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. In developed countries, chest pain accounts for at least 1% of all visits to a general practitioner, 5% of all emergency department visits and 40% of emergency admissions to hospitals. 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). 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. Other patients with suspected angina and a lower likelihood of ischaemia should follow non-invasive diagnostic pathways. The current North American guidelines provide a qualified recommendation of an initial invasive diagnostic strategy with coronary angiography, 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), 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.

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. Since treatment decisions have prognostic importance and resource implications, misinterpretation of an angiogram could lead to inappropriate decisions, sub-optimal health outcomes 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 and by De Bruyne and Pijls 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. The indications for FFR, CFR and IMR are summarised in Table 1.
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,\(^{21}\) 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\(^{24}\) compared with angiography alone. FFR measurement can identify and exclude obstructive CAD with high diagnostic accuracy,\(^{22,32}\) even in patients with prior myocardial infarction (MI).\(^{36}\)

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.\(^{25}\) Ischaemic chest pain in patients without obstructive CAD can be classified as Type 1, microvascular angina\(^{8–12}\) (see Figure 2). Recent guidelines from the European Society of Cardiology\(^{7}\) have placed renewed emphasis on microvascular angina.

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**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. 50–70% angiographic severity) when functional information is lacking (Level I guideline recommendation)\(^{19}\)
|-----|---------------------------------------------
| Serial coronary stenoses |
| Intermediate left main stem disease |
| PCI/PCI D / PCI 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 |
| CFlp | Assessment of coronary collateral artery supply in stable angina and acute myocardial infarction |
| CFR | Assessment of coronary vascular function\(^{23,26}\)
| Diagnosis of microvascular angina\(^{7,12}\) |
| IMR | Assessment of coronary microvascular function\(^{27}\)
| Prognostic assessment in acute myocardial infarction\(^{28–30}\) |

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

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

**Fractional Flow Reserve (FFR)**

- FFR ≤ 0.80
  - Diagnosis: Flow-limiting stenosis
  - Preserved microvascular function
  - Treatment: PCI
- FFR > 0.80
  - Diagnosis: Non-flow-limiting stenosis
  - Preserved microvascular function
  - Treatment: Medical therapy, no PCI

**Coronary Flow Reserve (CFR)**

- CFR ≤ 0.80
  - Diagnosis: Flow-limiting stenosis
  - Microvascular dysfunction
  - Treatment: PCI
- CFR > 0.80
  - Diagnosis: Non-flow-limiting stenosis
  - Microvascular dysfunction
  - Treatment: Medical therapy, no PCI

**IMR (Index of Microvascular Resistance)**

- IMR = index of microvascular resistance
- PCI = percutaneous coronary intervention

**CFIp (Collateral Flow Index)**

- CFlp = pressure-derived collateral flow index
- CFR = coronary flow reserve
- FFR = fractional flow reserve
- PCI = percutaneous coronary intervention
- Pd = pressure distal to the lesion
- Pa = pressure proximal to the lesion
- Pv = the central venous pressure

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\(^{21}\) DEFER, \(^{32}\) FAME, \(^{33}\) FAME 2

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as a clinical and public health problem, and studies have found that microvascular angina has prognostic importance.\(^{1,13}\)

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.\(^{4}\) 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,\(^{8,9}\) but may also occur in atherosclerotic coronary disease.\(^{6}\) Vasodilator capacity is measured by stress testing or CFR.\(^{10,11}\)

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.\(^{12}\) However, the imaging information is essentially anatomical whereas diagnostic information on microvascular disease requires a functional test.\(^{1,3,4}\)

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% (see Table 1). A 0.014” coronary PressureWire guidewire (e.g. PressureWire Cortus 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.\(^{24,42}\)

### 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

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### Table 1

**Clinical circumstances for FFR and guidance on measurement**

<table>
<thead>
<tr>
<th>Circumstance</th>
<th>Guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiography</td>
<td>FFR can be used to rule-out lesion-level ischaemia in patients with mild or intermediate CAD.</td>
</tr>
</tbody>
</table>
equivocal LM disease, Hamilos et al. 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.

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. 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. A detailed discussion of these subjects is beyond the scope of this review, and references are mentioned for further reading.

**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, provide information about coronary vascular function (see Table 1).

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

Using thermodilution, CFR can be calculated according to this equation.

\[
\text{CFR} = \frac{\text{resting } T_{mn}}{\text{hyperaemic } T_{mn}}
\]

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 (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**

The apparent IMR is calculated by multiplying the distal coronary pressure by the mean transit time of a 3 ml bolus of saline 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:

\[
\text{IMRc} = \left[ (\text{Pa} - \text{Pv}) \times \text{Tmn} \right] \times \left[ (\text{Pd} - \text{Pw}) / (\text{Pa} - \text{Pw}) \right]
\]

When wedge and venous pressure are not available, IMR may be estimated using this equation:\(^ {52}\)

\[
\text{IMR} = \text{Pa} \times \text{Tmn} \times \text{FFR}_{\text{cor}}
\]

where

\[
\text{FFR}_{\text{cor}} = 1.34 \times \text{FFR}_{\text{myo}} - 0.32
\]

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 microvascular resistance. In the future, haemodynamic coronary assessment tools will become more sophisticated resulting in better assessment of CAD and its treatment.
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