markedly abnormal stress test, and isolated left main disease, an IVUS MLA of 8 mm^2 does not rule out significant left main stenosis.²⁴

FUTURE DIRECTIONS

IVUS provides detailed information about the composition and the distribution of the atherosclerotic plaque. Left main stenting is evolving as a viable alternative to coronary artery bypass surgery, albeit with a higher rate of repeat revascularization and the fear of stent thrombosis. IVUS guidance is being increasingly used to determine the percutaneous intervention strategy and to assess stent apposition of left main stents. IVUS can provide clear understanding of the involvement of the ostia of the left anterior descending and left circumflex arteries, thereby helping decide if the stenting should involve the distal left main bifurcation. In the future, information regarding plaque characteristics may play an important role in deciding whether the patient receives left main stenting, bypass surgery, or medical therapy. ■

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