



Physiologic Lesion Assessment: Fractional Flow Reserve

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Mohammad Sahebjalal and Nicholas Curzen

About Us University Hospital Southampton is a large teaching hospital in the south of England. It is a regional center for complex cardiac intervention as well as TAVI. Professor Curzen was Chief Investigator of the RIPCORD, FFRCT RIPCORD, COMET studies and is CI of the ongoing multi-center randomized RIPCORD II and FORECAST trials, both of which study the effect of physiology in addition to coronary anatomy.

Introduction

- Patient outcome following percutaneous coronary intervention (PCI) is predominantly determined by three factors: clinical presentation, comorbidities, and the decision-making process before, during, and after the PCI procedure.
- In order to justify *any intervention*, there needs to be reason to think that this will result in either (a) an improvement of symptoms or (b) an improvement in prognosis or (c) both.

M. Sahebjalal
Coronary Research Group, University Hospital
Southampton NHS Foundation Trust, Southampton, UK

N. Curzen (✉)
Coronary Research Group, University Hospital
Southampton NHS Foundation Trust, Southampton, UK

Faculty of Medicine, University of Southampton,
Southampton, UK
e-mail: nick.curzen@uhs.nhs.uk

- For the interventionalist, the skillful application of modern diagnostic tools and reference to the appropriate evidence base can facilitate delivery of optimal patient care.
- Coronary angiography has been used as a diagnostic tool for more than half a century; however it is now well established that coronary angiography alone has important flaws and, in particular, can correlate poorly with the functional importance of a stenosis within the epicardial arteries.
- Further, the evidence base increasingly points to lesion-level ischemia as our target for revascularization. The availability of invasive physiological lesion assessment has revolutionized our ability to define with precision the presence or absence of lesion-level ischemia [1].
- The aim of this chapter is to review the evidence for and the expanding role of physiological lesion assessment in our everyday interventional practice.

NOTE: Since this chapter was originally written, 2 large randomised trials (DEFINE FLAIR & SWEDEHEART) have demonstrated the equivalent clinical utility of iFR to direct management strategy compared to FFR. Specifically, *in these trials an iFR-guided revascularisation strategy was non-inferior to an FFR-guided strategy with respect to MACE*. Although outside the remit of this chapter, the authors support the use of either FFR or iFR for the purpose of improving the diagnostic accuracy and personalised

management of patients. The message is: USE FFR or IFR MORE in routine practice... don't waste energy on arguing which modality is best because they are both now well validated.

Coronary Physiology

Structure of Coronary Arteries

- Normal coronary arteries have a trilaminar structure consisting of the intima, media, and adventitia.
- The endothelial cells of the tunica intima, although once thought of as inert, play an important and dynamic role in regulation of hemostasis and vascular tone. They have a synthetic and metabolic capability to respond to any changes in hemodynamic forces, and it is this balance which maintains vascular homeostasis [2].
- Any disturbance in this balance, however, will predispose the vasculature to vasoconstriction and therefore disturbance of coronary blood flow. The complex interaction between chronic vascular inflammation and endothelial dysfunction is a precursor to the development of atheroma and its subsequent natural history.

Coronary Arteries and Perfusion

- The function of the coronary vasculature has been traditionally, and artificially, divided into three groups:
 - The epicardial vessels which are visible on angiography and offer little resistance to blood flow
 - The small arteries and arterioles ($>400\ \mu\text{m}$)
 - The capillary system and arterioles ($<400\ \mu\text{m}$), also known as restrictive vessels, which primarily control the myocardial distal flow [3–6]
- During increased oxygen demand, the resistance of the microvascular segment decreases, thus allowing for an increase in blood flow.
- The same can apply when there is an increase in resistance to blood flow in epicardial arteries due to a stenosis. The resistance in microvascular structure consequently reduces,

thereby maintaining total resistance and in turn preserving the resting coronary flow.

- Once the epicardial artery stenosis increases further, the total upstream resistance increases and results in decreased myocardial flow regardless of the small vessel bed. This consequently leads to myocardial ischemia and angina [2, 7].

Coronary Blood Flow

- The myocardium has the highest oxygen demand per tissue mass. The resting coronary blood flow is about 250 mL/min.
- Vascular tone plays an important role in regulating coronary blood flow and is determined by four main factors: perfusion pressure, myocardial compression, myocardial metabolism, and neurohormonal control [8].

Perfusion Pressure

- Coronary blood flow occurs mainly during diastole and, under normal conditions, coronary pressures are equal to the central aortic pressure throughout the epicardial vessel.
- It is this unique property of coronary perfusion, which has allowed interventionists the use of an unequivocal reference value during physiological assessment of a lesion (i.e., the central aortic pressure, Pa).

Myocardial Metabolism

- Coronary vascular resistance is primarily under metabolite control and even if neurohormonal controls are cut off the myocardium has the ability to match blood flow to its metabolic requirement [8].
- The exact nature of this is unclear; however, adenosine and adenosine triphosphate (ATP)-sensitive potassium channels have received considerable attention as effectors of coronary vascular tone.
- Adenosine is a potent coronary vasodilator and a metabolite of cardiac myocytes. It is believed that myocytes release adenosine as myocardial PO_2 falls resulting in increased coronary blood flow. Chilian et al. used dipyridamole, a nucleoside transport inhibitor, to promote release of endogenous adenosine and examine its effect on coronary

resistance. They discovered that during controlled conditions, the microvascular resistance fell to 27% indicating that adenosine exerts its greatest vasodilatory effect on microvasculature.

- ATP is another metabolic agent, which is believed to effect coronary vascular resistance. ATP-sensitive potassium channels are usually inhibited by intracellular ATP; thus, during hypoxia which results in decreased intracellular ATP, these channels are activated resulting in relaxation of smooth muscles, and therefore vasodilation.

Neurohormonal Controls

- Branches of the parasympathetic and sympathetic division of the autonomic nervous system supply the coronary vasculature. Both fibers are located within the vascular wall of large arteries with denser innervation being present in resistance arterioles and capillary tree.
- The stellate ganglion is the major source of cardiac sympathetic innervation and the vagus nerve supplies the efferent cholinergic nerves [8].
- Sympathetic control is mediated via α -adrenergic and β -adrenergic receptors within the microvascular structure. The response of the coronary microcirculation to α -adrenergic activation is vasoconstriction whereas activation of β -adrenergic receptors of the coronary vasculature produces vasodilation.

The Flaws of Angiographic Lesion Assessment

- Since its advent, the use of the angiogram to determine the presence and extent of coronary artery disease (CAD) has become a standard platform for patient diagnosis and management.
- It is clear, however, *that even very experienced operators cannot accurately define whether a specific angiographic stenosis is “significant” in a proportion of lesions, perhaps around 30%, if the currency of significance in this context is lesion-specific ischemia.*
- Observational reports derived from a variety of trials and studies have reinforced this discrepancy between the angiographic and physi-

ological significance of stenosis. Thus, as shown in Fig. 15.1, there are mild-to-moderate lesions that do cause ischemia and severe-looking lesions that do not.

- As the evidence increases that ischemia should be the target for revascularization, it becomes increasingly obvious that making an accurate diagnosis regarding lesion-specific ischemia is critical to accurate, bespoke management of patients [9].

Physiological Indices of the Coronary Circulation

Several indicators for measuring cardiac physiology have been proposed to guide clinical decision-making. These include coronary flow reserve (CFR), index of microvascular resistance (IMR), instantaneous wave-free ratio (iFR), and fractional flow reserve (FFR).

Coronary Flow Reserve

- Myocardial blood flow represents approximately 5% of cardiac flow. Due to the nature of myocardial activity there is a high oxygen demand, even at rest, and as a result the oxygen extraction is much higher compared to other organs.
- Coronary blood flow is able to supply oxygen effectively for any given myocardial demand and normally increases substantially in response to the increase in myocardial oxygen demand. This increase from baseline to maximal flow is termed the coronary flow reserve (CFR).
- CFR can be defined as the ratio of hyperemic blood flow to resting myocardial flow with a normal value of 4–6, indicating that the microvascular resistance can reduce by a factor of 4–6 [7].
- CFR measurement, however, is of limited value for clinical decision-making during PCI as it is a combined measurement of resistance in epicardial vessels as well as the microvasculature [2].

Index of Microvascular Resistance

- IMR is a relatively novel specific index of microvascular function, which, unlike CFR, is

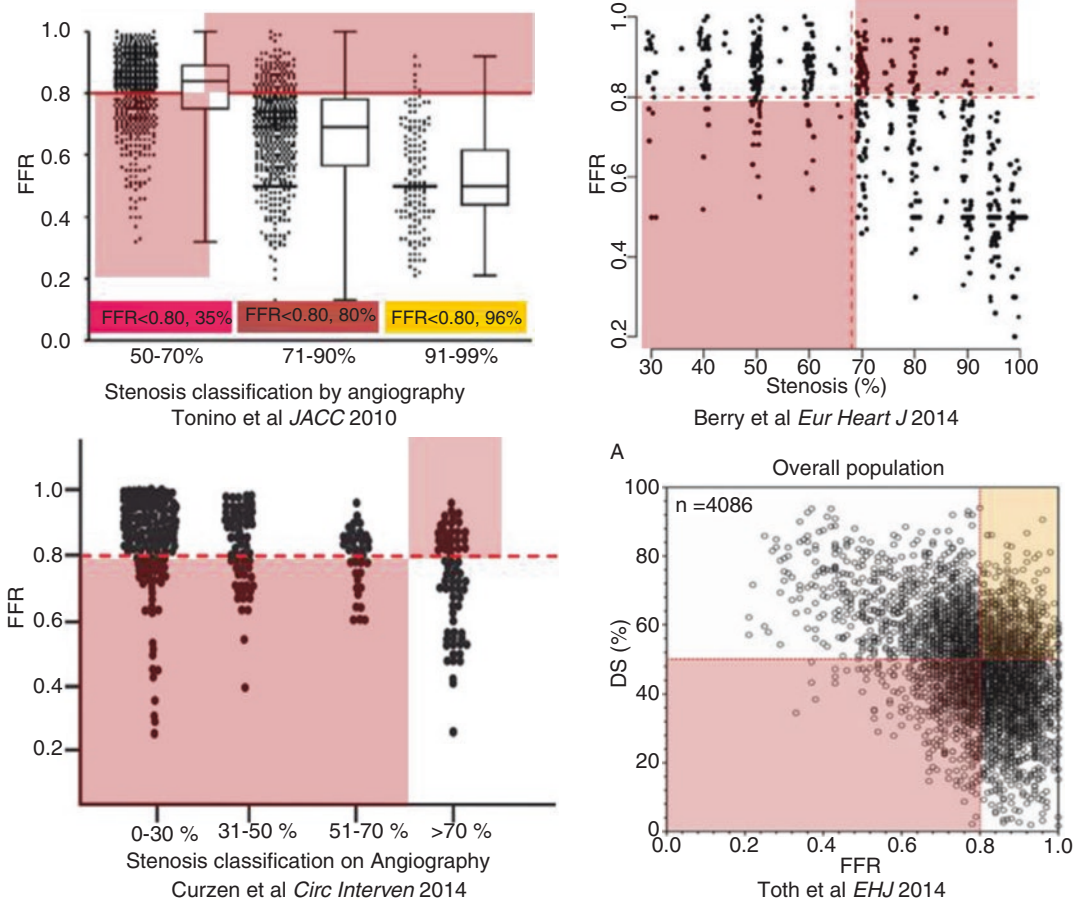


Fig. 15.1 Studies reinforcing discrepancy between the angiographic and physiological significance of a coronary artery stenosis [9]

independent of epicardial vascular disease and hemodynamic influences [7].

- Fearon and colleagues introduced the concept of Index of microvascular resistance with a notion that the mean transient time during hyperemia is inversely proportional to flow and therefore suggested that IMR can be calculated during maximum hyperemia using the following formula [1, 7]:

$$\text{IMR} = \text{distal coronary pressure (Pd)} \times \text{mean transient time}$$

- They validated this using a coronary thermodilution concept, which involved using a regular pressure wire with a microsensor mounted 3 cm from the tip of the wire to enable simul-

taneous pressure and temperature measurement after injecting 3 mL of saline at room temperature. From this they could measure the mean transit time [9].

- IMR has been well validated in animal studies and was recently used as an independent prognostic factor in patients with ST-segment-elevation myocardial infarction (STEMI). This study, in which 253 patients underwent IMR assessment immediately after having primary PCI, concluded that IMR measurement at the time of primary PCI for STEMI is an independent predictor for long-term clinical outcome, including death [10].
- IMR may be a useful method for predicting clinical outcome in acute MI patients in the future, although larger studies are required.

Fractional Flow Reserve

- Flow, pressure, and resistance are the important parameters in circulatory function, in an analogous manner to electrical circuits (Ohm's law $V=IR$). Absolute flow and resistance are very difficult to calculate as they are both dependent on myocardial mass and therefore no unequivocal normal value exists, making their impact on clinical decision-making modest [2, 7].
- Myocardial perfusion pressures, on the other hand, equal the central aortic pressure and therefore, across a normal coronary artery, the pressure is transmitted completely without any pressure loss to the most distal region.
- This is the basis for the concept that, *if downstream resistance can be assumed to be negligible* (i.e., the microcirculatory resistance is minimal), the pressure drop across an epicardial stenosis is proportional to flow, and the flow measured can therefore be expressed as a fraction of what the flow would have been if no epicardial stenosis was present. Negligible distal resistance is achieved by inducing maximal hyperemia in the microcirculation using agents including adenosine, papaverine, and regadenoson.
- *Fractional flow reserve (FFR) is thus the ratio of maximal blood flow in a stenotic artery distal to the stenosis in relation to the maximum blood flow in that artery if no stenosis was present.*
- This physiological parameter has been painstakingly correlated with noninvasive parameters of ischemia in order to produce an artificial, but highly reproducible, binary cut-off for the labelling of ischemic or non-ischemic stenosis around the FFR value of 0.8. This is important as the extent and presence of ischemia in CAD are the most relevant factors to patient outcome [2].
- Out of all the available indices of coronary physiology (Fig. 15.2), FFR is the best validated index aiding the interventionist in their clinical decision-making, although iFR data (see below) have accumulated quickly indicating the value of this parameter.

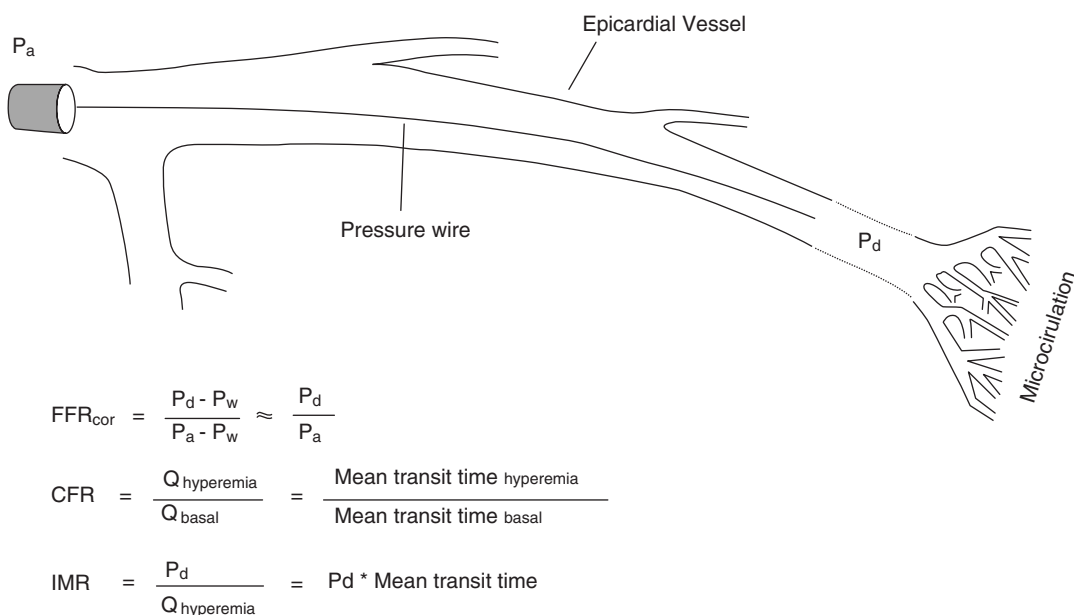


Fig. 15.2 Established measures of coronary physiology. The fractional flow reserve (FFR) is an index of epicardial coronary physiology and is measured during maximal hyperemia. The coronary flow reserve (CFR) is a measure of both the epicardial and microvascular physiology and is expressed as the ratio of hyperemic to basal flow, simpli-

fied to the ratio of basal to hyperemic mean transit time. The index of microcirculatory resistance (IMR) is a specific index of the microcirculation and is expressed as the product of P_d and mean transit time. P_w here indicates the coronary wedge pressure. Reproduced with permission from Haddad et al. *Circ Heart Fail* 2012;5:759–768

FFR Studies: The Evidence Base

The DEFER Study [11]

- DEFER is one of the three most important original trials which have set the benchmark for clinical use of FFR to determine best practice with prognostic benefit (Table 15.1).
- This multicenter randomized controlled trial was carried out in 12 hospitals across Europe and 2 hospitals in Asia between 1997 and 1998, recruiting 325 patients.

Key Finding

Note that NOT stenting coronary lesions that are FFR negative, regardless of the visual angiographic severity, is associated with an excellent clinical outcome on optimal medical therapy alone.

Table 15.1 Summary of the DEFER trial

Study components	Description
Design	Multicenter, prospective randomized controlled trial
Settings/method	Patients who had PCI planned were randomized to PCI or deferral of PCI. All patients then had FFR measurement. In both arms patients with FFR <0.75 received PCI and formed the control group In the PCI group, patients with FFR ≥0.75 received PCI and formed the PERFORM group. In the deferral of PCI group these patients did not receive PCI and were labelled the DEFER group
Type of stent	Bare-metal stents
Inclusion criteria	Elective PCI of a single angiographically significant stenosis (>50%) in a native coronary artery
Primary endpoint	Freedom from major adverse cardiac events (MACE) at 2-year follow-up
Results	89% vs. 83% (DEFER vs. PERFORM) of patients reached the primary endpoint (<i>p</i> = 0.27). Event-free survival at 5 years was 79% vs. 71% (DEFER vs. PERFORM)
Conclusion	In patients with stable angina and FFR of ≥0.75 or above, stenting does not improve their outcome
Clinical impact	Currently patients with stable angina and FFR ≥0.75 are treated with optimal medical therapy

Fractional Flow Reserve Versus Angiography for Guiding PCI in Patients with Multivessel Coronary Artery Disease (FAME) Study [12]

- FAME is one of the most important trials for determining clinical interventional practice since the advent of drug-eluting stents. It recruited patients who had already been committed to multivessel PCI by their supervising cardiologist.
- It set out to test the hypothesis that an FFR-guided strategy would be superior to an angiogram-guided strategy for these patients.
- This was a multicenter, randomized controlled trial across 5 centers in the USA and 15 in Europe between 2006 and 2007, recruiting a total of 1005 patients (Table 15.2).

Key Finding

Patients with multivessel disease considered to require PCI, an FFR-guided approach is associated with fewer vessels being stented, less stenting overall, as well as less contrast and radiation, but with a superior clinical outcome than an angiographically guided approach.

Table 15.2 Summary of the FAME trial

Study components	Description
Design	Multicenter, randomized controlled trial
Settings/method	Patients were assessed for PCI by angiogram, then randomized to FFR- or angiogram-guided therapy. In the FFR group, cardiologists only stented lesions with FFR ≤0.8
Type of stent	Drug-eluting stents (96.9%)
Inclusion criteria	Multivessel coronary disease with ≥50% stenosis in ≥2 epicardial vessels
Primary endpoint	Composite of death, MI, and repeat revascularization at 1 year
Main results	The primary outcome occurred in 18.3% vs. 12.2% (angio vs. FFR; <i>p</i> = 0.02), despite fewer vessels being treated with less stents, and using less contrast and fluoroscopy, in the FFR group. MACE at 2 years occurred in 22.4% vs. 17.9% (angio vs. FFR)
Conclusion	MACE was significantly lower in FFR-guided PCI at 1 year
Clinical impact	Increase in the use of FFR-guided coronary intervention in patients with multivessel disease

FAME II Study [13]

- FAME II was designed in response to the findings of the COURAGE trial, which controversially demonstrated that there was no clinical outcome advantage, over and above OMT, in PCI for patients with stable angina (Table 15.3).
- FAME II compared clinical outcome in patients with stable angina, and in whom there was at least one FFR-positive lesion, randomised to either OMT alone or OMT plus PCI.
- FAME II was conducted in 28 sites in Europe and North America, enrolling 1220 patients between 2010 and January 2012, at which point the trial was stopped early due to a significant difference in the primary endpoint between the two groups.
- Although FAME II suggests that there was a significant benefit in terms of a lower rate of the combined clinical endpoint, this was driven by a difference in urgent revascularization. There was no difference in the rate of death or MI. Nevertheless, it does demonstrate a superior clinical outcome in such patients for an OMT plus PCI strategy.

Table 15.3 Summary of the FAME II trial

Study components	Description
Design	Multicenter, randomized controlled trial
Settings/method	All patients underwent FFR assessment. Where FFR ≤ 0.8 , patients were randomized to PCI + OMT or OMT alone. If FFR was >0.8 , patients were included in a registry and 166 were randomly selected for follow-up
Type of stent	Drug-eluting stents
Inclusion criteria	Stable angina or documented ischemia on noninvasive testing with $\geq 50\%$ stenosis in a major epicardial vessel
Primary outcome	Composite of all-cause mortality, MI, and urgent revascularization at 2 years
Main results	For the primary endpoint, there was a significant difference between the PCI + OMT (4.3%) vs. OMT only (12.7%); $p < 0.001$
Conclusion	Outcomes were better in patients with stable coronary artery disease and FFR ≤ 0.8 if they had FFR-guided PCI
Clinical impact	Lesions with FFR ≤ 0.8 in patients with stable CAD are treated with PCI + OMT as a result of this study

Key Finding

In patients with FFR-positive lesions, OMT alone is associated with a worse clinical outcome than stenting plus OMT.

Does Routine Pressure Wire Assessment Influence Management Strategy at Coronary Angiography for Diagnosis of Chest Pain? (RIPCORDER) Study [14]

- RIPCORDER recruited 200 patients with stable chest pain who were listed for a diagnostic angiogram across 10 centers in the UK between 2008 and 2012 (Table 15.4).

Table 15.4 Summary of the RIPCORDER trial

Study components	Description
Design	Multicenter, open label
Settings/method	Patients with cardiac sounding chest pain underwent a coronary angiogram (CA), the supervising cardiologist (SC) made a management plan based on CA. Patients then had FFR assessment of all vessels of stentable/graftable diameter with results disclosed to the SC to make a second management plan. Management options were: OMT alone; PCI; CABG; more information required
Inclusion criteria	Patients awaiting elective angiogram for investigation of chest pain
Primary outcome	Effect on management of knowing FFR data + angiographic data compared to only knowing angiographic data
Results	Overall, management plan after disclosure of FFR data changed in 26% of patients and localization of functionally significant stenoses changed in 32%
Conclusion	There was a change in management strategy in just over a quarter of patients when FFR data was known compared to angiography assessment alone
Clinical impact	If FFR was measured routinely in all stentable/graftable vessels at the diagnostic angiogram stage, management of patients would be different in around one quarter of patients. This generates the hypothesis and provides the power calculation for the RIPCORDER2 randomised trial

- It asked the question: What difference to an angiogram-derived management plan would having FFR data of all stentable vessels make?

Key Finding

That having FFR data of all coronary vessels of stentable/graftable size, regardless of the severity of angiographic disease, routinely on patients undergoing diagnostic angiography changes the management in 26% of the population, because in 32% of lesions the angiogram does not predict significance as determined by FFR assessment of lesion-specific ischemia.

Key Finding

In patients with stable CAD, stenosis severity as assessed by FFR is a major and independent predictor of lesion-related outcome. *In other words, the lower the FFR, the worse the outcome for that lesion.* This probably reflects the amount of myocardium at risk.

A Prospective Natural History Study of Coronary Atherosclerosis Using Fractional Flow Reserve [15]

This study by the FAME investigators reported the 2-year clinical outcomes of 607 patients in whom FFR had been measured.

Key Points for Fractional Flow Reserve [1, 2, 7]

1. Universal normal value
Fractional flow reserve (FFR) has a universal “NORMAL” value of 1.
2. Immune from changes in hemodynamics
FFR measurement is not influenced by changes in systemic hemodynamics.
3. *Reproducible*: FFR is a reproducible and reliable measurement and it has been shown to be independent of any cardiac risk factors.
4. *Size matters*: The larger the myocardial mass supplied by an epicardial artery, the greater the flow, resulting in a larger gradient across a lesion and therefore lower FFR. This also

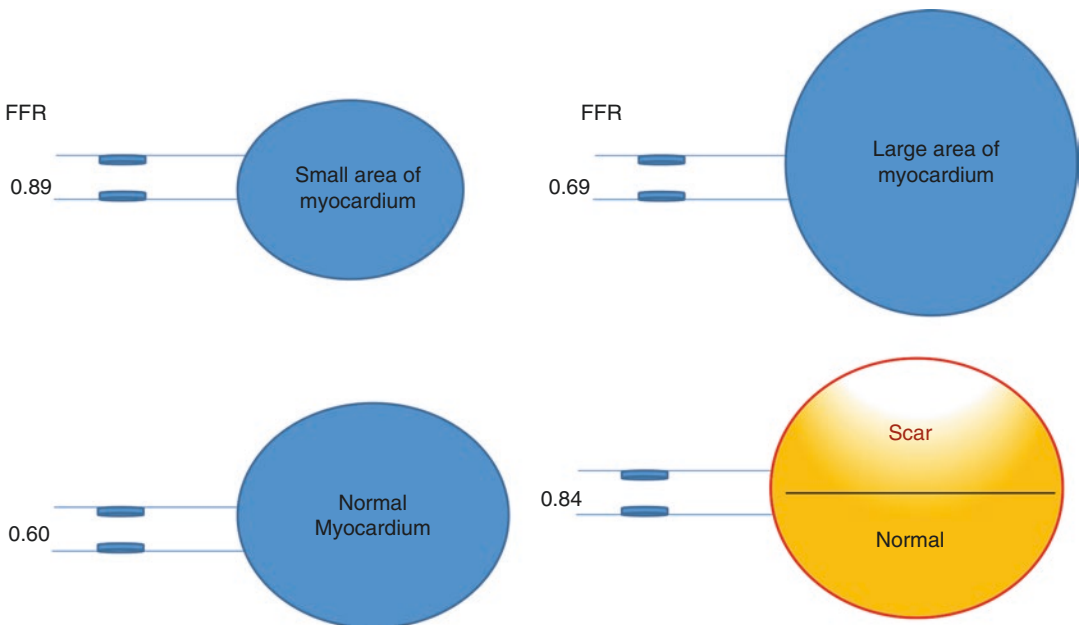


Fig. 15.3 Relationship between FFR and degree of myocardial mass

applies to FFR measurements after MI, where some of the muscle may have been replaced by scar tissue (Fig. 15.3).

Clinical Applications

Equipment [2, 7, 16]

Catheters

- It is our opinion that guide catheters should be used as default when pressure wire studies are being conducted.
- This not only provides better support than diagnostic catheters, but also gives the operator the option of proceeding using the pressure wire as the coronary angioplasty wire in rare cases of complication, or when PCI is the obvious appropriate treatment.
- **Catheter size:** We recommend using 6F catheters, although FFR measurements are frequently done using 5, 7, and 8F catheters. In the case of using large catheters, care should be taken to disengage the catheter from the coronary ostium when measurements are taken if there is any sign of pressure damping.
- **Side holes or no side holes:** Using a catheter with side holes can introduce error into FFR measurements. For example, a pressure gradient may exist between the side holes and the tip of the catheter, which can be more pronounced during maximal hyperemia causing inaccurate FFR readings. We therefore recommend using a guide catheter with no side holes to avoid incorrect FFR measurements.

Hyperemia

- The induction of maximum hyperemia is crucial to the principle of FFR measurement, as stated above, in order to ensure that the microvascular resistance is minimal and constant.
- Maximum hyperemia is achieved pharmacologically, with adenosine being the drug of choice.
- There has been controversy regarding use of intravenous (IV) versus intracoronary (IC) adenosine. This was addressed by

Jeremias et al. who examined this in 52 patients and concluded that intracoronary adenosine is equivalent to intravenous infusion in achieving maximum hyperemia [17]. Furthermore, contemporary data help to define the optimal intracoronary doses to be used.

- In our center we use intracoronary adenosine for most of our FFR measurements *except when there is an aorto-ostial lesion*, or if a pullback is desired, in which case an IV adenosine infusion is employed.
- Likewise it is important to make sure that epicardial vessels are also free of any unwanted spasm; *thus it is important to administer 200–300 mcg of intracoronary nitrates* to prevent and treat any unwanted spasm due to wire manipulation, prior to giving adenosine and taking FFR measurements [17].

Anticoagulation

- As soon as the decision is made to instrument the coronary tree, the use of the same anticoagulation regime as PCI is recommended.
- Patients should receive weight-adjusted unfractionated heparin (70–100 u/kg), achieving an activated clotting time (ACT) of ≥ 250 s [18].

Pressure Wire

- There are several pressure wires currently available for clinical use such as PrimeWire PRESTIGE (Volcano), PressureWire Aeris (St. Jude Medical), and COMET (Boston Scientific). Pressure sensors are either piezoelectric or optical.
- The pressure wire is a 0.014 in. wire with a 3 cm radio-opaque tip at the distal point on which the transducer is mounted (Fig. 15.4).
- Pressure wires have a tip load of 0.6–1.6 g (depending on the manufacturer) (Fig. 15.5) and are generally more challenging to handle compared to workhorse coronary wires, although this is improving with each new device and iteration.

Fig. 15.4 Pressure wire structure

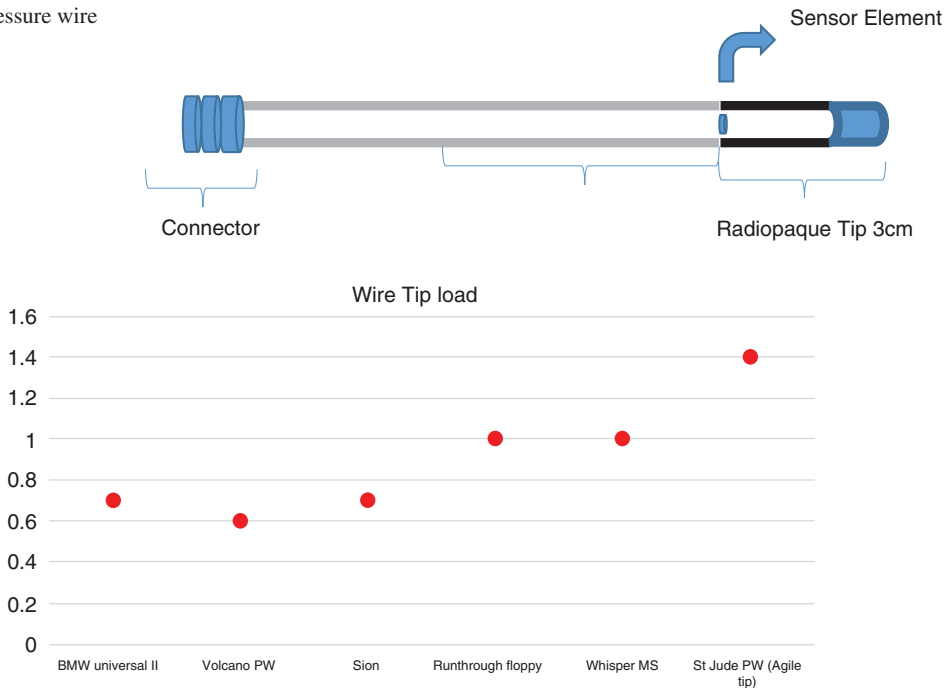


Fig. 15.5 Pressure wire tip loads. Comparison of pressure wire (PW) tip load to standard coronary wires

FFR Assessment of a Single Epicardial Lesion

How to Perform a Pressure Wire Study?

- The main indication for FFR measurement is to assess the functional/physiological relevance of a stenosis within an epicardial vessel [7, 19].
- A pressure wire study is an interventional skill and the wire needs to be handled with care and precision to minimize any complications.
- To be valid, FFR measurements should be undertaken with meticulous attention to detail. The following steps should be followed in order to successfully perform a pressure wire study of a non-ostial lesion.
 - Step 1: Choose an appropriate guide catheter and engage the coronary artery, monitoring for any pressure damping.
 - Step 2: Prepare the wire. Using the port at the end of the pressure wire holder, flush the pressure wire using a 20 mL syringe, then while resting the holder on a flat surface connect the pressure wire to the console, and zero the pressures. The pressure wire is now ready to be used.
 - Step 3: Prior to advancing the wire, anticoagulation should be considered in the form of 70–100u/Kg of unfractionated heparin.
 - Step 4: To avoid any epicardial vessel spasm, administer 200–300 mcg of intracoronary nitrates.
 - Step 5: Once the pressure wire is ready, shape the tip of the wire to the desired angle to aid maneuverability of the wire.
 - Step 6: Using the introducer needle, advance the wire through the Y-connector and up the catheter until the pressure sensor is just within the tip of the guide catheter.
 - Step 7: Once happy with the position of the sensor and if there is no pressure damping evident, the pressure wire should be equalized, after which the Pd/Pa reading should be 1.0 (Fig. 15.6). Note that if an introducer needle was used, this needs to be removed and the Y-connector shut, *before equalization*.



Fig. 15.6 Pressure wire equalization. The transducer is placed at the tip of the guide catheter before equalization is performed. The FFR value should be 1 before proceeding to assessing coronary lesions

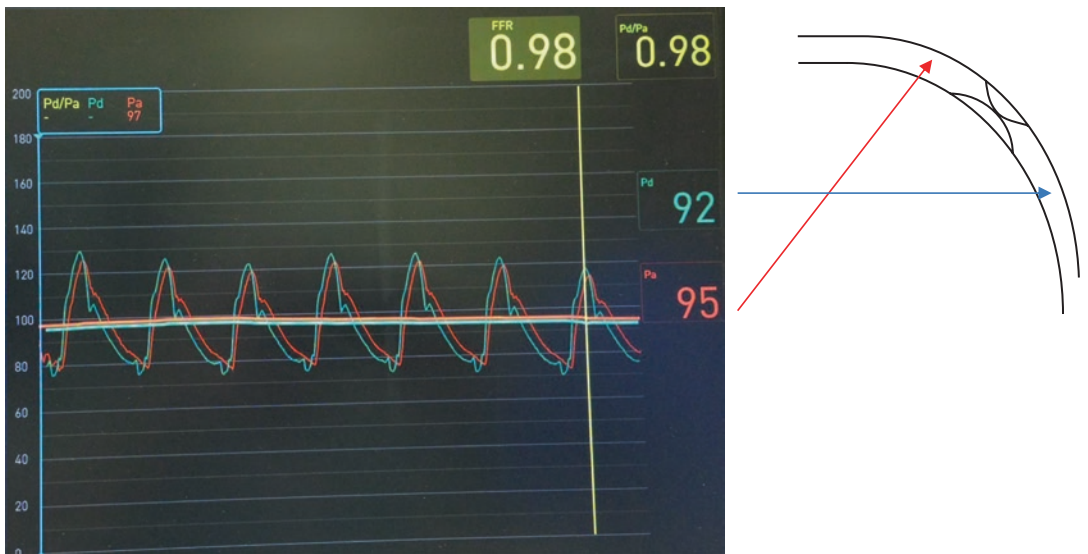


Fig. 15.7 Standard FFR readout. The pressure before the lesion is represented by the red line (Pa) and the pressure after the lesion is presented by blue line (Pd). The FFR result here is 0.98

- Step 8: Advance the wire distally until the pressure sensor is at least 2–3 cm beyond the lesion of interest. It is well established that there is turbulence within 1–2 cm distal to a stenosis and this turbulence can negate an accurate FFR reading, so the pressure transducer needs to be beyond this area. Remove your introducer needle and make sure that the Y-connector is closed.
- Step 9: To ensure maximum hyperemia and no epicardial vasoconstriction, administer 200–300 mcg of intracoronary nitrates.
- Step 10: When the pressure reading is stable, take the reading as the baseline Pd/Pa (Fig. 15.7).

- Step 11: Once happy with the resting FFR and position of the sensor, start adenosine infusion/administer IC adenosine, warning the patient of possible side effects. If IC adenosine is used, ensure that the guide catheter is well engaged and there is no pressure damping. It's a good idea to record a short test shot to document the position of the wire and catheter.
- Step 12: When the pressure tracing has stabilized at the lowest reading, this can be taken as FFR at maximum hyperemia. After IC adenosine this will occur within 10–15 s, but with IV adenosine a steady-state FFR often takes between 1 and 2 min.
- Step 13: If satisfied with the FFR measurement, the pressure wire should be pulled back so that the pressure sensor is once again within the guide catheter. This is to check for any drift, which can render the FFR measurement invalid (Fig. 15.8). The FFR at this point should be 1.0.
- Step 14: A check angiogram should be performed to make sure that there is no damage to the vessel.
- Note: The term “FFR” is only valid for measurements taken at maximal hyperemia. At all other times the reading is Pd/Pa, not FFR.

Tips and Tricks

- Be careful that you know where the pressure transducer is on the wire you are using. Generally, the transducer sits at the junction of the radiopaque tip, which is between 3 and 3.5 cm from the leading tip depending upon the manufacturer.
- Choose the appropriate guide for the vessel size to avoid any pressure damping or ventricularization of the pressure trace. Until such pressure distortion is resolved, FFR readings will not be valid.
- If an introducer needle is used, make sure that this is fully outside and the Y-connector closed before equalizing or taking any measurements.
- The transducer needs to be mid-chest (5 cm below the sternum) for equalization and measurement.
- Drift of the pressure can occur, especially after a long procedure, and this can affect the accuracy of the measurements. This can be identified from the waveform as both curves will be identical in shape with a dicotic notch clearly visible. If suspected, you should check for drift by bringing the pressure wire back so that the sensor is at the tip of the guide. If there

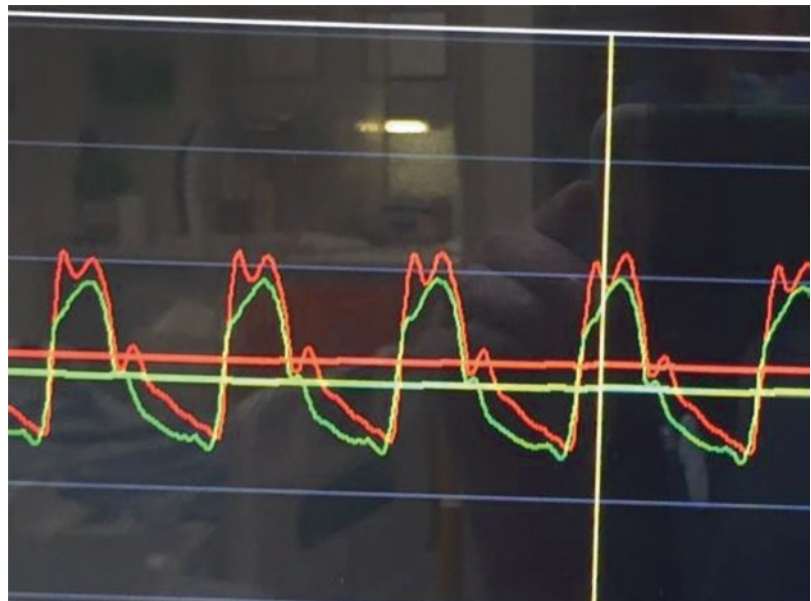


Fig. 15.8 Example of pressure wire drift. Red (Pa) and green (Pd) waveforms are identical with the dicotic notch visible

were drift or any doubt about the FFR measurement, it is safer to re-equalize and take the FFR measurement again (i.e., if the measurement just doesn't seem to make sense then start again!) (Fig. 15.8).

- If the decision is made to treat a lesion, the pressure wire can be disconnected from the transducer to allow PCI treatment to be carried out. On reconnecting the wire, however, care needs to be taken to ensure that the electrodes at the end of the wire are clean and dry before inserting this back into the transducer.
- There is actually quite good evidence that rechecking the FFR distal to the stented segment can predict outcome after the PCI, and so this can be used to check the physiological outcome of the intervention. The lower the post-stent FFR, the higher the MACE rate at follow-up [20].

FFR Assessment in Multiple Epicardial Lesions

Assessment of Diffusely Diseased Vessels

- Given that atherosclerosis can be diffuse and affect long segments of the epicardial coronary artery it is therefore possible for the FFR to be positive in vessels in which there is no obvious discrete coronary lesion.
- This is a relatively common reason for a vessel being labelled as angiographically not being significant but is FFR positive [1, 7, 16, 19].

Serial Stenoses

- When there are several lesions along the course of an artery, FFR taken distal to all the lesions is still perfectly valid to assess whether the vessel is ischemic. However, this will not identify the relative contributions of the stenoses that have been included. It simply assesses the overall drop in pressure along the measured length of the vessel. Increasingly, a pull-

back FFR measurement is recommended for this situation.

- The principle of pullback is that, *during continuous maximal hyperemia induced by adenosine infusion*, the wire is slowly pulled back from distal to proximal within the vessel, paying particular attention to points at which the FFR steps up sharply, thus indicating a more important stenosis inducing hemodynamic alteration. This can be an extremely effective technique, if done very carefully, with which to identify the most important lesion.
- However, it introduces extensive potential for misinterpretation of the result. *If the most distal lesion is the most hemodynamically significant in a series of two or more then the FFR reading proximal to that lesion will underestimate all upstream lesions until the distal lesion is treated.*
- As a result, the hemodynamically significant distal lesion tends to falsely reduce the pressure gradient across the proximal lesion, resulting in overestimation of the FFR [1, 16].

FFR Assessment of an Ostial Lesion

Pressure wire assessment of an ostial lesion requires precision and care especially when it is the left main stem (LMS).

Left Main Stem Assessment

- The presence of significant disease in the LMS is prognostically important and requires treatment. By contrast, there is good evidence that revascularization of hemodynamically insignificant LMS lesions is not beneficial.
- The use of FFR assessment for LMS lesions, as long as the basic rules of data acquisition in relation to avoiding damping and ventricularization of the trace are followed, has a good evidence base [1, 7, 16].

- It is also essential to bear in mind that in the presence of other epicardial vessel lesions, the serial stenosis principle is highly relevant when assessing LMS lesions. Specifically, downstream lesions in the left anterior descending (LAD) and circumflex (LCx) arteries can have a major influence on the interpretation of the result.
- This was looked at by Fearon and De Bruyne in 2012, by using a previously validated *in vitro* model of coronary circulation to create a fixed intermediate stenosis of the LMS and variable downstream LAD and LCx stenoses, and concluded that in the presence of proximal or mid-LAD or LCx disease LM SFFR can be reliably measured if the pressure wire is placed in the uninvolved epicardial artery [21].
- The implication of this study from a clinical standpoint is that if FFR of a LMS lesion taken in a relatively disease-free branch is ≤ 0.8 , this indicates that the LMS is hemodynamically significant, regardless of disease in the other main branch.
- Only rarely could the FFR in the disease-free branch be >0.8 when assessing a LM lesion, and be underestimating the FFR because of a tight proximal lesion in the other branch.

Tips and Tricks of Performing a Pressure Wire Study of an Ostial Lesion

- All the steps previously explained on how to conduct a pressure wire study still apply and the following additional steps need to be taken into account when performing an ostial lesion pressure wire study:
 - Guide catheter needs to be disengaged slightly. *This therefore mandates IV adenosine infusion use to induce maximal hyperemia.*
 - Guide with side holes should not be used.
 - The pressure wire needs to be equalized in the aorta with the guide slightly disengaged.

FFR in Acute Coronary Syndromes

FFR in ST-Elevation Myocardial Infarction

- During STEMI, the aim of primary PCI is to restore TIMI 3 flow.
- FFR measurement of the culprit vessel is unreliable because of high microvascular resistance in the distal bed resulting from vessel spasm, thrombus embolization, and edema. By contrast, there is no contraindication to measurement of FFR in non-culprit vessels in STEMI patients [22].
- In DANAMI3-PRIMULTI, patients presenting with STEMI who had other clinically significant coronary stenoses in addition to the lesion in the infarct-related artery (IRA) were randomized to FFR-guided intervention versus no intervention of the non-culprit lesions after successful intervention of the IRA [23].
- The authors concluded that not only use of FFR is safe in functional assessment of non-culprit lesions in STEMI patients but also complete revascularization guided by FFR measurements significantly reduced the risk of repeat revascularization [22].
- The safety of guidewire-based measurement of coronary physiology using IV adenosine was also assessed by Berry et al. in a prospective study where the FFR was measured at the end of primary PCI. They found that invasive FFR measurement in STEMI patients is feasible and can be performed safely using IV adenosine [24].

FFR in Non-ST-Elevation Myocardial Infarction

- It is believed that microvascular resistance in the infarcted territory is inversely proportional to the amount of viable myocardium rendering the FFR measurement of an epicardial vessel lesion valid [1, 20].
- The concept of FFR-guided management of patients with non-ST-elevation myocardial infarction (NSTEMI) was examined in the

FAMOUS-NSTEMI trial. This prospective, multicenter, randomized controlled trial enrolled 350 NSTEMI patients with ≥ 1 coronary stenoses of at least 30% as assessed on angiography.

- FFR was measured in both groups, but the results were only disclosed to the operator in the FFR-guided group [25].
- The study showed that the number of patients treated with OMT (without revascularization) was significantly higher in the FFR-guided group compared to the angio-guided group (22.7% vs. 13.2%; $p = 0.02$).
- Berry et al. also confirmed the safety and feasibility of using FFR measurement in 350 NSTEMI patients [24].

FFR After Coronary Intervention

- FFR measurement after PCI can also be used as a prognostic tool. Specifically, an FFR value of 0.9 has been associated with better long-term outcome and a reduction in revascularization.
- Pijls et al. examined 750 patients with post-procedural FFR measurement and related this to MACE at 6 months.
- The authors found that in patients with a post-procedural FFR of 0.9–0.95 the event rate at 6 months was 6% compared to 32% of patients with postprocedural FFR of less than 0.9. They therefore concluded that FFR after stenting is a strong predictor of outcome at 6 months [18, 19].
- One recent meta-analysis of 8 relevant studies (including a total of 1337 patients) concluded that persistently low FFR following PCI is associated with an adverse clinical outcome [20].

Low FFR Despite a Good Angiographic Result

- Despite achieving an apparently good angiographic result after stenting, a repeat FFR

measurement distal to the stented segment may still be suboptimal [1, 7, 16]. This can be due to several causes.

- Most commonly it is due to either suboptimal stent size or inadequate expansion of the stented segment, or due to geographical miss of the hemodynamically significant lesion.
- This scenario is a cast-iron indication for intracoronary imaging assessment.

Conclusion

- The clinical applicability of pressure wire assessment of CAD is the product of many years of meticulous validation. The clinical trial data have provided us with clear evidence that FFR-guided PCI practice is associated with better clinical outcomes at lower overall cost than purely angiographic guidance.
- The next important challenge is to apply the increasing persuasive evidence that FFR guidance is useful at the stage of the diagnostic angiogram in order to optimize patient management.
- RIPCORD showed that patient management plans were affected in 26% of cases when FFR measurements were revealed to the operator, because the angiogram did not predict whether a lesion was ischemic or not in 32% of vessels [14].
- A large number of studies have now confirmed the same discrepancy between the assessment of angiographic lesion severity and FFR assessment of ischemia.
- This has occurred consistently in around 30% of lesions and this leads to a management change in between 22 and 48% of cases [25–31].
- It is clear that there are angiographically tight lesions that are FFR negative and mild-looking lesions that are FFR positive. The consequence of this is that it is NOT logical to target FFR only at “intermediate” lesions.
- The appropriate use of FFR requires meticulous attention to detail and a thorough understanding of the technique.

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