3

Assessment of Intermediate Coronary Lesions

Akshay K. Khandelwal, MD

John J. Young, MD

Abstract

Coronary flow reserve (CFR), fractional flow reserve (FFR), and intravascular ultrasound (IVUS) can be used to help determine the significance of an intermediate coronary lesion. Both CFR and FFR physiologically test the pressure-flow mechanics of coronary circulation. CFR is used infrequently because of the variable contribution of the microcirculation and the more involved technique required. FFR is easier to interpret because it assesses the functional significance of only the lesion, and has more rigorous data to support its use. IVUS has the ability to anatomically measure the significance of a coronary lesion and has also been compared to FFR to support its use. Both IVUS and FFR have roles to play in the assessment of intermediate coronary lesions, including left main disease, bifurcation stenoses and serial stenoses. Given recent information regarding stable coronary disease, functional assessment of intermediate coronary lesions may remain limited to coronary distributions with objective evidence of ischemia.

Introduction

Intermediate coronary lesions, defined as stenoses >40% but <70% of the coronary luminal diameter, can be difficult to assess angiographically because of significant inter-observer and intra-observer variability. Quantitative coronary angiography (QCA) has not completely remedied this situation. Appropriate lesion assessment is critical in the diagnostic phase if patients are referred for angiography without noninvasive determination of ischemia, as well as in the interventional phase in order to determine the adequacy of lesion treatment. Techniques available in the cardiac catheterization lab include coronary flow reserve (CFR), fractional flow reserve (FFR), and intravascular ultrasound (IVUS), and their use varies with lesion subsets.

Coronary Blood Flow

Coronary blood flow is maintained at three levels: the epicardial arteries (which at basal flow rates play a minimal role, even in the presence of significant disease), the coronary precapillary arterioles (which contribute significantly), and subendocardial wall tension. Alterations in the microcirculation that occur in situations such as diabetes, left ventricular hypertrophy, and myocardial ischemia/infarction can impair functionality of the coronary precapillary arterioles. The normal ability of adults to augment coronary blood *flow* (three to five times normal with physiologic or pharmacologic provocation) can be blunted by the presence of a significant epicardial *pressure* gradient from a fixed stenosis. Compensation normally provided by the precapillary arterioles is challenged and the direct contribution of epicardial resistance to flow is unmasked. This *pressure-flow* relationship and the physiological significance of a lesion can be assessed and measured via two major mechanisms: CFR and FFR.

Coronary Flow Reserve

Coronary flow reserve (CFR) is defined as the ratio of maximal coronary flow with hyperemia to baseline flow. CFR tests the ability of the epicardial stenosis and microcirculatory resistance (acting at the precapillary arteriolar level), to maintain flow. A 175-cm long, 0.014-in-diameter steerable Doppler guidewire, with a 12 MHz piezoelectric ultrasound transducer at the wire tip is used to determine volumetric flow. The wire should be placed via standard interventional technique distal to the lesion in question and basal flow measured. Subsequently, maximal coronary hyperemia is stimulated (usually with intracoronary adenosine), and thus CFR is calculated (normal CFR >2). Abnormal CFR indicates significant epicardial stenosis, abnormal microcirculation, or both, and has been correlated with defects on nuclear stress imaging [(1)]. Altered hemodynamics such as heart rate, blood pressure, and contractility affect coronary flow and thus can impact CFR. Relative CRF (rCFR) differentiates the contributions of epicardial stensosis and the microcirulatory disturbances to impaired flow reserve, and is the ratio of the CFR in the target vessel to the CFR of the reference vessel. This assumes that the microcirculatory contribution to flow is uniform (which cancels out), and what remains is a direct comparison of epicardial resistance of the target vessel and of the reference vessel (normal rCFR is 0.8 to 1.0). Relative CFR cannot be used in patients with three-vessel coronary artery disease, as there is no disease-free vessel to provide reference epicardial resistance; nor can it be used in patients with regional dysfunction because of heterogenous microcirculation. Other indices of CFR, including proximal/distal flow ratio (P/D) and diastolic to systolic velocity ratio (DSVR), are too inconsistent for practical utilization.

Fractional Flow Reserve

As opposed to flow measurement, fractional flow reserve (FFR) is a pressure-derived ratio that estimates blood flow through a stenotic lesion at maximal hyperemia. Because basal flow is excluded from the calculation, FFR is considered relatively independent of flow and is impacted less by altered hemodynamics. In addition, FFR has the advantage of being lesion-specific and does not require a "reference vessel" for improved accuracy. For these reasons, CFR has largely been replaced by FFR. FFR is calculated using a 175- or 300-cm-length, 0.014-in-diameter pressure wire with a pressure sensor 30 mm from the tip. The wire is calibrated and introduced using standard interventional techniques, first placing the pressure sensor at the tip of the guide to equilibrate with the measured arterial pressure (Pa). The wire is then advanced so that the pressure sensor is 5 to 10 artery-diameters distal to the lesion in question in order to truly measure post-stenotic laminar flow. Maximal hyperemia is pharmacologically stimulated (often with intracoronary adenosine), and both Pa (at the guide tip) and distal coronary pressure (Pd, at the pressure sensor) are simultaneously measured. FFR is calculated as Pa/Pd, and a value <0.75 implies significance, with values between 0.75 and 0.80 considered a "gray zone." In studies this value strongly correlates with noninvasive ischemia and post-intervention resolution of abnormal FFR also correlates with resolution of noninvasive ischemia [(2)]. Furthermore, there is 5-year prospective and retrospective data that interventions on intermediate lesions with FFR of ≥0.75 can be safely deferred with an annual risk of cardiac death or myocardial infarction <1% [(3,4)].

The FFR wire also has the ability to sense temperature, and thus thermodilution-CFR can be measured using the same wire. While thermodilution-CFR results compare with Doppler-based CFR results, there are no studies that correlate Doppler-based CFR with noninvasive estimations of ischemia, or outcomes.

Intravascular Ultrasound

Intravascular ultrasound (IVUS) relies on anatomic measurements of lesion severity. It is a catheter-based imaging system that features a mechanical 30 or 40 Mhz transducer close to the tip, connected to a computer/recorder console and is introduced over a 0.014-in-diameter wire through a 6- or 5-French guide using standard interventional techniques. IVUS relies on distinguishing the echo-lucent lumen, echo-intense intima, echo-lucent media, and echo-intense adventitia to define the vessel wall. Using standard software packages, the lumen border can be identified and measurements of the minimum lumen diameter (MLD) and minimum lumen area (MLA) made for assessment of lesion severity. An MLD <1.8 cm or MLA < 4.0 cm^2 in a major epicardial vessel indicates significant stenosis and correlates with FFR <0.75 [5]. Other uses of IVUS include determination of measurements such as cross-sectional plaque area (external elastic membrane area – MLA), features of vessel wall architecture (such as presence of calcium, fibrous tissue), and plaque characteristics (such as presence of lipid pool and ruptured plaque appearance). Analysis of different radiofrequency signals can help identify unique elements of vessel architecture ("virtual histology"), but the practical value of this feature has not yet been determined.

Lesion-Specific Assessment

Left main disease

Left main disease assessment has therapeutic and prognostic significance and can be difficult as demonstrated by the Coronary Artery Surgery Study (CASS) trial [6]. Studies using FFR suggest that similar to coronary artery disease in other major epicardial arteries, left main disease with FFR ≥0.75 can be treated medically and intervention safely deferred with excellent rates of 3- to 4-year survival and freedom from major adverse cardiovascular events (MACE) [7,8]. Left main disease has also been assessed by IVUS, and an MLD >2.8 mm or MLA >6.0 mm^2 (probably >7.5 mm^2 in diabetics) has been shown to have low 1-year event rates [9]. Assessment by pressure wire has the advantage of avoiding pitfalls with ostial assessment and allowing interventional equipment to be delivered over the wire; although it is not a preferred wire of choice for intervention due to inferior functionality. While IVUS can have difficulty with ostial assessment and discerning the distal left main because of bifurcation/trifurcation disease, it has significant advantages in allowing assessment of plaque morphology and calcium deposition within the left main and ostial left anterior descending and circumflex arteries. IVUS can also help direct the choice of interventional equipment and technique should one choose a percutaneous approach to revascularization, and is a preferred strategy post-intervention to ensure optimal treatment results.

Bifurcation and ostial disease

Bifurcation and ostial disease can be difficult to assess because of overlapping vessels and uncertain vessel take-off. Left main ostial disease assessment can be particularly problematic because of catheter seating and aortic overlap. IVUS assessment can be tricky as it is difficult to ensure that the catheter is coaxial to the ostium, or in the case of bifurcation disease, truly measuring the branch vessel at an appropriate axis. This becomes particularly important if repeated measurements such as pre- and post-intervention assessment are required. However, IVUS has the advantage of post-interventional determination of adequate stent deployment and coverage of the ostium. FFR does not require actual delineation of the ostium or the bifurcation, only that the pressure sensor is distal to the lesion in question. As such, FFR has excellent reliability and reproducibility.

Serial intermediate stenoses.

While a formula to derive FFR significance of two serial intermediate stenoses does exist, it is complicated and often a simple pressure "pull-back" across each individual lesion is used for assessment. More commonly, IVUS can be utilized for anatomic individual lesion assessment.

Cfr Vs. Ffr Vs. Ivus

Both CFR and FFR have compared favorably to non-invasive ischemic assessment of coronary lesions [1,2]. Thus, they enjoy the status of serving as a "cath lab stress test" that can be performed while the patient is on the table allowing for a seamless transition from diagnostic to an interventional procedure. Although IVUS determines lesion severity anatomically and not physiologically, it has also been shown to have excellent correlation with FFR results [5].

Role of Assessment of Intermediate Lesion

Recent data suggests that most stable coronary artery lesions in select patients can be treated with intense medical therapy and percutaneous revascularization reserved for treatment failure [10]. With the exception of left main disease, assessment of intermediate lesions may not be necessary until patients have failed aggressive medical treatment and lifestyle modification, or if revascularization is performed primarily for the purpose of improving symptoms. This recent trial evidence is consistent with prior data demonstrating no improvement in survival or prevention of myocardial infarction (MI), at least with bare metal stents, compared to medical therapy alone. The role of drug-eluting stents (DES) in the treatment of intermediate lesions is largely unknown at this time. While short-term, retrospective pooled analyses appear to show low rates of major adverse events [11], DES primary effect is in reducing restenosis and target lesion revascularization. Although the patient populations differ, the low rate of MI observed (3%) with DES treatment of intermediate lesions is still greater than documented mortality *and* MI associated with the FFR-guided deferral of treatment with single vessel coronary artery disease to five year follow-up (<1% annual cardiac death or MI) (3). Moreover, the effects of late DES thrombosis may tip the balance in the favor of FFR-guided therapy even further. Randomized, long-term trial data of DES vs. FFR-guided (or IVUS-guided) deferral of intermediate stenoses in patients with both single-vessel and multi-vessel disease would be required to adequately address this question.

Summary

CFR, FFR, and IVUS are useful tools in the cath lab that can assist in further elucidation of intermediate coronary artery stenoses. Each technique has its particular strengths and weaknesses depending on the type of coronary lesion, and most contemporary cath labs utilize either FFR or IVUS because of reliable, reproducible, evidence-based results. Deferral of PCI of non-significant lesions assessed by FFR- or IVUS-guidance is a proven, safe strategy that even the advent of DES may not be able to alter, although further studies are warranted.

Figure 1. **FFR use in the assessment of intermediate RCA disease.** The angiographic image (left) shows an intermediate stenosis of the mid RCA. FFR performed (right) demonstrates FFR of 0.89 with hyperemia, indicating that this lesion does not require intervention and can be treated medically (used with permission, RADI corporation)

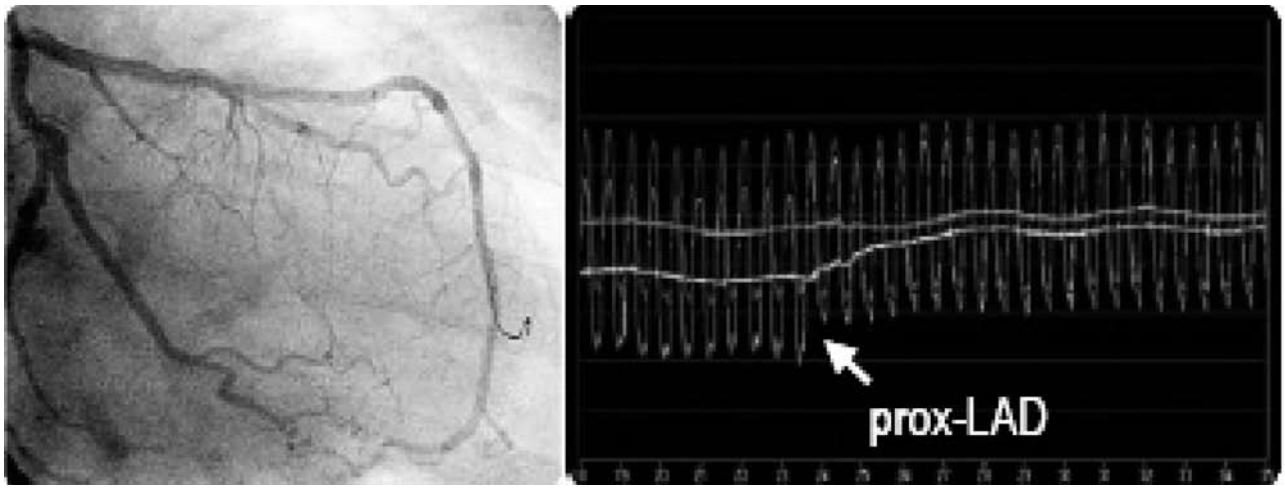

Figure 2. **FFR use in the assessment of intermediate LAD disease.** The angiographic image (left) shows an intermediate lesion of the proximal LAD after PCI of the mid LAD. FFR performed by pull-back (right) indicates that this lesion is hemodynamically significant (FFR 0.69). This proximal lesion was subsequently treated with PCI (used with permission, RADI corporation).

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