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Improving the Utility of Coronary Angiography: The Use of Adjuvant Imaging and Physiological Assessment

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1. Introduction

The most important role of coronary angiography is to delineate coronary lesions that cause inducible ischaemia. It remains the primary tool influencing the decision to undertake revascularization and patient outcomes [1] [2-4]. However, there are inherent limitations to diagnostic angiography. These pitfalls include difficulties delineating eccentric plaque (that can be underappreciated in the absence of multiple angiographic views), difficulty assessing lesions of moderate severity, the assessment of overall plaque burden and the composition, appreciation of ostial lesions, culprit lesion assessment in acute infarct patients and side branch analysis in bifurcation lesions. Heavily calcified lesions can also produce hazy angiographic appearances which often leaves the operator at a loss to determine the actual true lumen path and in some circumstances even misdiagnose calcification as “pseudothrombus” [5]. This latter phenomenon significantly changes the approach to intervention. The artery can be put at risk of perforation in the absence of adequate lesion preparation or wire induced dissection as calcified plaque is often undermined, complex and much more difficult to wire than soft thrombus.

Furthermore, angiography is usually used in isolation to guide intervention and ensure an adequate final stent result. FFR, IVUS and OCT can all be used to assess final PCI results and stent performance over time.

To aid decision making processes, adjunctive tools are becoming essential in “getting it right” in the catheterization laboratory. In this chapter, the use of FFR, IVUS and OCT for assessing left main and non left-main coronary artery disease will be discussed.

2. An overview of FFR

Fractional Flow Reserve (FFR) is the ratio of two flows - maximal flow in the diseased vessel expressed as a ratio to maximal flow if the vessel was theoretically normal[6]. During the procedure, a 0.014 inch pressure sensor coronary guide wire is advanced beyond a coronary stenosis and under conditions of maximal hyperaemia, distal pressure recorded and divided by guiding catheter pressure. The procedure requires routine anticoagulation, a calibration process [zeroing and equalization of the aortic (guiding catheter pressure Pa) with the pressure wire (Pd) and attainment of maximal hyperaemia (this is usually achieved by intravenous or intracoronary adenosine)][6]. FFR is a robust technique and reproducible which is remarkable in that the microcirculation is able to vasodilate to the same degree each time and is independent of heart rate and blood pressure [7,8]. It takes into account length of lesion, lesion severity, amount of myocardium supplied, viability and contribution of collateral blood flow [3,9,10]. It is now considered the gold standard for invasive functional assessment of the physiological significance of coronary stenosis. It has recently been given a Class Ia indication for guiding PCI in multivessel coronary disease by the European Society of Cardiology [6].

2.1. Practicalities of FFR

Pressure Transducers: The current pressure transducers usually comprise a regular transducer for aortic pressure (Pa) recorded through the guiding catheter and the second pressure (Pd beyond the stenosis) via a miniaturized sensor-tipped pressure wire that is connected to a small computerized interface. Of note, a new wireless system is also about to enter the commercial arena. Mean pressure recordings are essential as these form the numerator and denominator of the FFR formula, not peak systolic pressure. It is optional to record Pv (central venous or right atrial pressure) via a central line if the operator wishes to correct FFR for right atrial pressure – a concept that has been reborn in the modern FFR era whereby filling pressures in cardiac failure patients may be significantly elevated and can affect FFR recordings.

Medications: As is usual in any case where coronary wires are placed down coronary arteries, systemic anticoagulation (unfractionated heparin, low molecular weight heparin or bivalirudin) is essential to avoid wire induced coronary thrombus. At our institution, the usual practice is to administer heparin to achieve an ACT of at least 250 seconds. Intracoronary nitrate is then administered to overcome epicardial vessel vasospasm and for achieving hyperaemia, either intracoronary or intravenous adenosine. Our preference is for intravenous adenosine via a femoral venous sheath, although all that is required is to achieve hyperaemia – the route of administration is not as important. Intracoronary adenosine can also be given, however, this is not suitable when there are side holes in the guiding catheter, when ostial disease exists and when the aim of the study is to achieve a “pull-back” over the course of a coronary artery. Alternative agents for achieving maximal hyperaemia include intracoronary papaverine, intracoronary ATP, intravenous dipyridamole and intravenous dobutamine, however these have not been as widely adopted.

Catheters: In general, 5Fr or 6 Fr guiding catheters are used for performing FFR. This then allows the operator to immediately go on to perform an intervention based on the FFR result or indeed fix a wire induced dissection without needing to change catheters. The latter is a rare phenomenon in experienced hands and with modern steerable soft tip pressure wires. Larger French sizes are generally avoided on account of increased risk of catheter induced ostial spasm and the possibility of reducing proximal coronary artery pressure.

Basic Formula for FFR:

$$\text{FFR} = Q_s/Q_n$$

Q_s = flow in diseased artery and Q_n = flow in artery if theoretically normal

$$\text{Therefore: FFR} = [P_d - P_v/R] / [P_a - P_v/R]$$

P_d = pressure distal to stenosis; P_a = aortic or guiding catheter pressure

P_v = venous or right atrial pressure

R = resistance

Given P_v is assumed to be negligible equal and at maximal hyperaemia R (resistance) is minimal then $\text{FFR} = P_d/P_a$

2.2. Summary for the sequence of events for performing FFR

1. Systemic Heparin to achieve ACT of at least 250 sec
2. Guiding Catheter sitting at ostium of coronary artery without damping
3. Zero guide and pressure wire
4. Remove wire introducer
5. Intracoronary GTN to overcome epicardial conduit resistance
6. Flush with saline
7. Equalize pressure wire and guiding catheter transducers
8. Cross stenosis with the pressure wire (N.B. the pressure sensor is at the junction of the radiolucent and radio-opaque segments of the wire)
9. Run intravenous adenosine (our preferred method) to achieve maximal hyperaemia
10. Record FFR tracing with at least 2-3 min of adenosine
11. Remain vigilant for pressure signal drift and catheter damping
12. Pullback recording is reasonable across tandem stenoses or diffuse plaque



Figure 1. Typical Example of FFR Recording (n.b. mean Pd and Pa pressures and automatic FFR recording as well as transient bradycardia consistent with adenosine)

2.3. Pitfalls in FFR

Like most tools in coronary intervention, Fractional Flow Reserve is not immune to technical mistakes [11]. It is important to be aware of the following various pitfalls to ensure that the FFR measurement is both valid and reproducible.

- Use of a guide wire introducer:** when used through the Y connector, there is a subtle leak of aortic guiding catheter pressure. Although it tends to only be small (<10mmHg), when the FFR is near the ischemic zone, this small difference may have important implications. It is therefore recommended that when equalizing, measuring FFR and checking for drift at the end of the procedure, that the wire introducer be removed.
- Not clearing the catheter of contrast:** ensuring that the guiding catheter is cleared of contrast during equalization and FFR measurement is important to avoid subtle contrast induced damping of pressure waveform. To overcome this, the guiding catheter should be flushed with saline at the time of equalization and FFR measurement. It is important to note ST changes at this time as over-enthusiastic flushing of the guiding catheter can lead to ischaemia induced ventricular fibrillation. It is advisable to flush in stages giving the patient a break between 5-second flushes until the catheter is clear of contrast on fluoroscopy.

- c. **Damping of pressure by the guiding catheter:** this is particularly true with diseased ostia and when using large guiding catheters. It creates a gradient between the guiding catheter and the proximal segment of the coronary artery and may only be unmasked during maximal hyperaemia. It is important to monitor the Pa waveform at baseline and during the FFR measurement and if indeed there is damping, the guiding catheter needs to be “backed out” over the wire to ensure the Pa measurement is valid. This usually necessitates the use of intravenous adenosine to maintain maximal hyperaemia during the FFR recording. If guiding catheter damping is not appreciated, the obtained FFR value will be artificially higher and the true severity of the stenosis underestimated.
- d. **Guiding Catheter with Side Holes:** it is technically obvious to avoid intracoronary adenosine in this setting however it is also important to always disengage the guide because the side holes may actually confound true proximal coronary pressure measurement. Therefore, if side holes are used, intravenous adenosine and a guiding catheter sitting out of the ostium are imperative for an accurate FFR recording.
- e. **Signal Drift:** High fidelity equipment make problems of signal drift less likely. However the problem can still occur. This issue is detected when an apparent gradient appears between Pd and Pa without a change in waveform of the distal pressure. It should be checked for at the end of the FFR procedure by ensuring that equalization still holds true when the coronary wire is withdrawn back into the guiding catheter. This is an internal check for the operator to ensure the final FFR reading is valid. In practical terms however, a pullback curve will also overcome this limitation.
- f. **Maximal Hyperaemia:** It cannot be emphasized enough that there is no such thing as a resting FFR. It is only at maximal hyperaemia that resistance is minimal and that flow develops a linear relationship to pressure – a vital prerequisite for the FFR equation to hold true. Not achieving maximal hyperaemia will usually overestimate the FFR value and therefore underestimate the true severity of a coronary stenosis. At the usual dose of intravenous adenosine 140mcg/kg/min via a central sheath, all patients usually achieve maximal hyperaemia within 2 minutes. Patients will often complain of chest tightness and dyspnoea and there will be a transient rise in blood pressure before the Pd value reduces and adopts an ischaemic waveform with diastolic blunting. At this stage, increasing the dose of adenosine will not alter the FFR value and the clinician will be comfortable that maximal hyperaemia is achieved. It is not unusual for PR prolongation or transient heart block to occur which can also be used as surrogate measures of maximal hyperaemia [12].

3. An overview of IVUS

Intravascular ultrasound is a catheter based pullback technique that provides invasive cross-sectional tomographic imaging [13,14]. The ultrasound signal is produced by sending an electrical current through a crystal element on the transducer. Sound waves are reflected or

pass through structures depending on their acoustic impedance. The scanning process provides both a qualitative and quantitative assessment of the artery. Vessel wall, atherosclerotic burden and plaque composition can all be assessed and with a well defined lumen-intima interface, measurements made of lesion severity such as minimum lumen area.

3.1. IVUS assessment of wall layers

The intima is a single layer of endothelial cells that is largely defined by its interface with blood in the lumen [15]. Saline or contrast flush can help delineate this interface in complex undermined plaque or when this interface may be ambiguous in cases such as lumen filling defects or intramural haematoma.

The media is composed of smooth muscle cells and does not reflect ultrasound and therefore appears as a dark ring during the pullback [15]. It is often used to help size stents along with reference lumen dimensions.

The adventitia is a matrix of collagen and elastin and reflects ultrasound markedly to give a whitish appearance on the outer segments of the vessel wall [15].

3.2. IVUS transducer type

There are two main types of transducers commercially available - a rotational single transducer and multiple stationary transducers in a phased array system [16]. The following table compares the current commercially available products.

Comparison	Boston Scientific	Volcano	Volcano
Commercial Name	iCross	Eagle Eye Platinum	Revolution
Imaging Method	IVUS	IVUS	IVUS
Scanning Design	Rotational	Phased Array	Rotational
Frequency	40 MHz	20 MHz	45 MHz
Overall Profile	3.2 Fr	3.5 Fr	3.2 Fr
Tip Entry Profile	0.022"	0.019"	
Guide Catheter	6Fr	5Fr	6Fr
Delivery	Monorail	Rapid Exchange	Monorail

Table 1.

The most commonly used device in our institution is the rotational system. There is a drive cable that rotates a single transducer element at the tip. The imaging system is located within a protective sheath that is very soft and creates a fluid interface for the imaging transducer. The two main artifacts that are encountered include wire artifact and occasionally NURD (Non-uniform Rotational Distortion) [16].

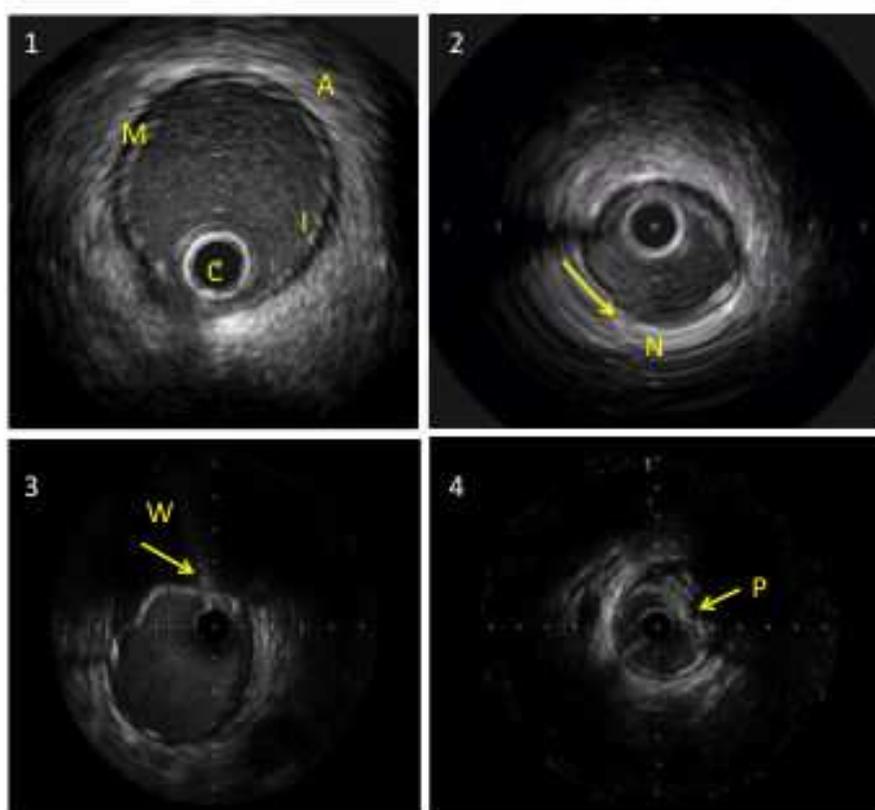


Figure 2. Panel 1: Adventitia (A), Media (M), Intima (I) and Catheter (C), Panel 2: NURD (N), Panel 3: Wire Artifact, Panel 4: Eccentric fibrous plaque (P)

3.3. Plaque morphology by IVUS

Calcified Plaque has marked acoustic shadowing with signal drop out and appears white on IVUS [15]. If circumferential calcification exists, this may prompt the operator to perform rotablation to ensure full stent expansion. Eccentric masses of bulky calcified plaque should also alert the operator to the potential risk of vessel perforation during percutaneous coronary intervention (particularly if a cutting balloon is used or if aggressive postdilation is performed) or focal stent under expansion. Generally, when only part of the vessel perimeter is rigid, aggressive postdilation will force stent expansion into the direction of least resistance.

IVUS is also able to detect soft plaque, fibrous tissue and in-stent restenosis. Positive and negative remodeling are also easily identified and generally best identified by IVUS.

Definition of diagnostic IVUS parameters for describing parameters of lesion significance as per the “JACC IVUS Consensus Document” [17]:

Term	Description
Lumen Cross-Sectional Area (CSA)	The area defined by the luminal border
Minimum Lumen Diameter (MLD)	The shortest diameter through the centre point of the lumen
Maximum Lumen Diameter	The maximum diameter through the centre point of the lumen
Lumen Eccentricity	(Maximum lumen – MLD)/Maximum Lumen Diameter
Lumen Area Stenosis	(Reference Lumen CSA – Minimum lumen CSA)/Reference Lumen CSA
Lumen Diameter Stenosis	(Reference Diameter – MLD)/Reference Diameter

Table 2.

Reference segments can be proximal and distal to the tightest point of the lesion and are usually arbitrarily defined to be within 10 mm of the MLA at a point with the least disease and not involving any side-branches.

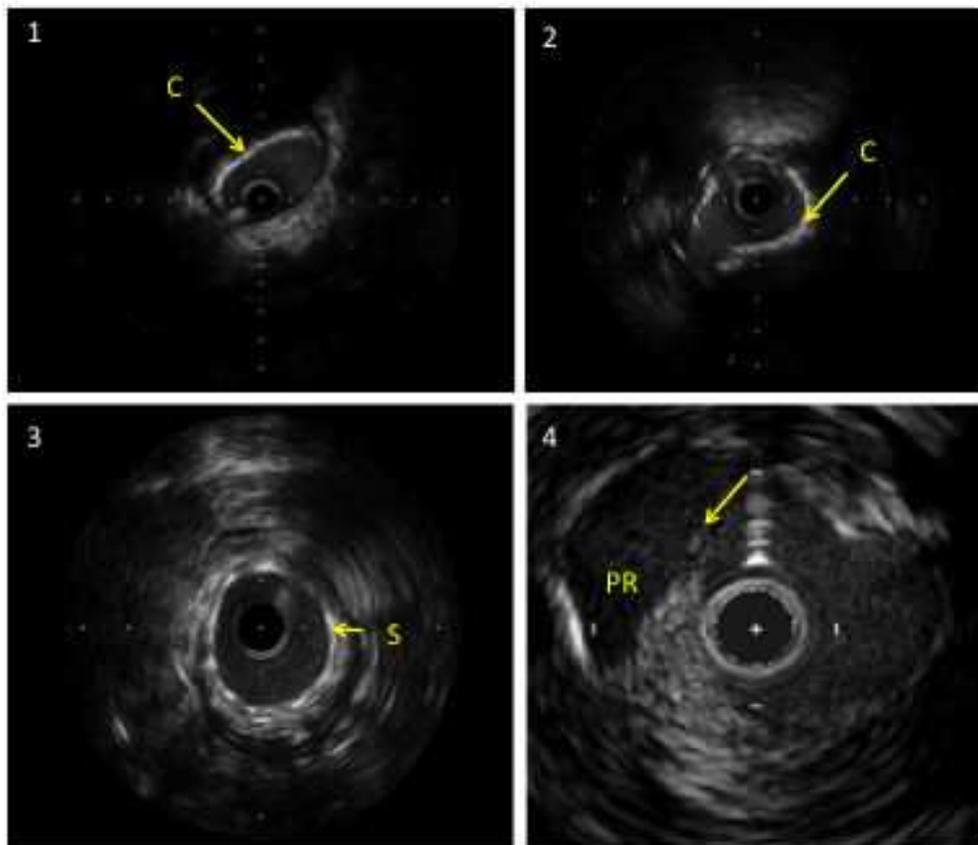


Figure 3. Panel 1: 180 degree arc of calcium (C), Panel 2: Near 360 degree ring of calcium (C)–this would warrant rotablator, Panel 3: Post Rota-PCI with full stent expansion (S), Panel 4: Plaque rupture (PR)–unstable plaque during ACS

3.4. IVUS to guide intervention

Despite the relatively attractive ability to size stents and ensure adequate apposition and full stent expansion, there is unfortunately a lack of evidence that IVUS improves the incidence of MACE in patients undergoing stenting although 6-month angiographic diameters may be improved (refer to table below). The exception to this however is in the left main interventional area whereby the use of IVUS improves outcomes [18].

Study	Number (N)	End Point	Result
Albiero et al [19]	312	6mth angio	IVUS better
Blasini et al [20]	212	6 mth angio	IVUS better
Choi et al [21]	278	Acute closure; 6 month angio	IVUS better
Gaster et al [22]	108	6 mth angio	IVUS better
AVID [23]	759	12 mth TLR	IVUS better
CRUISE [24]	499	9 mth TVR	IVUS better
OPTICUS [25]	550	6 mth angio; 12mth MACE	NO DIFFERENCE
PRESTO [26]	9070	9 mth MACE	NO DIFFERENCE
RESIST [27]	155	18mth MACE	NO SIGNIFICANT DIFFERENCE
SIPS [28]	269	2 year TLR	IVUS better
TULIP [29]	144	12 mth MACE	IVUS better

Table 3. IVUS vs Angiographic Guidance of Bare Metal Stent Implantation

The use of IVUS in elucidating the mechanism of in-stent restenosis is also important particularly given that it may not be as benign as initially thought. Walters et al. have described that an acute coronary syndrome is a common presentation for in-stent restenosis [30]. Angiography alone tends to overestimate the degree of restenosis and usually offers little information regarding the mechanism such as stent undersizing, incomplete expansion, strut fracture and geographic miss. Now that we have arrived in the OCT era, we may gain further insights into neoatherosclerosis as apposed to proliferative fibrous neointima as the pathology behind restenosis.

4. Overview of optical coherence tomography

OCT is an intravascular imaging modality akin to intravascular ultrasound (IVUS), however, where IVUS uses sound, OCT uses light. The use of near infrared frequency (1300 nm) light waves has remarkably increased resolution. OCT, unlike IVUS, requires a bloodless field. This was originally achieved with proximal occlusion (i.e. time-domain OCT) but in its

most recent iteration, has been achieved by contrast injection with Fourier Domain OCT. This has significantly improved the user-friendliness of OCT. The characteristics of IVUS, TD-OCT and FD-OCT are detailed below:

	IVUS	TD-OCT	FD-OCT
Axial resolution, micron	100	10-15	10-15
Wavelength	Ultrasound	Near-infrared	Near-infrared
Frame rate, frames/sec	30	20	100
Maximum scan diameter, mm	10	6.8	9.7
Proximal occlusion	No	Yes	No
Pullback rate, mm/s	1	1-3	20

Table 4.

4.1. Procedural detail

The currently available OCT catheter is a rapid exchange catheter compatible with a 6Fr guiding catheter. The OCT catheter has several markers and the position of the imaging optical lens is noted to be 25 mm from the tip of the catheter and 5 mm proximal to the proximal marker. It appears as a radiolucent gap in the imaging catheter. It is thus important to note that a considerable length of catheter is needed to be placed beyond a stenosis and therefore a suitable landing zone is required that is of reasonable caliber and not excessively tortuous. A calibration process is performed prior to image acquisition – z offset or auto-calibration whereby marker fiducials are placed equidistant around the border of the catheter on the computer interface. With an automated injection system, we advocate a contrast injection of 4mL/sec, 14mL volume for the left coronary system; 3mL/sec, 12 mL for the right coronary system. For manual injection, usually 10mL contrast at reasonably sustained injection pressure will be sufficient to opacify the vessel. Ischemic electrocardiographic changes are not infrequent but almost always self-limiting; arrhythmia is rare and less frequent than with TD-OCT. REF Other complications such as those from guiding catheters and coronary wires are not attributable to OCT per se but are a part of the inherent risk of the procedure. The main advantages with the FD-OCT over TD-OCT are the faster pullback speed (20mm/sec) and the avoidance of proximal vessel occlusion, with potentially clearer images and larger reference segment dimensions [31]. The safety and feasibility of FD-OCT has been widely reported [32-34]. Slowing the pullback speed to 10 mm/sec can enhance the imaging detail particularly if imaging for stent complications at the end of a PCI.

4.2. Current uses of OCT

Sine 1996, a lot of work has been performed evaluating the correlation of OCT with histopathology – an essential prerequisite to describing vessel pathology. Exquisite images and detailed analysis of plaque composition [35] can be achieved including clarification of lipid

rich plaque, fibrous plaque, calcified nodules, macrophages, intimal disruption, red and white thrombus and thin capped fibroatheroma. OCT has revolutionized the assessment of stent performance with an unrivalled ability to detect malapposition, stent expansion, edge dissection, prolapse, filling defects, strut appearance and strut coverage. It can even discriminate between neointima and neo-atherosclerosis with regard to in-stent restenosis and detect neorevascularisation. OCT is in its infancy in its ability to define flow-limiting stenoses on the basis of lesion parameters for severity (akin to IVUS measurements).

Histopathological Features	OCT Features
Fibrous	Homogeneous, Signal Rich, Birefringent
Calcified	Heterogenous, Signal Poor, Sharp Border
Lipid Rich	Signal Rich at the Top; High attenuation regions
Macrophage Foam Cells	Heterogenous; lumpy; signal rich; high attenuation
Intima	Signal rich layer near the lumen
Media	Signal poor middle layer
Adventitia	Signal rich, heterogenous outer layer

Table 5.

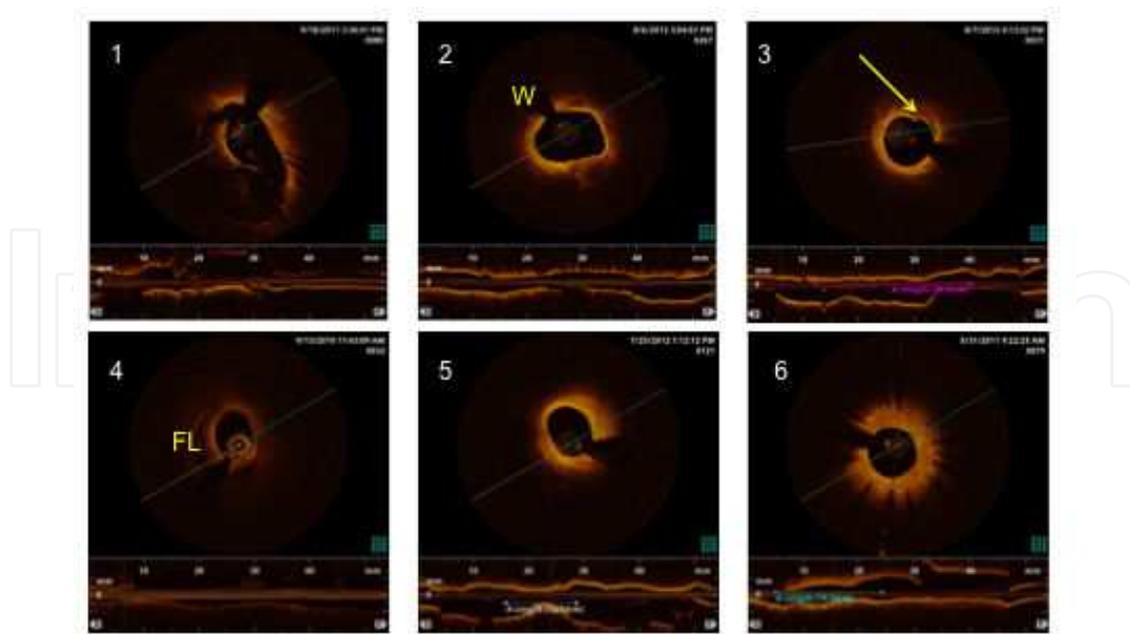


Figure 4. Panel 1: Blood swirl artifact ; Panel 2: Wire artifact (W) ; Panel 3: Stitch artifact from catheter movement (arrow) ; Panel 4: Spontaneous coronary dissection with visible false lumen (FL) ; Panel 5: Fibrous Plaque ; Panel 6: Proliferative neointima within a stent

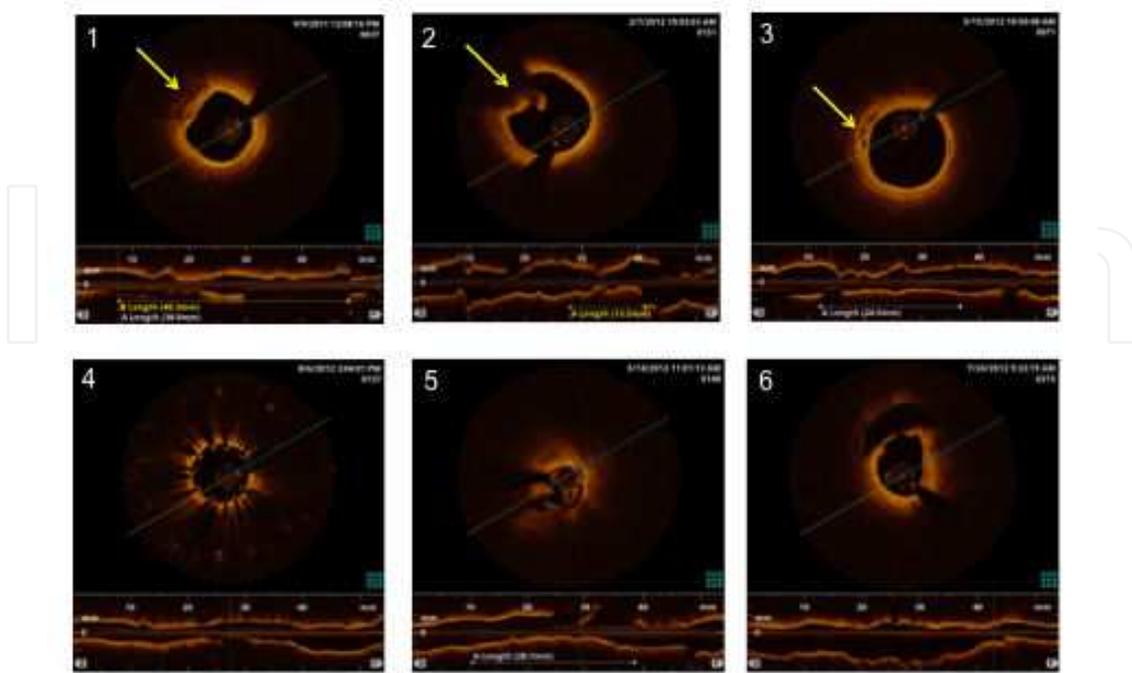


Figure 5. Panel 1: Calcified Nodule (arrow); Panel 2: Red thrombus (arrow) ; Panel 3: Vasa Vasorum (arrow) ; Panel 4: Covered stent – uncovered 7 years post deployment; Panel 5: Lipid rich plaque that is catheter hugging ; Panel 6: disrupted intima with a small cavity

4.3. Despite the overall attractiveness of OCT, some drawbacks include

- Need for extra contrast
- Limited ability to image very large vessels given limited depth of penetration (imaging >4.5 mm diameter vessels is difficult)
- Difficulty to image true aorto-ostial disease (IVUS is preferred in this scenario)
- Blood pool artifact (this occurs when the lumen is not devoid of blood because of inadequate contrast injection – the erythrocytes cause a severe scatter of light)
- Stitch artifact (usually only subtle and not a major issue; this artifact relates mostly to catheter movement within the vessel and appears as an abrupt step in the vessel wall)
- If the catheter does not sit coaxially within the vessel then an oblique cut may be made through the lumen and vessel wall
- Given the imaging catheter remains in the artery, there may be a tendency to straighten the vessel, cause vessel concertina and perhaps even distort stents of questionable longitudinal strength

- In the early phases of operator inexperience, there can be difficulty identifying calcium and differentiating it from lipid rich plaque

5. Assessment of moderate coronary artery disease – Non Left Main

The presence of myocardial ischemia is an important determinant of adverse cardiac outcome [36,37]. Revascularization of stenotic coronary lesions, by eliminating myocardial ischemia can improve patient symptoms, functional status and in patients with proven ischaemia, reduce death and major adverse cardiovascular events [38-40]. Importantly, for stenotic lesions that do not induce ischemia, medical therapy alone is likely to be equally effective with less benefit for revascularization [2,3,40]. While most patients undergo non-invasive testing to detect the presence of myocardial ischemia prior to consideration of angiography many patients with high clinical likelihood of CAD are catheterized without functional testing. Additionally, noninvasive stress imaging studies may be non-diagnostic and are limited in their ability to accurately localize culprit lesions in patients with multivessel CAD [41]. Ultimately where revascularization is considered, patients undergo coronary angiography.

Proving ischaemic burden in intermediate lesions requires invasive adjunctive tools – pressure derived measurements using FFR aim at functional evaluation whilst intravascular ultrasound (IVUS) and OCT provide anatomical clarification of the vessel anatomy and lesion dimensions. Both intracoronary IVUS and OCT can be used to measure lesion and vessel parameters such as minimum luminal area and diameter. Unlike IVUS, OCT has only just begun to be validated against FFR. Given FFR is now the gold standard of invasive physiological assessment of the stenosis functional significance, there are studies underway to validate lesion parameters for severity on OCT with the physiological information obtained by FFR.

5.1. Coronary angiography and stenosis significance

Coronary angiography is a 2-dimensional lumenogram of a 3-dimensional vascular lumen. It reports stenosis severity as a ratio of the lesion minimal lumen diameter to the adjacent "normal" reference segment. But, coronary atherosclerosis is a diffuse process and the accuracy of angiographic assessment is limited by the inability to identify both "diseased" and "normal" vessel segments. Histopathological studies have demonstrated that angiography fails to detect atheroma until the area stenosis approaches 40-50% as this is the approximate critical level at which further expansion of the external elastic membrane is not possible and so plaque begins to encroach upon the lumen. Furthermore, eccentric plaque produces an eccentric lumen that can give conflicting degrees of angiographic narrowing dependant on the viewing angulations. Despite improvements in quantitative coronary angiographic (QCA) techniques, coronary angiography frequently fails to identify the accurate hemodynamic significance of coronary stenoses, particularly those between 30% and 70% diameter stenosis [42-44]. The assessment and management of these "intermediate coronary lesions",

then becomes a dilemma for the clinician. In this context, a more reliable technique at the time of angiography is vital to direct appropriate revascularization or medical therapy in a single setting. Fractional flow reserve (FFR) assessment and Intravascular ultrasound (IVUS) are two such techniques which are now part of standard clinical practice in guiding treatment of patients with intermediate coronary lesions [43,44] [45].

5.2. Fractional flow reserve and stenosis significance

Coronary pressure wire-derived FFR is now the technique of choice used in the cardiac catheterization laboratory to determine the functional significance of a coronary stenosis [45]. This method relies on the decrease in intra-arterial pressure induced by a stenosis to determine whether the lesion is producing physiologically significant ischemia. As described previously, Fractional flow reserve (FFR) is defined as the ratio of flow in the stenotic artery to the flow in the same artery in the theoretic absence of the stenosis [46]. Pressure is used as a surrogate of flow and FFR can be calculated by measuring the pressure difference across a stenosis under maximal hyperemia induced usually by adenosine. The pressure distal to the stenosis is accurately measured by a 0.014-inch pressure sensor angioplasty guidewire passed distal to the stenosis. FFR in a normal coronary artery = 1.0. FFR values of <0.75 (normal 1.0) are associated with positive functional stress tests in numerous comparative studies [sensitivity (88%), specificity (100%), positive predictive value (100%), and overall accuracy (93%)[45]. FFR values >0.80 are associated with negative ischemic results with a predictive accuracy of 95% [45]. Deferring revascularisation based on non-significant FFR values (>0.75) are associated with rates of death or myocardial infarction lower than that after routine stenting [3]. In patients with multivessel coronary artery disease FFR-guided PCI is associated with reduced major adverse cardiac events [40]. Furthermore, De Bruyne et al have recently demonstrated that managing patients medically (deferring PCI) with lesions that have documented ischaemic burden (defined as FFR < 0.80) have an increased risk of urgent revascularisation [47].

Author	Ref	Patients	No	Test	Threshold
De Bruyne	Circ 1995	1-VD	60	Bic ECG	0.72
Pijls	Circ 1995	1-VD (PCI)	60	Bic ECG	0.74
Pijls	NEJM 1996	1-VD	45	Bic ECG; Thallium; Dob ECHO	0.75
Bartunek	JACC 1996	1-VD	75	Dob ECHO	0.78
Chamuleau	JACC 2000	MVD	127	MIBI	0.74
Abe	Circ 2000	1-VD	46	Thallium	0.75
De Bruyne	Circ 2001	Post MI	57	MIBI	0.75-0.80

Table 6.

5.3. Fractional flow reserve corrected for right atrial pressure and stenosis significance

The original FFR calculation was derived from the following formula: $FFR = (Pd - Pv) / (Pa - Pv)$ where Pd is distal mean pressure, Pa is aortic/guiding catheter mean pressure and Pv is central venous/RA (right atrial) pressure [48,49]. Effectively, this is an FFR corrected for right atrial pressure (FFR_{RA}). FFR_{RA} was used in some [49,50] but not all of the original validation studies to determine which FFR values best predicts an ischaemic burden [51-53]. In all recent studies validating IVUS with FFR and FFR with revascularisation/outcomes, FFR was never corrected for RA pressure. The simplified formula $FFR = Pd/Pa$ was used largely based on the assumption that Pv was minimal and therefore did not greatly influence the final FFR result. Furthermore, previous data suggested that a correlation existed between FFR and positron emission tomography (PET) derived myocardial blood flow indices even when RA pressure was omitted [50]. However, this was a small series of low risk patients with a mean RA pressure of 5 mmHg. This does not necessarily reflect the cohort of patients coming through a high volume tertiary hospital with congestive cardiac failure patients in which filling pressure may not be insignificant. This led Layland et al to compare FFR_{RA} with FFR in assessing coronary stenoses in a real world cohort. They demonstrated that right atrial pressure does in fact influence the FFR and tends to shift it downward into the ischaemic threshold [54]. It is not known however, whether FFR_{RA} (as opposed to FFR) can be used to guide intervention or whether it would better correlate with IVUS or OCT parameters for lesion severity.

5.4. Intravascular ultrasound (IVUS) and stenosis significance

As previously described, intravascular ultrasound is a catheter-based technique that provides high-resolution (up to 150microns) cross-sectional tomographic images of the coronary lumen and the coronary arterial wall that can be visualized in real time. It is currently the commonest intravascular imaging modality used as an adjunct to coronary angiography and PCI. Intravascular ultrasound is simple to perform, and its use is associated with very low complication rates [55]. IVUS does not provide direct hemodynamic data of a coronary lesion. However, several studies have demonstrated a strong correlation between IVUS lesion parameter and ischemia by myocardial perfusion imaging [56], and FFR [57,58]. Parameters that correlated with an FFR value ≤ 0.75 were area stenosis ($>60-70\%$), minimal lumen cross-sectional area $\leq 3.0 - 4.0\text{mm}^2$ and minimal lumen diameter ≤ 1.8 mm. IVUS is used in preference to FFR when:

1. Precise information on extent of the atherosclerosis, plaque characteristics including degree of calcification and accurate vessel size are required.
2. FFR assessment is contraindicated; significant conducting system disease or bradyarrhythmia or severe asthma precluding the use of adenosine.
3. Situations where FFR values may be misleading; previous MI with significant scar, diffuse coronary disease, microvascular disease, significant left ventricular hypertrophy.

The traditional cutoff of MLA <4 mm^2 on IVUS has been questioned in recent studies, and it is now thought that an MLA of <2.4 mm^2 may better predict a significant lesion [57-59]. Ulti-

mately, it is still unclear which of the two MLA cutoff's is more efficient in predicting significant stenoses, and future IVUS and OCT studies may also suffer from this "shifting goalpost" phenomenon. This reflects the need for more studies validating anatomical with physiological data.

In our catheterization laboratory about half of the stenosis assessments are done with IVUS. In some centers' it is the primary tool used [60]. There is a growing trend in our laboratory now for using OCT instead of IVUS for plaque characterisation and vessel dimensions.

5.5. Optical coherence tomography and stenosis significance

Optical coherence tomography (OCT) is a recently introduced medical imaging technology. It is an optical analogue of IVUS and measures the back-reflection of near-infrared light directed at tissues and generates images with a resolution close to 10micron; 10-15X greater than IVUS. With the current generation of FD-OCT imaging engines, it is also up to 20 times faster in imaging [35]. The safety of OCT imaging has been well described [61,62]. Given its significantly higher resolution, OCT has many advantages over IVUS both in atherosclerotic plaque assessment and in evaluating the acute and long-term effects of PCI [35]. It is likely to replace IVUS as the primary intravascular imaging modality.

Author	Year	Against	N	Cut-Off MLA (mm ²)	Ref Area
Nishioka	1999	SPECT	70	4.0	11.4+/-3.9
Takagi	1999	FFR 0.75	51	3.0	9.3+/-2.7
Lee	2010	FFR 0.75	94	2.0	5.7 +/- 2.0
Kang	2011	FFR 0.80	236	2.4	7.6 +/-2.5
Ben-Dor	2011	FFR 0.80	92	3.2	RVD >2.5
Koo	2011	FFR 0.80	267	2.8	6.8 +/- 2.5
F1RST	2011	FFR 0.80	320	3.0	RVD 2.9
Gonzalo	2012	FFR 0.80	56	OCT 1.95	6.5 +/- 2.7

Table 7.

With its better definition of the intimal-luminal interface and higher resolution compared to IVUS, OCT may improve accuracy and reduce observer variability in intravascular luminal cross-sectional measurements; in this context OCT may be particularly useful in assessing (intermediate) coronary stenosis severity. However, unlike IVUS which has many studies validating it against FFR albeit with differing MLA results, there has only been one such trial using OCT [59]. In this study, it was demonstrated that an MLA of 1.95 mm² was most efficient at predicting physiological significance. Gonzalo et al. [59] also demonstrated that OCT was more efficient than IVUS in predicting stenosis severity and that the geometric cutoff values for both

OCT and IVUS were indeed much smaller than the traditional 4 mm². However, this study did not correct FFR for right atrial pressure nor did it include OCT values indexed to the size of the patient or reference vessel (in a bid to roughly adjust for mass of myocardium supplied) – two corrections that may improve the correlation between OCT and FFR and affect the anatomical parameter and its value that best predicts an FFR ≤ 0.80. Further studies are therefore a vital prerequisite before OCT can be validly used to establish stenosis significance.

In-vitro studies with a vascular phantom have shown that not only do OCT luminal measurements correlate strongly with IVUS but they are more accurate than IVUS [63]. Both in vitro and in vivo studies suggest, however, that OCT measurements tend to be smaller than IVUS measurements probably because of its better luminal definition [62,64]. Therefore, direct translation of IVUS parameters of stenosis significance to OCT is not appropriate or valid. Specific in vivo validation data against FFR is required.

6. Other uses for FFR

FFR can be used to guide PCI formally to ensure full stent expansion based on FFR > 0.94 [65] and can also be used to evaluate side branch “pinching” post PCI. Koo et al demonstrated that when the side branch was < 75% stenosed post PCI, the FFR was never in the ischaemic range and when it was > 75% stenosed, it only fell into the ischaemic range approximately 1/3 of the time [66]. This emphasizes a common issue of over-interpreting the side branch appearance in PCI cases and vindicates bifurcation studies such as Nordic-Baltic Bifurcation Study III [67] where by a simple approach to the side-branch is usually all that is required.

The use of FFR in vein grafts or in cases of severe left ventricular hypertrophy has not yet been validated. Nor, is it a useful tool in the acute setting such as a STEMI when the microvasculature pressures are high and thereby the FFR falsely elevated [6].

The pressure sensor wire also has a temperature sensing function that enables it to detect changes in temperature with saline flushes. Although beyond the scope of this chapter, it has allowed the FFR wire to also measure microcirculatory function (Index of Microcirculatory Resistance or IMR). The basic physiology behind IMR relates to transit time and temperature change detected by the wire sensor after flushing 3mls of saline via the guiding catheter. Ultimately, transit time is inversely proportional to microcirculatory resistance [68]. Although IMR is still largely a research tool, it has been shown to correlate with peak CK enzyme rise post STEMI and therefore offers a proof of concept that microvascular obstruction post ACS is detrimental [69].

7. Assessment of the ambiguous left main

7.1. Background

The accurate detection and description of disease of the left main coronary artery (LMCA) is of fundamental importance in the evaluation of patients in the catheterization laboratory.

Significant LMCA stenosis carries a poor prognosis without appropriate revascularization. [70-72] Therefore, the presence or absence of left main disease has a critical impact on therapeutic decision making following angiographic evaluation.

Angiographic assessment of the LMCA can be challenging. The anatomical plane of the LMCA, issues with vessel overlap, elliptical vessel configuration and plaque eccentricity all contribute to potential difficulty in accurately quantifying LMCA disease with conventional coronary angiography alone. In cases where LMCA disease severity is ambiguous, indeterminate or equivocal, adjunctive intravascular imaging or physiological assessment is of key importance.[18]

Fractional flow reserve (FFR) offers a real time stress physiological assessment of coronary pressure dynamics. Intravascular ultrasound (IVUS) is able to define the anatomy of the LMCA. Both of these technologies allow for the potential to improve LMCA assessment and attendant clinical outcomes and are discussed further below. Optical coherence tomography (OCT) has a limited role in LMCA assessment, especially for ostial LMCA disease, largely due to the dependence on having a contrast filled lumen to allow satisfactory imaging resolution to occur. [73]

7.2. Fractional flow reserve physiological assessment

FFR has been evaluated in several studies in the setting of LMCA disease. A cut off value for the Pd/Pa (pressure distal/pressure aortic) ratio, following induction of hyperaemia, of $<0.75 - 0.8$ has been demonstrated to safely discriminate between patients who should be referred for revascularization, usually coronary artery bypass grafting, as opposed to ongoing medical therapy and observation. [74-81] Patients with readings between $0.75 - 0.8$ have physiology in a range that requires further study. In patients with intermediate readings of this kind the clinical context, as well consideration to additional evaluation with intravascular ultrasound become important.

The FFR technique involves the placement of a high fidelity pressure sensor beyond the left main plaque just as described in the “non left main” section previously. Consideration should be given to performing the procedure in both the left anterior descending and left circumflex artery to ensure concordance of results – this is particularly important if the circumflex is dominant [18]. Once the wire is in position and the catheter flushed with 100 – 200 mcg of intracoronary nitroglycerine followed by saline, hyperaemia is induced with the use of adenosine, 140 - 180 mcg/kg/min via intravenous infusion (central or peripheral). Higher doses may be required if a systemic response is not demonstrated. Venous infusion is preferred, however, adenosine can also be delivered by intracoronary bolus and studies in the area suggest no major difference between the three administration methods, [82,83] although intracoronary bolus doses of up to 720 mcg on each injection may be required.[84]

There are several potential pitfalls to FFR evaluation of the left main. Of utmost importance is the particular issue of guiding catheter damping and potential obstructive interference with coronary flow. Disengagement of the guide catheter is required for accurate evaluation in order to not underestimate the significance of the FFR. If a peripheral line is used for the

adenosine infusion, care should be taken to ensure that the peripheral intravenous site is flushing normally and appropriately connected. Maximal hyperaemia will be achieved in most patients by two to three minutes, at which point the infusion can be ceased. An alternative to the infusion of adenosine is intracoronary bolus injection, but this is potentially a less robust [85] method and can be practically difficult if guide catheter pressure damping mandates catheter disengagement. A further potential confounder is the role of right atrial pressure in FFR assessment. Although FFR adjusted for right atrial pressure was tested by Layland et al in the non-left main subset, adjusting for assessment of left main has not been conducted although a similar phenomenon would be expected – that being as FFR approaches the ischaemic zone, right atrial pressure becomes increasingly important.[54] This is an area that requires further investigation.

7.3. Intravascular ultrasound assessment

Intravascular ultrasound (IVUS) of the LMCA provides sonographically derived images of the LMCA lumen and vessel wall. As a result, IVUS provides real time anatomical and pathological information in 2 dimensions. IVUS parameters have been evaluated in multiple studies in the setting of LMCA disease. Initial work that correlated IVUS data with clinical outcomes demonstrated a relationship between IVUS derived minimal luminal diameter (MLD) and minimal lumen area (MLA) at a lesion site with major adverse cardiovascular events (MACE).[86] [87]These initial studies, however, did not mandate any specific cut off values for treatment decisions. A clinical outcome based study by Fassa et al subsequently demonstrated that deferral of revascularization is the appropriate strategy where the LMCA MLA is $\geq 7.5 \text{ mm}^2$. [88]More recent work has revised this measurement down to $\geq 6 \text{ mm}^2$. [89]

Given the clinically validated findings for FFR, IVUS has also been investigated utilizing FFR as a gold standard comparator. In a cohort of 51 North American patients Jasti et al demonstrated that an MLD $\leq 2.8 \text{ mm}^2$ or an MLA $\leq 5.9 \text{ mm}^2$ correlated strongly with a FFR < 0.75 . This study also correlated FFR measurements with clinical outcomes and confirmed the appropriateness of an FFR cut off of < 0.75 . [90]Kang et al performed a similar correlation study in 55 South Korean patients. They found a MLA cut off of $< 4.1 \text{ mm}^2$ correlated well with a FFR < 0.75 and a MLA cut off of $< 4.8 \text{ mm}^2$ correlated with a FFR of < 0.8 . However, evaluation of clinical outcomes was not performed as was done in the study by Jasti et al. In addition, the applicability of the study by Kang et al to patients of European ethnicity is unclear. Both studies also demonstrated that relative disease burden metrics such as plaque burden and area stenosis were insufficiently predictive of FFR measurements to be useful in clinical practice.

Based on the above data, a cut off of $\leq 5.9 \text{ mm}^2$ for MLA, if using IVUS alone, should be used in determining referral for LMCA revascularization following IVUS evaluation. Where there is uncertainty or ambiguity around measurements or their relevance in specific patients, strong consideration should be given to adjunctive FFR evaluation.

8. Case examples

Case #1: FFR and IVUS of Left Main

A 48 year-old gentleman presents with ischaemic sounding chest pain, troponin 1.3 ng/L and subtle precordial ST depression on his ECG. He has a background history of smoking, dyslipidaemia and a strong family history of premature coronary disease.

Angiography revealed an ambiguous left main with a complex hazy calcified roof. There was an impression of severe ostial plaque with only a narrow jet of contrast effluxing back into the left coronary cusp.

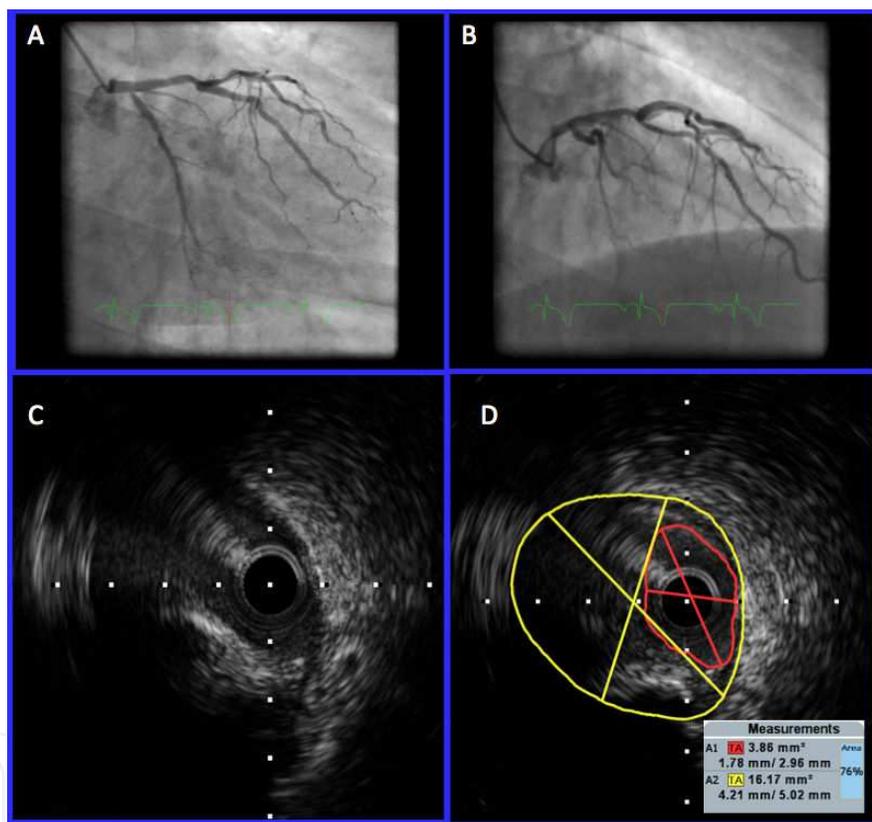


Figure 6. Angiographic (A and B) views and IVUS of left main (panels C and D)

The patient clearly had a left main lesion with an MLD < 2.8 mm and MLA < 5.9 mm² and an FFR < 0.71 which was all consistent with a haemodynamically significant lesion. On the basis of physiological and anatomical confirmation of severity, the patient was sent for CABG and made an uneventful recovery. This case highlights the importance of careful inspection of the angiogram in multiple views, consideration of the pitfalls of angiography and the combined use of IVUS and FFR to assess ambiguous left main plaque.

Case #2: FFR and OCT of a moderate RCA lesion:

A 65 year old female presented with a long history of exertional chest discomfort and dyspnoea. A stress echocardiogram demonstrated possible mild exercise induced basal inferior wall hypokinesia. She had a background history of severe uncontrolled hypertension. Her left coronary tree was unremarkable. A 50% mid RCA lesion was interrogated by OCT and FFR – refer to figures 8 and 9.

Given an MLA > 1.95mm² on OCT and FFR > 0.80, the lesion was not stented. The recommendation was for improved blood pressure control. This case highlights the importance of thorough assessment of moderate lesions despite a typical symptom profile of angina. This patient almost certainly had hypertensive heart disease as a cause of her shortness of breath and chest discomfort.

Case #3: Use of IVUS and OCT to diagnose spontaneous coronary dissection:

A 37 year-old female with a family history of coronary disease presents with chest pain, elevated biomarkers and ST praecordial T wave inversion on her 12 lead ECG a few months postpartum.

Angiography revealed diffuse narrowing of distal left anterior descending artery (refer to figure 10).

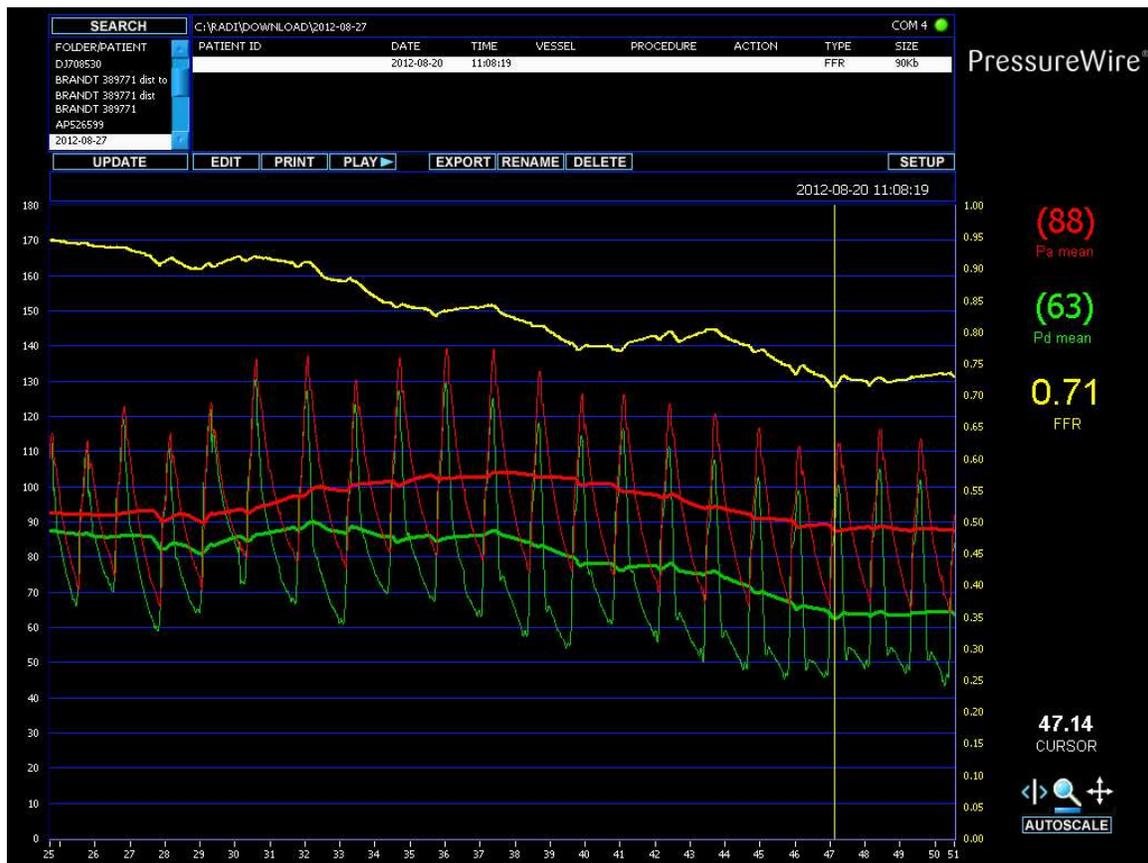
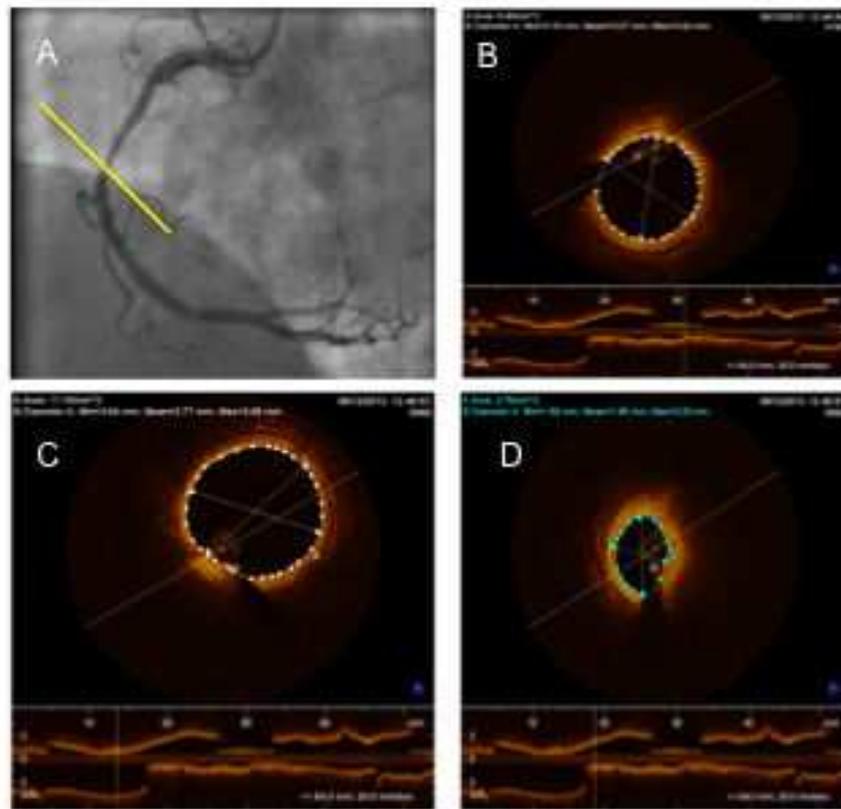


Figure 7. FFR of Left Main into LAD – dramatic drop in FFR to 0.71

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Figure 8. Panel A: Moderate RCA lesion with yellow line through the tightest point, Panel B: Proximal Reference Dimensions, Panel C: Distal Reference Dimensions, Panel D: MLA and MLD

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Figure 9. FFR clearly not in the ischaemic zone

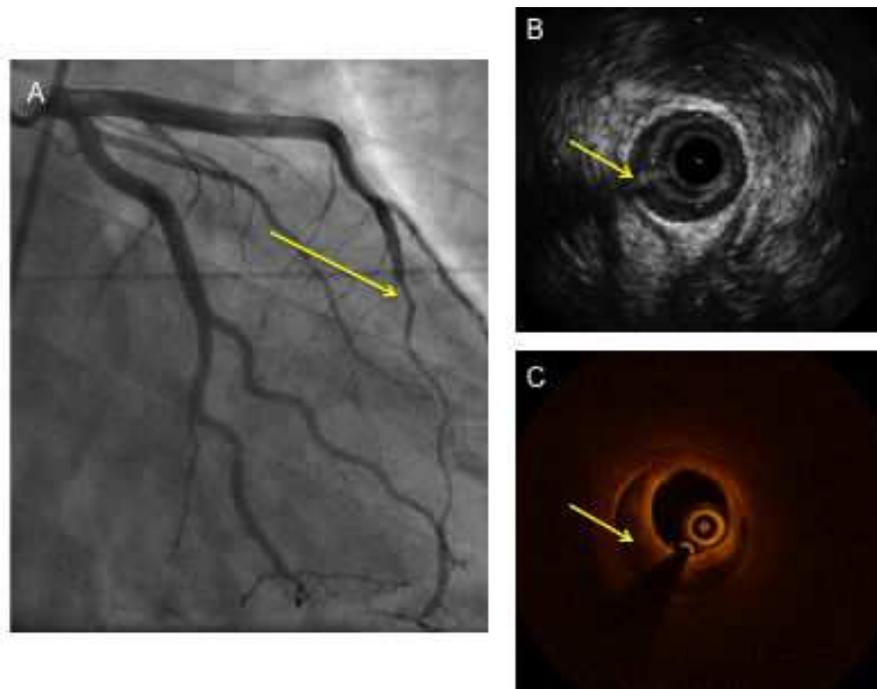


Figure 10. Angiogram, IVUS and OCT of the mid to distal LAD, Panel A: Arrow points to abrupt change in vessel caliber, Panel B: IVUS with intramural haematoma (arrow), Panel C: OCT with intramural haematoma (arrow)

IVUS and OCT both confirmed spontaneous coronary dissection as the cause of the angiographic appearance with clear evidence of intramural haematoma. The patient was managed conservatively and made an uneventful recovery.

9. Concluding statement

This chapter has highlighted some of the most important points regarding FFR, OCT and IVUS. In essence, these modalities are complimentary and it is up to the experienced operator to decide on when one modality may have a clear advantage over another (e.g. IVUS being more appropriate than OCT for imaging true aorto-ostial disease). It is generally accepted that FFR is the most useful tool to help decide when to revascularise and IVUS/OCT to help decide on pathology, guide the intervention and optimise the PCI result.

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