Fractional Flow Reserve, Coronary Flow Reserve and the Index of Microvascular Resistance in Clinical Practice

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Introduction

Information on coronary physiology is increasingly important to inform treatment decisions in the cardiac catheter laboratory. The purpose of this article is to review the rationale and indications for fractional flow reserve (FFR), coronary flow reserve (CFR) and the index of microvascular resistance (IMR) in interventional cardiology practice. A second objective is to highlight strengths and limitations of FFR, CFR and IMR, and discuss their value in clinical practice.

The Public Health Burden of Coronary Heart Disease

Coronary heart disease is the major cause of premature morbidity and death globally.[1–3] In developed countries, chest pain accounts for at least 1% of all visits to a general practitioner,[4,5] 5% of all emergency department visits and 40% of emergency admissions to hospitals.[6] Angina pectoris, derived from the Latin verb *angere* and first described by William Heberden in 1772, is chest pain of cardiac origin. The pathophysiology of angina involves a relative deficiency of myocardial oxygen supply (i.e. ischaemia) and typically occurs after physical activity and stress. Angina is usually secondary to obstructive coronary artery disease (CAD), but it may also occur in the absence of a flow-limiting stenosis (i.e. microvascular angina).[7–12] This condition is prognostically important.[13,14] Another possible cause of angina involves a combination of epicardial and small vessel CAD, which together contribute to ischaemic symptoms. This pathophysiology may explain why angina persists and drug therapy is still needed in some patients even after successful percutaneous coronary intervention (PCI).

Diagnosis of Angina in the Catheter Laboratory

European clinical guidelines now recommend that symptomatic patients with a high likelihood of angina (e.g. 60–90% likelihood) should be referred directly for invasive coronary angiography without prior stress testing.[1,2] Other patients with suspected angina and a lower likelihood of ischaemia should follow non-invasive diagnostic pathways.[1,2] The current North American guidelines provide a qualified recommendation of an initial invasive diagnostic strategy with coronary angiography,[3] with invasive coronary angiography otherwise recommended following stress-testing. The European guidelines support a more direct, optimised approach to the management of symptomatic coronary disease. Skipping the non-invasive pathway and proceeding directly to invasive angiography means that patients who are most likely to have obstructive coronary disease will be managed more efficiently in terms of time and resources.

Limitations of Angiography-based Treatment Decisions

A coronary angiogram provides an anatomical assessment of the presence and extent of coronary disease severity. Treatment decisions, which include medical therapy, PCI or coronary artery bypass surgery (CABG),[15] are based on a visual interpretation of the coronary angiogram. Occasionally, treatment decisions are deferred in order to obtain further diagnostic information. However, visual interpretation of the coronary angiogram may be inaccurate, and clinical judgments made by individual cardiologists in everyday practice are subjective, potentially leading to misdiagnosis and incorrect treatment decisions.[16,17]

Making treatment decisions for patients with multiple coronary narrowings based on angiographic findings is particularly challenging since identifying the culprit stenosis (or stenoses) and discriminating flow-limiting from non-culprit flow disease is subjective and potentially unreliable.[15–18] Since treatment decisions have prognostic importance and resource implications, misinterpretation of an angiogram could lead to inappropriate decisions, sub-optimal health outcomes[16–18] and significant future healthcare costs.

Fractional Flow Reserve Measurement in the Catheter Laboratory – Clinical Utility

Diagnostic methods for assessing coronary artery function have rapidly evolved in recent years. Guidewire-based measurement of coronary blood pressure, temperature and resistance now provide new diagnostic possibilities. Seminal work by Gould and colleagues[19–21] and by De Bruyne and Pijls[22] facilitated by technological advantages provided by coronary guidewire sensor technology now mean that cardiologists can measure lesion-level ischaemia, coronary collateral supply and other parameters of microvascular function.[23,24] The indications for FFR, CFR and IMR are summarised in *Table 1*.

Table 1: Clinical Circumstances Where Fractional Flow Reserve, Pressure-derived Collateral Flow Index, Coronary Flow Reserve and Index of Microvascular Resistance May Have Diagnostic and Clinical Utility

FFR
Moderate coronary stenosis (e.g. 50–90% angiographic severity) when functional information is lacking (Level I guideline recommendation[15])
Serial coronary stenoses
Intermediate left main stem disease
Post-PCI / stent optimisation
Side branch lesion severity
Saphenous vein graft disease severity
Non-culprit lesions in acute coronary syndromes
Non-coronary indication: assessment of aortic valve stenosis severity
CFIp
Assessment of coronary collateral artery supply in stable angina and acute myocardial infarction
CFR
Assessment of coronary vascular function[23,25,26]
Diagnosis of microvascular angina[8–12]
IMR
Assessment of coronary microvascular function[27]
Prognostic assessment in acute myocardial infarction[28–30]

CFIp = pressure-derived collateral flow index; CFR = coronary flow reserve; FFR = fractional flow reserve; IMR = index of microvascular resistance; PCI = percutaneous coronary intervention.

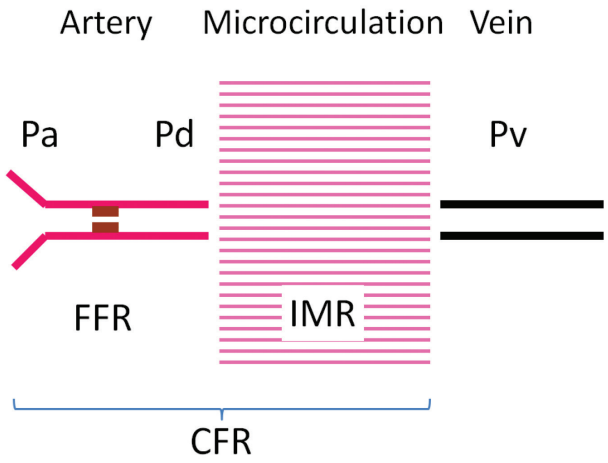
Fractional Flow Reserve for the Diagnosis of Flow-limiting Coronary Artery Disease

Coronary stenosis severity and lesion-level ischaemia can be assessed invasively based on the myocardial fractional flow reserve (FFR = resting distal coronary pressure to aortic pressure ratio [Pd/Pa] during hyperaemia and the ischaemic threshold ≤0.80)[22,31,32] (see *Figure 1*). When coronary resistance is minimised, flow becomes linearly related to blood pressure in the physiological range. Thus, FFR is a surrogate measure of flow limitation and lesion-level ischaemia. Recent studies (Deferral versus Performance of PTCA in Patients without Documented Ischemia [DEFER],[31] Fractional Flow Reserve versus Angiography for Multivessel Evaluation [FAME][32] and FFR-Guided Percutaneous Coronary Intervention plus Optimal Medical Therapy versus Medical Therapy Alone in Patients with Stable Coronary Artery Disease [FAME 2][33]) in patients with stable CAD have put forward a new evidence-based approach to diagnostic decisions. FFR ≤0.80 derived from the pressure guidewire is an evidence-based physiological threshold indicative of obstructive coronary disease that could benefit from revascularisation. Alternatively, FFR >0.80 implies that medical therapy rather than revascularisation is indicated[32,33] (see *Figure 2*).

The diagnostic categorisations and treatment recommendations are provided as an indicative guide. Clinicians should follow clinical guidelines[1,3,15] in clinical practice. IMR is not included in this figure since more information is needed to establish cut-off values for microvascular dysfunction.

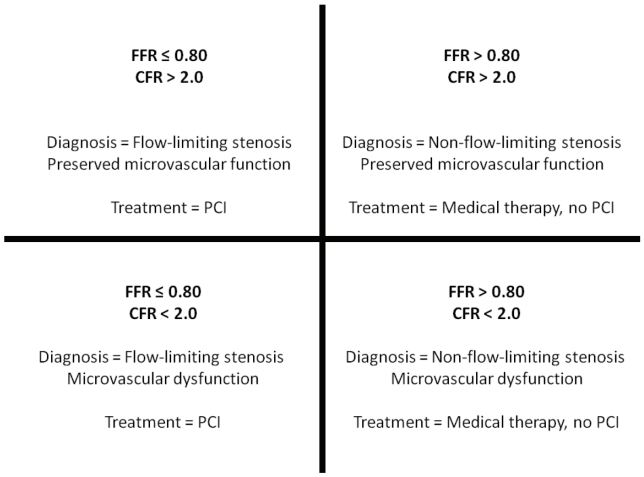
The DEFER,[31] FAME[32] and FAME 2[33] studies demonstrated the benefits of using FFR measurement to more accurately identify stenoses that are flow-limiting and guide PCI with resulting improved outcomes and reduced costs[34] compared with angiography alone. FFR measurement can identify and exclude obstructive CAD with high diagnostic accuracy,[22,35] even in patients with prior myocardial infarction (MI).[36]

Figure 1: Myocardial Fractional Flow Reserve – Fractional Flow Reserve = Pd/Pa During Hyperaemia



CFR = coronary flow reserve; FFR = fractional flow reserve; IMR = index of microvascular resistance; Pd = pressure distal to the lesion; Pa = pressure proximal to the lesion; Pv = the central venous pressure.

Figure 2: Diagnosis and Treatment Based on Fractional Flow Reserve and Coronary Flow Reserve Values



CFR = coronary flow reserve; FFR = fractional flow reserve; PCI = percutaneous coronary intervention.

The FAME trial[32] found marked discordance between angiographic and FFR assessment of stenosis severity with a general over-estimation of disease severity with angiography.[35]

Clinical guidelines conclude that when non-invasive diagnostic stress test information is not available, FFR is helpful[15] and that FFR is indicated for moderate coronary stenoses (e.g. 50–90%) when functional information is lacking[15] (see *Table 1*). In the UK, the British Cardiovascular Intervention Society has recognised the clinical importance of FFR. Measuring FFR is considered an Interventional Diagnostic Procedure[37] relevant for reimbursement

Fractional Flow Reserve and Microvascular Angina

Microvascular angina is defined as the occurrence of typical angina symptoms that respond to anti-angina therapies in patients without obstructive CAD.[7–12] Ischaemic chest pain in patients without obstructive CAD can be classified as Type 1, microvascular angina[1,9,10] (see *Figure 2*). Recent guidelines from the European Society of Cardiology[1] have placed renewed emphasis on microvascular angina

as a clinical and public health problem, and studies have found that microvascular angina has prognostic importance.[13,14]

Myocardial perfusion is regulated by arterioles (10–200 m diameter) within the muscle and epicardium (pre-arterioles, 200–500 m). These small blood vessels contribute about 50% and 25% to total coronary vascular resistance, respectively.[8] The pathophysiology of coronary microvascular disease involves a reduction in the number of microvascular arterioles and potential microvascular hypertrophy. The number of microvascular capillaries correlates inversely with symptoms. Coronary microvascular abnormalities are classically associated with hypertension,[38,39] but may also occur in atherosclerotic coronary disease.[40] Vasodilator capacity is measured by stress testing or CFR.[19,40,41]

Historically, limitations in testing methods have made it difficult to diagnose microvascular disease. A coronary angiogram is the reference test for the diagnosis of CAD.[15] However, the imaging information is essentially anatomical whereas diagnostic information on microvascular disease requires a functional test.[1,2,20]

From a practical perspective, FFR can be used to rule-out lesion-level ischaemia in patients with mild or intermediate CAD (see *Table 1*). In this case, microvascular angina may be the final diagnosis if symptoms, response to drug therapy and non-invasive tests are indicative of ischaemia. Since the PressureWire™ Certus™ guidewire can measure microvascular function as well as FFR, microvascular angina can now be assessed in the catheter laboratory (see *Table 1*).

Catheter Laboratory Measurements – Practical Considerations

Fractional Flow Reserve

Clinical guidelines recommend FFR measurements for lesions with a stenosis severity of 50–90%[15] (see *Table 1*). A 0.014" coronary PressureWire guidewire (e.g. PressureWire Certus or PressureWire Aeris™ guidewire) should be used for making FFR measurements. More detailed information on the clinical circumstances for FFR and guidance on measurement can be found in *Table 1*. FFR also has prognostic value for assessing the final results of PCI. Pijls et al.[42] have shown that a FFR >0.95 is associated with a lower rate of adverse outcomes that are more likely to occur with post-PCI FFR values <0.95. Expert review articles have provided guidance on the practical considerations for FFR measurement.[24,43]

Fractional Flow Reserve in Routine Practice

FFR is straightforward to acquire and with training and experience should only add a few minutes to the diagnostic procedure. However, optimal data acquisition and interpretation require a good understanding of the methodology. FFR values are influenced by practical considerations and patient-level and coronary factors. Practical considerations for FFR measurement based on the author's clinical practice and experience are listed in *Table 2*. Patient-level factors relevant to FFR measurement include obtaining a haemodynamic response to adenosine. The coronary artery characteristics relevant to FFR measurement include left main (LM) disease, chronic total occlusion (CTO), tandem lesions and acute coronary syndromes (ACS).

Fractional Flow Reserve in Selected Circumstances

Given the prognostic significance of the LM coronary artery, treatment decisions for revascularisation or medical therapy alone are particularly important. In a cohort study of 213 patients with angiographically

Table 2: Tips and Tricks for Optimal Measurement of Fractional Flow Reserve

Practical Considerations for Fractional Flow Reserve Measurement
Patient should be fasting and, since caffeine increases the rate of adenosine catabolism, should have avoided caffeine-containing drinks for at least 12 hours; withhold theophylline-containing drugs the morning of the procedure
Use a ≥6 French guide catheter
Ensure therapeutic anticoagulation as per standard catheter laboratory practice for coronary instrumentation
Before passing the wire into the guide catheter, calibrate it and ensure to equalise the Pa and Pd pressure tracings using the RadiAnalyzer™ Xpress instrument
Ensure the guide catheter is coaxial and disengaged from the coronary ostium with no damped waveform
Intracoronary nitrate (200 m) should be given initially in all patients to minimise vascular tone
Ensure the guide catheter is flushed and no iodinated contrast is retained (since contrast has vasodilator effects)
Ensure the pressure sensor is ideally 60 mm distal to the lesion (i.e. two marker lengths)
Ensure the distal end of the pressure wire is in the main vessel, not a side branch
Administration of Intravenous Adenosine
Venous access with a central vein (4 French or 5 French catheter) or a proximal arm vein (e.g. antecubital fossa)
Administer intravenous adenosine (140 µg/kg/min) with a rise in heart rate (rise) and fall in blood pressure (including separation of systolic and diastolic recordings versus baseline). Adenosine is contraindicated in patients with significant asthma (e.g. routine use of bronchodilator therapy and heart block)
Response to adenosine: typical changes in blood pressure, heart rate and symptoms should be recorded prospectively to confirm a haemodynamic response to adenosine. Following a two-minute infusion period, typical haemodynamic changes indicative of a functional response to adenosine response are: • symptoms of chest tightness, chest pain, wheeze • fall in systolic blood pressure by 20% of the resting value • fall in diastolic blood pressure by >20% of the resting value • widening of pulse pressure • rise in heart rate >10% from baseline
When the response to adenosine is inadequate, the standard dose of adenosine (140 µg/kg/min) should be increased up to 210 µg/kg/min in order to best ensure maximal hyperaemia
With steady state hyperaemia (typically after 60 s of adenosine infusion), record the lowest FFR value
For grey-zone FFR values: ≥0.81 and ≤0.82, consider repeating the FFR measurements with a higher dose of adenosine (e.g. 180–210 µg/kg/min) to confirm the FFR reading
Administration of Intracoronary Adenosine
Intracoronary adenosine may be preferred according to local availability, or if peripheral/central venous access is inadequate
Doses for intracoronary adenosine: • left coronary artery = 60 µg • right coronary artery = 40 µg
If ever the intracoronary adenosine is used and a negative FFR is obtained (FFR >0.80), then this result may be reconfirmed during intravenous adenosine infusion, if appropriate
Fractional Flow Reserve Quality Assurance
Obtaining a second FFR value during the same diagnostic procedure is good practice, especially for FFR values close to the ischaemic threshold of 0.80
At the end of the FFR assessment and if the wire has been pulled back (as clinically appropriate), verify that Pa and Pd are equal and that there has been no drift in baseline. If there is drift, consider repeating the FFR assessment to obtain a valid FFR

FFR = fractional flow reserve; Pd = pressure distal to the lesion; Pa = pressure proximal to the lesion.

equivocal LM disease, Hamilos et al.[44] found that the prognosis of patients managed medically based on FFR >0.80 was similar to that of patients with FFR ≤0.80 who underwent CABG. This result indicates that FFR-guided treatment decisions in patients with equivocal LM disease are associated with favourable outcomes. In patients with downstream disease, FFR is only affected if the stenosis in the branch artery is proximal and very severe.[45]

In CTOs, a FFR value in a collateral donor artery will be lower than would be the case if there were no collateral connections. After PCI and restoration of flow, the FFR in the collateral donor artery will rise. Therefore, where clinically appropriate, PCI should be performed first in the recipient artery. Then FFR may be more reliably evaluated in lesions in the collateral donor artery. In tandem lesions, a pull-back recording during hyperaemia should be performed in order to determine whether one or more of the lesions is making a functionally important contribution to the FFR value. This would be revealed as a step-up in the FFR value >0.80 as the wire is pulled back across the stenosis of interest.[43] PCI should be performed in the most severe lesion first and then FFR can be re-assessed afterward.

Several factors may influence the validity of FFR in ACS patients. If MI has occurred, the patient's microcirculation may be severely injured and theoretically may compromise the response to adenosine. Thus, acute measurement of FFR in the culprit coronary artery during primary PCI is not recommended. However, FFR measurement in non-culprit lesions remains valid and is indeed the subject of current research.[46] A detailed discussion of these subjects is beyond the scope of this review, and references are mentioned for further reading.

Resting Pressure Indices

The relationship between the distal and proximal coronary (aortic) pressures is influenced by stenosis severity both throughout the cardiac cycle or when restricted to diastole. However, the relationships between a resting pressure index and FFR are closest at the extremes of the range (the coefficient of determination [R^2] is >0.9 for mild and severe stenosis). In the clinically important range for treatment decisions (i.e. FFR between 0.60 and 0.90), the diagnostic accuracy for lesion-level ischaemia revealed by FFR ≤0.80 is moderate at best.[47] The diagnostic accuracy of a hybrid approach and safety of treatment decisions based on a hybrid approach are unknown.

Coronary Wedge Pressure and Fractional Coronary Collateral Supply

Coronary collateral connections represent a nascent or adaptive response to ischaemia and alterations in hydrostatic pressure.[25] For example, when antegrade flow is interrupted, such as during coronary balloon inflation, the pressure measured in the distal vessel beyond the occlusion (i.e. wedge pressure [Pw]) reflects the collateral coronary supply.[25,43] The pressure-derived fractional coronary collateral flow index takes the venous pressure into account and can be calculated according to the following equation:

$$CFIp = (Pw - Pv) / (Pa - Pv)$$

(Pv is venous pressure ideally measured from the right atrium and Pa is the aortic pressure measured from the guide catheter.)

Coronary wedge pressure is typically 0.1– 0.3 in humans, and values >0.20 indicate an adequate collateral supply that may limit infarct size in acute MI.[25] The wedge pressure, therefore, provides an indication of the coronary collateral supply in patients with stable and acute coronary disease.

Coronary Flow Reserve

Since coronary flow and resistance are inversely related, microvascular function can be measured by integrating pressure and temperature measured simultaneously using thermodilution-based measurements of coronary artery flow and pressure. These measurements, which can be made using a pressure- and temperature-sensitive coronary guidewire,[26] provide information about coronary vascular function (see *Table 1*).

CFR represents the vasodilator capacity of the coronary vascular bed during hyperaemia and is measured by indicator thermodilution (see *Table 3*). A bolus of saline (i.e. 3 mL) at room temperature injected through the guide catheter will mix with antegrade coronary blood flow at body temperature, causing a transient reduction in temperature that is measured by the thermistor, located 3 cm from the distal end of the guidewire. The thermodilution curve is reflected by a transit time. Accepting the variability that may occur with this type of measurement, the mean transit time for three saline injections is displayed at rest and during pharmacological hyperaemia.[26]

Table 3: Key Steps for Thermodilution Measurements

CFR page on the RadiAnalyzer™ Xpress console, 'record'
The pressure wire should be placed in the mid-distal segment of the coronary artery
Ensure steady resting conditions
Use a three-way valve system for saline injection
Flush the guide catheter of all contrast and air bubbles, and ensure that it is engaged in the coronary ostium
Ensure the aortic pressure (Pa, RED) is recorded (i.e. the arterial pressure transducer is open)
3 mL bolus injections of room temperature saline (x 3) (a temperature decline of at least 2 ºC should typically be obtained; repeat the injections for an outlying transit time to ensure all three curves are similar)
Switch on IV adenosine (140 µg/kg/min) and wait for two minutes (confirm clinical response to adenosine)
Flush the guide catheter of saline that may have warmed in the guide catheter inside the patient
3 mL bolus injections of room temperature saline (x 3) during hyperaemia

Using thermodilution, CFR can be calculated according to this equation:
CFR = resting Tmn / hyperaemic Tmn
A normal CFR is >2.0 and CFR values >4.0 are indicative of vascular health. A low CFR potentially indicates microvascular dysfunction, which may explain angina symptoms, especially when FFR is normal (>0.80). CFR = coronary flow reserve; IV = intravenous; pressure proximal to the lesion .

Index of Microvascular Resistance

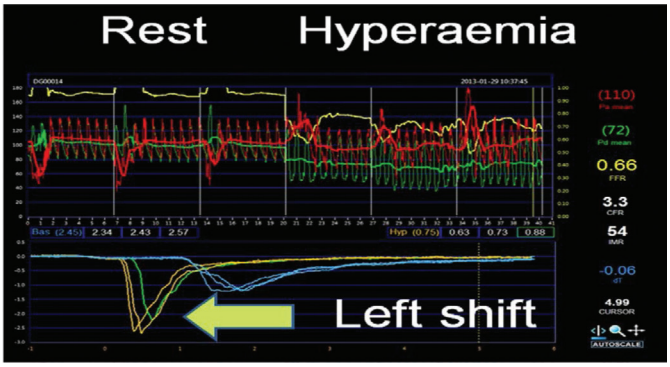
Myocardial resistance is mainly determined by the microcirculation. IMR is a coronary guidewire-based measure of coronary microvascular function[48,49] (see *Table 1*). IMR provides information on microvascular dysfunction that could be informative both in stable patients and also in patients with acute or recent MI (see *Table 1*). Compared with FFR, less information is known about IMR, and it is not known whether therapeutic reduction of IMR (e.g. with an intracoronary vasodilator) confers clinical benefits. Nor is it known whether treatment decisions based on an IMR threshold might have prognostic benefits (as has been shown to be the case with FFR.

In a simplified form, assuming coronary flow and myocardial flow are equal and that the contribution of collateral flow is negligible, then:

IMR = distal coronary pressure / coronary flow

IMR can be used to study the pathophysiology of microvascular function in patients with stable symptoms[27,50,51] and in acute MI[28,29,51] where it has prognostic importance.[30] An IMR <20 is in the normal range, and an IMR >30 is elevated (i.e. microvascular dysfunction in acute or stable coronary disease) (see *Figure 3*). IMR at the end of PCI is higher in patients who have subsequent evidence of procedure-related MI.[50]

Figure 3: Measurement of the Index of Microvascular Resistance



Pressure and thermodilution measurements are obtained on the coronary flow reserve (CFR) page. The recording is obtained from a pressure wire study in the right posterior descending coronary artery of a patient with angina. The recording was obtained before percutaneous coronary intervention (PCI).

The mean transit time at rest was 2.45 s (blue) and the mean transit time during hyperaemia was 0.75 s. The fractional flow reserve (FFR) was 0.66 and CFR, 3.30. The index of microvascular resistance (IMR) was 54 and should be corrected for the wedge pressure. When wedge pressure is not available, IMR can be estimated by using FFR_{cor} rather than FFR_{myo}, according to the following equation:[52]
$FFR_{cor} = 1.34 \times FFR_{myo} - 0.32$

The apparent IMR is calculated by multiplying the distal coronary pressure by the mean transit time of a 3 ml bolus of saline at room temperature during coronary hyperaemia induced by intravenous adenosine[49] (see *Table 3*). Pressure and temperature are measured simultaneously since the pressure-sensor and thermistor are located at the same point on the coronary guidewire (3 cm from the distal end). IMR may be expressed as mmHg x s, or it can be reported in units since it is an index. The mean distal coronary pressures must be recorded during maximal hyperaemia. Previous studies in patients with stable coronary disease have established that IMR measurement is repeatable and independent of haemodynamic variations, including heart rate, blood pressure and myocardial contractility.[53]

Since a coronary stenosis may be associated with a recruitable collateral supply, the coronary wedge pressure and venous pressure should be used to estimate IMR when IMR is measured in an obstructed coronary artery,[54] according to the following equation:

IMRc = [(Pa – Pv) x Tmn] x [(Pd – Pw) / (Pa – Pw)]

When wedge and venous pressure are not available, IMR may be estimated using this equation:[52]

$IMR = Pa \times Tmn \times FFR_{cor}$

where

$FFR_{cor} = 1.34 \times FFR_{myo} - 0.32$

IMR is straightforward to measure and takes just a few minutes. From a practical point of view, it is important to ensure that the guide catheter is flushed with saline before each injection since warmed saline within the guide could contribute to variations in the thermodilution curves. It is also essential to eradicate air bubbles from the tubing and guide catheter.

We recommend performing the thermodilution test initially during resting conditions and then following induction of hyperaemia with intravenous adenosine. The resting measurement provides the basal resistance index. Following induction of hyperaemia, one would expect to observe a left shift in the transit times, indicating an increase in coronary flow velocity due to minimisation of coronary resistance. The resistance reserve ratio (RRR) is the ratio of basal resistance / IMR. Emerging data suggest this ratio has discriminatory value in patients with stable and unstable coronary disease.[51]

Summary

While the limitations of angiography-based treatment decisions regarding revascularisation have been well documented, diagnostic methods for assessing coronary artery function have evolved rapidly in recent years. Moreover, it is now possible to assess FFR, CFR and IMR conveniently in the catheter laboratory with a coronary pressure guidewire. Of these assessment tools, FFR has become increasingly important for decision-making as evidenced by significant clinical trials, including DEFER, FAME and FAME 2.

On the other hand, CFR and IMR can serve as complementary tools by providing extensive information about epicardial and microvasculature resistance. In the future, haemodynamic coronary assessment tools will become more sophisticated resulting in better assessment of CAD and its treatment. ■

1. Montalescot G, Sechtem U, Achenbach S, et al., 2013 ESC guidelines on the management of stable coronary artery disease: The Task Force on the management of stable coronary disease of the European Society, *Eur Heart J*, 2013;34(38):2949–3003.
2. Cooper A, Calvert N, Skinner J, et al., *Chest pain of recent onset: Assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin,* London, UK: National Clinical Guideline Centre for Acute and Chronic Conditions, 2010:35.
3. Fihn SD, Gardin JM, Abrams J, et al., 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons, *Circulation*, 2012;126(25):e354–471.
4. Ruigómez A, Rodriguez LA, Wallander MA, et al., Chest pain in general practice: incidence, comorbidity and mortality, *Fam Pract*, 2006;23(2):167–74.
5. Nilsson S, Scheike M, Engblom D, et al., Chest pain and ischaemic heart disease in primary care, *Br J Gen Pract*, 2003;53(490):378–82.
6. Murphy NF, MacIntyre K, Capewell S, et al., Hospital discharge rates for suspected acute coronary syndromes between 1990 and 2000: population based analysis, *BMJ*, 2004;328(7453):1413–4.
7. Marzilli M, Merz CN, Boden WE, et al., Obstructive coronary atherosclerosis and ischemic heart disease: an elusive link!, *J Am Coll Cardiol*, 2012;60(11):951–6.
8. Kaul S, Jayaweera AR, Myocardial capillaries and coronary flow reserve, *J Am Coll Cardiol*, 2008;52(17):1399–401.
9. Camici PG, Crea F, Coronary microvascular dysfunction, *N Engl J Med*, 2007;356(8):830–40.
10. Herrmann J, Kaski JC, Lerman A, Coronary microvascular dysfunction in the clinical setting: From mystery to reality, *Eur Heart J*, 2012;33(22):2771–82b.
11. Yilmaz A, Sechtem U, Angina pectoris in patients with normal coronary angiograms: current pathophysiological concepts and therapeutic options, *Heart*, 2012;98(13):1020–9.
12. Sharaf BL, Pepine CJ, Kerensky RA, et al., Detailed angiographic analysis of women with suspected ischemic chest pain (pilot phase data from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation [WISE] Study Angiographic Core Laboratory), *Am J Cardiol*, 2001;87(8):937–41; A3.
13. Johnson BD, Shaw LJ, Buchthal SD, et al., Prognosis in women with myocardial ischemia in the absence of obstructive coronary disease: results from the National Institutes of Health-National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE), *Circulation,* 2004;109(24):2993–9.
14. Suwaidi JA, Hamasaki S, Higano ST, et al., Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction, *Circulation*, 2000;101(9):948–54.
15. Wijns W, Kolh P, Danchin N, et al., Guidelines on myocardial revascularization, *Eur Heart J*, 2010;31(20):2501–55.
16. Selby JV, Fireman BH, Lundstrom RJ, et al., Variation among hospitals in coronary-angiography practices and outcomes after myocardial infarction in a large health maintenance organization, *N Engl J Med*, 1996;335(25):1888–96.
17. White CW, Wright CB, Doty DB, et al., Does visual interpretation of the coronary arteriogram predicts the physiologic importance of a coronary stenosis?, *N Engl J Med*, 1984;310(13):819–24.
18. Carrick D, Behan M, Foo F, et al., Usefulness of fractional flow reserve to improve diagnostic efficiency in patients with non-ST elevation myocardial infarction, *Am J Cardiol*, 2013;111(1):45–50.
19. Gould KL, Lipscomb K, Hamilton GW, Physiologic basis for assessing critical coronary stenosis. Instantaneous flow response and regional distribution during coronary hyperemia as measures of coronary flow reserve, *Am J Cardiol*, 1974;33(1):87–94.
20. Gould KL, Lipscomb K, Effects of coronary stenoses on coronary flow reserve and resistance, *Am J Cardiol*, 1974;34(1):48–55.
21. Gould KL, Pressure-flow characteristics of coronary stenoses in unsedated dogs at rest and during coronary vasodilation, *Circ Res*, 1978;43(2):242–53.
22. Pijls NH, De Bruyne B, Peels K, et al., Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses, *N Engl J Med*, 1996;334(26):1703–8.
23. Gould KL, Does coronary flow trump anatomy?, *JACC Cardiovascular Imaging*, 2009;2(8):1009–23.
24. Kern MJ, Samady H, Current concepts of integrated coronary physiology in the catheterization laboratory, *J Am Coll Cardiol*, 2010;55(3):173–85.
25. Berry C, Balachandran KP, L'Allier PL, et al., Importance of collateral circulation in coronary heart disease, *Eur Heart J*, 2007;28(3):278–91.
26. Barbato E, Aarnoudse W, Aengevaeren WR, et al., Validation of coronary flow reserve measurements by thermodilution in clinical practice, *Eur Heart J*, 2004;25(3):219–23.
27. Melikian N, Vercauteren S, Fearon WF, et al., Quantitative assessment of coronary microvascular function in patients with and without epicardial atherosclerosis, *EuroIntervention*, 2010;5(8):939–45.
28. McGeoch R, Watkins S, Berry C, et al., The index of microcirculatory resistance measured acutely predicts the extent and severity of myocardial infarction in patients with ST-segment elevation myocardial infarction, *JACC Cardiovasc Interv*, 2010;3(7):715–22.
29. Payne AR, Berry C, Doolin O, et al., Microvascular Resistance Predicts Myocardial Salvage and Infarct Characteristics in ST-Elevation Myocardial Infarction, *J Am Heart Assoc,* 2012;1(4):e002246.
30. Fearon WF, Low AF, Yong AS, et al., Prognostic value of the Index of Microcirculatory Resistance measured after primary percutaneous coronary intervention, *Circulation*, 2013;127(24):2436–41.
31. Pijls NH, van Schaardenburgh P, Manoharan G, et al., Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study, *J Am Coll Cardiol*, 2007;49(21):2105–11.
32. Tonino PA, de Bruyne B, Pijls NH, et al., Fractional flow reserve versus angiography for guiding percutaneous coronary intervention, *N Engl J Med*, 2009;360(3):213–24.
33. De Bruyne B, Pijls NH, Kalesan B, et al., Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease, *N Engl J Med*, 2012;367(11):991–1001.
34. Fearon WF, Bornschein B, Tonino PA, et al., Economic evaluation of fractional flow reserve-guided percutaneous coronary intervention in patients with multivessel disease, *Circulation*, 2010;122(24):2545–50.
35. Tonino PA, Fearon WF, De Bruyne B, et al., Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation, *J Am Coll Cardiol*, 2010;55(25):2816–21.
36. De Bruyne B, Pijls NH, Bartunek J, et al., Fractional flow reserve in patients with prior myocardial infarction, *Circulation*, 2001;104(2):157–62.
37. British Cardiovascular Intervention Society, PCI Dataset information, 2013. Available at: www.bcis.org.uk/pages/page_box_contents.asp?pageid=693&navcatid=25 (Accessed 5 February 2014).
38. Campbell DJ, Somaratn JB, Jenkins AJ, et al., Differences in myocardial structure and coronary microvasculature between men and women with coronary artery disease. *Hypertension*, 2011;57(2):186–92.
39. Mundhenke M, Schwartzkopff B, Strauer BE, Structural analysis of arteriolar and myocardial remodelling in the subendocardial region of patients with hypertensive heart disease and hypertrophic cardiomyopathy, *Virchows Arch*, 1997;431(4):265–73.
40. Escaned J, Flores A, García-Pavía P, et al., Assessment of microcirculatory remodeling with intracoronary flow velocity and pressure measurements: validation with endomyocardial sampling in cardiac allografts, *Circulation*, 2009;120(16):1561–8.
41. Tsagalou EP, Anastasiou-Nana M, Agapitos E, et al., Depressed coronary flow reserve is associated with decreased myocardial capillary density in patients with heart failure due to idiopathic dilated cardiomyopathy, *J Am Coll Cardiol*, 2008;52(17):1391–8.
42. Pijls NH, Klauss V, Siebert U, et al., Coronary pressure measurement after stenting predicts adverse events at follow-up: A multicenter registry, *Circulation*, 2002;105(25):2950–4.
43. Pijls NH, Kern MJ, Yock PG, De Bruyne B, Practice and potential pitfalls of coronary pressure measurement, *Catheter Cardiovasc Interv*, 2000;49(1):1–16.
44. Hamilos M, Muller O, Cuisset T, et al., Long-term clinical outcome after fractional flow reserve-guided treatment in patients with angiographically equivocal left main coronary artery stenosis, *Circulation*, 2009;120(15):1505–12.
45. Yong AS, Daniels D, De Bruyne B, et al., Fractional flow reserve assessment of left main stenosis in the presence of downstream coronary stenoses, *Circ Cardiovasc Interv*, 2013;6(2):161–5.
46. Berry C, Layland J, Sood A, et al., Fractional flow reserve versus angiography in guiding management to optimise outcomes in non–ST-elevation myocardial infarction (FAMOUS-NSTEMI): Rationale and design of a randomized controlled clinical trial, *Am Heart J*, 2013;166(4): 662–8.e3.
47. Berry C, van 't Veer M, Witt N, et al., VERIFY (VERification of Instantaneous Wave-Free Ratio and Fractional Flow Reserve for the Assessment of Coronary Artery Stenosis Severity in EverydaY Practice): a multicenter study in consecutive patients, *J Am Coll Cardiol*, 2013;61(13):1421–7.
48. Aarnoudse W, van den Berg P, van de Vosse F, et al., Myocardial resistance assessed by guidewire-based pressure-temperature measurement: in vitro validation, *Catheter Cardiovasc Interv*, 2004;62(1):56–63.
49. Fearon WF, Balsam LB, Farouque HM, et al., Novel index for invasively assessing the coronary microcirculation, *Circulation*, 2003;107(25):3129–32.
50. Layland JJ, Whitbourn RJ, Burns AT, et al., The index of microvascular resistance identifies patients with periprocedural myocardial infarction in elective percutaneous coronary intervention, *Heart*, 2012;98(20):1492–7.
51. Layland J, Carrick D, McEntegart M, et al., Vasodilatory capacity of the coronary microcirculation is preserved in selected patients with non-ST-segment-elevation myocardial infarction, *Circ Cardiovasc Interv*, 2013;6(3):231–6.
52. Yong AS, Layland J, Fearon WF, et al., Calculation of the index of microcirculatory resistance without coronary wedge pressure measurement in the presence of epicardial stenosis, *JACC Cardiovasc Interv*, 2013;6(1):53–8.
53. Yong AS, Ho M, Shah MG, et al., Coronary microcirculatory resistance is independent of epicardial stenosis, *Circ Cardiovasc Interv*, 2012;5(1):103–8, S1–2.
54. Layland J, MacIsaac AI, Burns AT, et al., When collateral supply is accounted for epicardial stenosis does not increase microvascular resistance, *Circ Cardiovasc Interv*, 2012;5(1):97–102.