Novel insights into the complexity of ischaemic heart disease derived from combined coronary pressure and flow velocity measurements

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Chapter 3

Fractional flow reserve as a surrogate for inducible myocardial ischaemia

van de Hoef TP, Meuwissen M, Escaned J, Davies JE, Siebes M, Spaan JA, Piek JJ

ABSTRACT

Documentation of inducible myocardial ischaemia, related to the coronary stenosis of interest, is of increasing importance in lesion selection for percutaneous coronary intervention (PCI). Fractional flow reserve (FFR) is an easily understood, routine diagnostic modality that has become part of daily clinical practice, and is used as a surrogate technique for noninvasive assessment of myocardial ischaemia. However, the application of a single, discrete, cut-off value for FFR-guided lesion selection for PCI, and its adoption in contemporary revascularization guidelines, has limited the requirement for a thorough understanding of the physiological basis of FFR. This limitation constitutes an obstacle for the adequate use and interpretation of this technique, and also for the understanding of new and future modalities of physiological functional intracoronary testing. In this Review, we revisit the fundamental elements of coronary physiology in the absence or presence of coronary artery disease. We provide insight into three essential characteristics of FFR as a diagnostic tool in contemporary clinical practice—the theoretical framework of FFR and its associated limitations; the characteristics and role of FFR as a surrogate for noninvasively assessed myocardial ischaemia; and the requirement and associated caveats of potent vasodilatory drugs to induce maximal vasodilatation of the coronary vascular bed.
INTRODUCTION

Data from the COURAGE trial, as well as nonrandomized studies, have cast doubts on the life-saving potential of percutaneous coronary intervention (PCI), prompting a re-evaluation of its prognostic benefit in patients with stable coronary artery disease (CAD). The prognostic benefit of PCI among these patients seems to be limited to coronary stenoses that cause a large area of myocardium to become ischaemic. As a corollary, renewed emphasis has been placed on the importance of performing PCI only in those stenoses that objectively induce myocardial ischaemia. This restriction is of particular importance because the widespread performance of ad hoc PCI during diagnostic coronary angiography has been advocated as a safe therapeutic approach, and facilitated, noninvasive access to the coronary anatomy has reduced the role of functional imaging as a gatekeeper to conventional coronary angiography.

In response to accumulating evidence that coronary angiography alone fails to depict accurately the haemodynamic impact of coronary artery stenoses, intracoronary physiology-based techniques were developed as surrogates for the noninvasive assessment of inducible myocardial ischaemia. These techniques enabled the functional relevance of CAD to be evaluated in the cardiac catheterization laboratory. In this context, fractional flow reserve (FFR) has emerged as a feasible diagnostic modality in the contemporary armamentarium of interventionalists. Evidence gathered over the past 15 years has shown that, compared with angiographic guidance, FFR-guided revascularization improves clinical outcomes in patients with stable CAD. Consequently, in the absence of noninvasive stress test results, the use of FFR for the assessment of the functional severity of coronary stenoses of intermediate severity has a class I, level of evidence A recommendation in the latest European clinical practice guidelines on myocardial revascularization, as well as a class IIa, level of evidence A recommendation in the ACC/AHA guidelines. Moreover, at a time of economic restrictions, evidence that FFR-guided revascularization is cost-effective has influenced health-care stakeholders to request proof of the functional relevance of the coronary stenosis before PCI as a prerequisite for reimbursement of procedural costs.

Importantly, the widespread adoption of FFR-guided decision-making in contemporary revascularization guidelines has been based on a single discrete cut-off value to identify stenoses that should be revascularized, which has limited the requirement for a thorough understanding of the physiological basis and diagnostic characteristics of this comprehensive tool. This incomplete understanding is an obstacle, not only for the adequate use and interpretation of FFR, but also for the understanding of new and future modalities of physiological functional intracoronary testing. In this Review, we revisit the fundamental elements of coronary physiology in the absence or presence of CAD, to provide insight into the essential characteristics of FFR as a diagnostic tool in contempo-
rary clinical practice. Our aims are to explain the fundamental limitations of FFR-based stenosis evaluation, and clarify essential differences between FFR and other tests for the assessment of functional stenosis severity. Understanding these fundamental principles will advance the interpretation of FFR, and extend the comprehension of future developments in the physiological evaluation of CAD.

**PHYSIOLOGICAL FOUNDATIONS OF FFR**

The concept of FFR is based on a simplified theoretical framework of the coronary circulation. To appreciate the implications of this simplification, the essential elements of coronary physiology in the absence or presence of obstructive CAD, as well as the fundamental principles of the FFR concept, must first be understood.

**Control of myocardial blood flow**

Coronary blood flow is modulated by regulation of vascular tone at multiple levels in the coronary tree through changes in intrinsic myogenic tone, endothelial cell signalling, metabolic effectors, and neurohumoral control. The combination of these processes is termed coronary autoregulation. At a constant level of myocardial demand, coronary autoregulation responses induce dilatation and constriction of coronary arterioles to ensure constant coronary blood flow within a physiological range of coronary perfusion pressures. Similarly, at a constant coronary perfusion pressure, coronary blood flow can increase in response to increased myocardial demand; this phenomenon is called metabolic adaptation. Autoregulation and metabolic adaptation are inter-related, and maintain coronary blood flow at a level that accommodates myocardial demand (Figure 1).

During maximal vasodilatation of the coronary vascular bed, a state referred to as maximal hyperaemia, arteriolar control of coronary blood flow is largely abolished, and coronary blood flow then depends on perfusion pressure (Figure 1). The relationship between perfusion pressure and coronary blood flow during hyperaemia is not linear—it is straight within the physiological perfusion pressure range, but curves towards the pressure axis at lower perfusion pressures. Moreover, within this physiological perfusion pressure range, the relationship between pressure and flow is straight but not linear, since linearity requires the curve to be straight over the full pressure range and to pass through the origin (Figure 1). The relationship is most accurately described as incremental–linear. These characteristics of the relationship between perfusion pressure and coronary flow are important in all physiological concepts related to the evaluation of the functional severity of coronary lesions, and have implications for the validity and limitations of these concepts.
effects of stenoses on pressure and flow

An epicardial stenosis causes a pressure drop over the narrowed epicardial segment, thereby limiting coronary blood flow to the distal myocardium. The total pressure drop across a stenosis is the sum of losses caused by viscous friction along the entrance and throat of the lesion that increase with flow in a linear fashion (according to Poiseuille’s Law), and losses incurred by convective acceleration along the narrowed section (according to Bernoulli’s Law). These losses are not recovered at the exit of the stenosis, owing to flow separation and eddy formation as the high-velocity jet leaves the stenosis (Figure 2). These exit losses increase with the square of flow velocity, and the resulting graphical representation has a curvilinear shape (Figure 3). For a given stenosis geometry, the relationship between the pressure drop and flow velocity describes its particular haemodynamic characteristics (Figure 3). This relationship is described by the quadratic equation ΔP = Av + Bv^2, where ΔP is the pressure drop across the stenosis, v is flow velocity, and the coefficients A and B are a function of stenosis geometry and rheological properties of blood. The most-important geometric parameter is the minimum diameter of the stenosis, the inverse fourth power of which is in the equations of both A and B. Without a diameter reduction, the equation reduces to the linear (Poiseuille) term (Fig-

Figure 1 | The coronary pressure–flow relationship. Coronary blood flow at rest (solid lines) is controlled to match myocardial oxygen demand and to counteract variations in perfusion pressure by parallel changes in microvascular resistance, resulting in an autoregulatory plateau. During coronary vasodilatation, control is exhausted and blood flow depends on perfusion pressure (dotted line). The coronary pressure–flow relationship is concave at low perfusion pressures. The zero-flow intercept on the pressure axis (Pzf) slightly exceeds venous pressure (Pv). Straight extrapolation of the hyperaemic pressure-flow relationship results in an incremental–linear relationship that intercepts the pressure axis at the coronary wedge pressure (Pw), which incorporates collateral flow, heart rate, and ventricular wall tension. Small vessel disease or abnormal left ventricular function decreases the slope of the pressure-flow relationship (curved arrow). Elevated left ventricular end-diastolic pressure or left ventricular hypertrophy cause a parallel shift to the right (straight arrow).

Effects of stenoses on pressure and flow
Figure 2 | Diagram of stenosis flow field. The pressure gradient across a stenosis is determined by the sum of viscous and separation losses. Pressure is lost owing to viscous friction along the entrance and throat of the narrowed section (Poiseuille’s law). In addition, the area reduction leads to convective acceleration along the stenosis, whereby pressure is converted to kinetic energy (Bernoulli’s law). Flow separation and the formation of eddies prevent complete pressure recovery at the exit. Measurement of intracoronary haemodynamics includes proximal perfusion pressure (Pa), coronary pressure and flow velocity distal to the stenosis (Pd and Vd, respectively), and the venous pressure (Pv), which is usually assumed to be negligible. ∆P is the difference between Pd and Pa. Normal diameter (Dn), stenosis diameter (Ds), proximal velocity (Vn), and stenosis velocity (Vs) are indicated.

Figure 3 | The relationship between stenosis pressure drop and flow velocity. This relationship describes the haemodynamic characteristics for a given stenosis geometry, and becomes steeper with increasing stenosis severity (from stenosis A to C). The pressure drop (ΔP) at rest (blue squares) and at maximal hyperaemia (red circles) is determined by baseline microvascular resistance and the vasodilatory capacity of the downstream resistance vessels. The relationship between ΔP and flow velocity (v) is described by ΔP = Av + Bv^2, where the first and second terms represent the losses caused by viscous friction and flow separation at the exit, respectively. The coefficients A and B are a function of stenosis geometry and the rheological properties of blood. The flow-limiting behaviour of a coronary stenosis is largely caused by the inertial exit losses that scale with the square of the flow. Without a stenosis, the second term is zero, and ΔP = Av.
The plot of the pressure gradient against the flow velocity serves as the fingerprint of an individual stenosis, depicting how the translesional pressure drop is determined by the changes in flow through the stenosis, which in turn result from changes in distal microvascular resistance.

**Haemodynamic consequences of coronary stenoses**

In 1974, Gould et al. demonstrated that hyperaemic blood flow was affected only when the coronary lumen was reduced by at least 50%. Resting coronary blood flow remained unaltered until the coronary lumen diameter was reduced by at least 85%, because of the counteractive effects of coronary autoregulation. With progressive narrowing of the coronary lumen, coronary autoregulation maintains a constant coronary blood flow through compensatory vasodilatation of the distal coronary resistance vessels (Figure 4). This process results in a gradual reduction of the available coronary vasodilatory reserve, whereby the reserve is largely exhausted distal to stenoses >50%.

**Figure 4** | The coronary pressure–flow relationship in the absence and presence of stenosis. In the absence of stenosis, the hyperaemic coronary pressure–flow relationship is essentially straight with a nonzero pressure intercept. The resistance of an epicardial narrowing progressively limits maximal flow, thus reducing CFR, which is defined as the ratio of hyperaemic flow (Qs) to basal flow (Qb). The limiting effect of a stenosis on maximal flow is alternately expressed by FFR, which is fundamentally defined as the ratio of maximum flow in the presence of a stenosis (Qs) to maximum flow that could theoretically be achieved if there were no stenosis (Qn). Note that coronary input pressure is on the x-axis (unlike Figure 1). Venous pressure (Pv), the zero-flow intercept on the pressure axis (Pzf), and extrapolated wedge pressure (Pw) are indicated. Abbreviations: CFR, coronary flow reserve; FFR, fractional flow reserve.
lumen diameter. The concept of coronary flow reserve has been used as a measure of functional coronary lesion severity for many years. Coronary flow reserve is defined as the ratio of mean coronary blood flow during maximal hyperaemia to mean coronary flow during basal conditions (Figure 4), and reflects the magnitude of the vasodilatory reserve of the coronary circulation. However, because coronary flow reserve is expressed as a ratio, it is dependent on both basal and hyperaemic flow conditions, and its sensitivity to changes in basal flow is considered an important conceptual limitation. Basal flow is principally determined by the autoregulatory response to epicardial narrowing, but is also determined by physiological and pathophysiological factors unrelated to stenosis geometry or severity, albeit to a lesser degree. Consequently, the value of coronary flow reserve to define the functional severity of a stenosis is frequently assumed to be limited. With the introduction of easier-to-use physiological techniques based on intracoronary pressure, the limitations of the coronary flow reserve, as well as its relative complexity, have led to the abandonment of coronary flow reserve as a measure of functional lesion severity in daily clinical practice.

THE CONCEPT OF FFR

The development of an intracoronary pressure-derived method to determine the flow-limiting characteristics of a coronary stenosis by Young and colleagues in 1977 ultimately led to the introduction of the concept of FFR by Pijls and colleagues in 1993. In this concept, the maximally achievable myocardial flow in the presence of a stenosis, as a fraction of the maximal values that can be expected in the absence of a stenosis, is estimated from measurements of coronary pressure (Figure 4), a concept later termed myocardial fractional flow reserve (FFRmyo). The cornerstone of the concept on which FFR is based is the assumption of a proportional linear relationship between coronary perfusion pressure and flow during maximal dilatation of the coronary vascular bed. By extension, pressure measurements can, theoretically, be used to estimate coronary blood flow in the presence of a stenosis relative to coronary blood flow in the absence of a stenosis. If coronary pressure is indeed proportional to flow, the ratio between these flows can be obtained from a ratio between pressure measured distal to a stenosis by a sensor-equipped guidewire (theoretical coronary flow in the presence of a stenosis), and aortic pressure measured simultaneously by a pressure transducer connected to the arterial sheath (theoretical coronary flow in the absence of a stenosis). Therefore, this pressure ratio can be used to estimate the functional severity of a stenosis similar to the concept of coronary flow reserve (Figure 4).

As both distal coronary pressure and aortic pressure are measured during maximal vasodilatation, FFR is independent of factors influencing basal flow conditions. Moreover,
FFR is fairly unaffected by changes in haemodynamics, strengthening the applicability of FFR to estimate functional coronary stenosis severity relative to the coronary flow reserve concept.

FFRmyo is defined for the perfusion of the myocardium, but FFR can be calculated separately for the myocardium and the epicardial coronary artery. Calculation of the coronary FFR (FFRcor), which refers to the ratio of maximal blood flow in the target coronary artery to the hypothetical maximal blood flow in the same artery in the absence of a stenosis, requires the exclusion of contributions to myocardial blood flow other than the main coronary vessel, such as coronary collaterals or bypass grafts. Therefore, FFRcor is defined as \( \frac{P_d - P_w}{P_a - P_w} \), where \( P_a \) represents mean aortic pressure, \( P_d \) represents mean distal coronary pressure, and \( P_w \) represents coronary wedge pressure, which is assumed to be an estimate of collateral flow supply (Figure 4). FFRmyo refers to the ratio of maximal blood flow in the target myocardium to the hypothetical maximal blood flow in the same territory in the absence of a stenosis (FFRmyo = \( \frac{P_d}{P_a} \)). For simplicity, the use of FFR in place of FFRmyo has become customary, and we follow this format in this Review.

**FFR TO DOCUMENT MYOCARDIAL ISCHAEMIA**

**Cut-off validation for inducible ischaemia**

FFR has been validated extensively for its accuracy in identifying coronary stenoses that are associated with reversible myocardial ischaemia by noninvasive stress testing (Table 1). During the fairly short history of this technique, four different FFR values have been proposed as the optimal cut-off value to identify such stenoses. An FFR cut-off value of 0.66 was first proposed by De Bruyne and colleagues, as this value most-accurately reflected the results from electrocardiographic exercise tolerance testing, with an associated sensitivity and specificity of approximately 86%. A second cut-off value of 0.74 was proposed by Pijls et al. on the basis of a comparison with electrocardiographic exercise tolerance testing before and after revascularization. Shortly thereafter, an increased cut-off value of 0.75 was proposed, again by Pijls and colleagues, on the basis of a multitest comparison with electrocardiographic exercise tolerance testing, stress echocardiography, and myocardial perfusion imaging, and this cut-off value was adopted in the first decision-making studies using FFR, including the DEFER study. The extremely high diagnostic accuracy of these FFR cut-offs in the exercise tolerance testing and the multitest study (97% and 93%, respectively) was received with reluctance by many cardiologists, particularly when subsequent studies performed by other investigators repeatedly failed to demonstrate similar diagnostic efficacy. Nonetheless, in the DEFER study, delaying revascularization was shown to
<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients (lesions)</th>
<th>Ischaemic test</th>
<th>Best cut-off value</th>
<th>Accuracy (%)</th>
<th>Clinical setting</th>
</tr>
</thead>
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<tr>
<td><strong>Intravenous adenosine infusion (140 μg/kg/min)</strong></td>
<td></td>
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</tr>
<tr>
<td>Pijls (1995)&lt;sup&gt;116&lt;/sup&gt;</td>
<td>60 (60)</td>
<td>X-ECG</td>
<td>0.74</td>
<td>97</td>
<td>SVD</td>
</tr>
<tr>
<td>Pijls (1996)&lt;sup&gt;33&lt;/sup&gt;</td>
<td>45 (45)</td>
<td>X-ECG, MPS, DSE</td>
<td>0.75</td>
<td>93</td>
<td>SVD</td>
</tr>
<tr>
<td>Jimenez-Navarro (2001)&lt;sup&gt;119&lt;/sup&gt;</td>
<td>21 (21)</td>
<td>DSE</td>
<td>0.75</td>
<td>90</td>
<td>SVD</td>
</tr>
<tr>
<td>Rieber (2004)&lt;sup&gt;120&lt;/sup&gt;</td>
<td>48 (48)</td>
<td>MPS, DSE</td>
<td>0.75</td>
<td>76–81</td>
<td>MVD</td>
</tr>
<tr>
<td>Erhard (2005)&lt;sup&gt;121&lt;/sup&gt;</td>
<td>47 (47)</td>
<td>MPS, DSE</td>
<td>0.75</td>
<td>77</td>
<td>MVD</td>
</tr>
<tr>
<td>Hacker (2005)&lt;sup&gt;122&lt;/sup&gt;</td>
<td>50 (50)</td>
<td>MPS</td>
<td>0.75</td>
<td>86</td>
<td>SVD</td>
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<td><strong>271 (271)</strong></td>
<td>N/A</td>
<td><strong>0.75</strong></td>
<td><strong>87</strong></td>
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</tr>
<tr>
<td><strong>Intracoronary adenosine bolus (maximum 40–60 μg)</strong></td>
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<td></td>
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<tr>
<td>Tron (1995)&lt;sup&gt;123&lt;/sup&gt;</td>
<td>62 (70)</td>
<td>MPS</td>
<td>0.69</td>
<td>67</td>
<td>1, 2, and 3-VD</td>
</tr>
<tr>
<td>Bartunek (1997)&lt;sup&gt;124&lt;/sup&gt;</td>
<td>37 (37)</td>
<td>DSE</td>
<td>0.67</td>
<td>90</td>
<td>SVD</td>
</tr>
<tr>
<td>Caymaz (2000)&lt;sup&gt;125&lt;/sup&gt;</td>
<td>30 (40)</td>
<td>MPS</td>
<td>0.75</td>
<td>95</td>
<td>SVD</td>
</tr>
<tr>
<td>Fearon (2000)&lt;sup&gt;126&lt;/sup&gt;</td>
<td>10 (10)</td>
<td>MPS</td>
<td>0.75</td>
<td>95</td>
<td>SVD</td>
</tr>
<tr>
<td>Chamuleau (2001)&lt;sup&gt;127&lt;/sup&gt;</td>
<td>127 (161)</td>
<td>MPS</td>
<td>0.74</td>
<td>77</td>
<td>MVD</td>
</tr>
<tr>
<td>Seo (2002)&lt;sup&gt;128&lt;/sup&gt;</td>
<td>25 (25)</td>
<td>MPS</td>
<td>0.75</td>
<td>60</td>
<td>Previous MI</td>
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<td>Kruger (2005)&lt;sup&gt;129&lt;/sup&gt;</td>
<td>42 (42)</td>
<td>MPS</td>
<td>0.75</td>
<td>88</td>
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<td>Samady (2006)&lt;sup&gt;130&lt;/sup&gt;</td>
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<td>MPS, DSE</td>
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<td>92</td>
<td>Previous MI</td>
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<td>van de Hoef (2012)&lt;sup&gt;130&lt;/sup&gt;</td>
<td>232 (299)</td>
<td>MPS</td>
<td>0.76</td>
<td>74</td>
<td>MVD</td>
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<td><strong>Total or average (as applicable)</strong></td>
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<td>N/A</td>
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<td><strong>83</strong></td>
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</tr>
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<td>60 (60)</td>
<td>X-ECG, MPS</td>
<td>0.66</td>
<td>87</td>
<td>SVD</td>
</tr>
<tr>
<td>(Intracoronary papaverine or adenosine)</td>
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<tr>
<td>Bartunek (1996)&lt;sup&gt;131&lt;/sup&gt;</td>
<td>75 (75)</td>
<td>DSE</td>
<td>0.75</td>
<td>81</td>
<td>SVD</td>
</tr>
<tr>
<td>(Intracoronary papaverine or adenosine)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Abe (2000)&lt;sup&gt;132&lt;/sup&gt;</td>
<td>46 (46)</td>
<td>MPS</td>
<td>0.75</td>
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<td>SVD</td>
</tr>
<tr>
<td>(Intravenous ATP)</td>
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<td></td>
</tr>
<tr>
<td>De Bruyne (2001)&lt;sup&gt;133&lt;/sup&gt;</td>
<td>57 (57)</td>
<td>MPS</td>
<td>0.78</td>
<td>85</td>
<td>Previous MI</td>
</tr>
<tr>
<td>(Intravenous or intracoronary adenosine, or intravenous ATP)</td>
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<td></td>
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<tr>
<td>Yanagisawa (2002)&lt;sup&gt;134&lt;/sup&gt;</td>
<td>165 (194)</td>
<td>MPS</td>
<td>0.75</td>
<td>76</td>
<td>Previous MI</td>
</tr>
<tr>
<td>(Intracoronary papaverine)</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Ziaee (2004)&lt;sup&gt;135&lt;/sup&gt;</td>
<td>55 (55)</td>
<td>MPS, X-ECG, DSE</td>
<td>0.75</td>
<td>88</td>
<td>Ostial</td>
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<tr>
<td>(Intravenous or intracoronary adenosine)</td>
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<td></td>
</tr>
<tr>
<td>Morishima (2004)&lt;sup&gt;136&lt;/sup&gt;</td>
<td>20 (20)</td>
<td>MPS</td>
<td>0.75</td>
<td>85</td>
<td>SVD</td>
</tr>
<tr>
<td>(Intracoronary papaverine)</td>
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<td></td>
<td></td>
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<tr>
<td>Kobori (2005)&lt;sup&gt;137&lt;/sup&gt;</td>
<td>147 (155)</td>
<td>MPS</td>
<td>0.75</td>
<td>70</td>
<td>Restenosis</td>
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<td>(Intracoronary papaverine)</td>
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*Note: X-ECG denotes exercise electrocardiography, MPS denotes myocardial perfusion scintigraphy, DSE denotes dobutamine stress echocardiography, ISR denotes in-stent restenosis, and MVD denotes multivessel disease.*
be safe in lesions with an FFR ≥0.75. In the multitest validation study an FFR <0.75 had been shown conclusively to detect haemodynamically relevant stenoses (with 100% sensitivity); however, an FFR >0.80 had a >90% sensitivity to exclude the presence of ischaemia-generating stenoses. 33 The latter was, therefore, proposed as a fourth FFR cut-off value.7,8,40 Investigators in the subsequent decision-making FAME 7 and FAME 240 studies, in which the added value of FFR-guided clinical decision-making was evaluated, have used the 0.80 FFR cut-off value. These studies provided evidence for the clinical benefit of FFR-guided revascularization at the 0.80 cut-off value, and have defined the role of FFR in daily clinical practice. 7,40 In clinical practice, revascularization is currently recommended for lesions with an FFR <0.75, whereas deferral of revascularization is advocated for lesions with an FFR >0.80, and the existence of an FFR 'grey zone' from 0.75 to 0.80 is widely recognized. 10,41,42 Within this range, revascularization should be based on broadened clinical judgement, including assessment of anatomical features, symptoms, results of noninvasive testing (where available), and the patient-specific risk–benefit profile.42-44 In addition to this grey zone, originating from the dichotomized validation of FFR, biological variance in physiological parameters can lead to uncertainty in decisions based on rigid cut-off values, specifically in patients whose FFR values lie close to the cut-off threshold.45 In general, these findings emphasize the important limitations of a fixed cut-off value within a variable biological system, which should be taken into consideration in clinical decision-making. With such an approach, clinical outcomes after FFR-guided revascularization are excellent compared with those after angiographic guidance.46 The recognition of a diagnostic FFR grey zone is of particular importance when considering the pivotal FAME 2 study,60 in which the added value of coronary revascularization was compared with optimal medical therapy in patients with a coronary stenosis with an FFR ≤0.80. Revascularization of lesions with an FFR value

<table>
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<tr>
<th>Study</th>
<th>Number of patients (lesions)</th>
<th>Ischaemic test</th>
<th>Best cut-off value</th>
<th>Accuracy (%)</th>
<th>Clinical setting</th>
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<td>Ragosta (2007)138</td>
<td>36 (36)</td>
<td>MPS</td>
<td>0.75</td>
<td>69</td>
<td>MVD</td>
</tr>
<tr>
<td>(Intracoronary adenosine, 30–40 µg in the RCA, 80–100 µg in the LCA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total or average (as applicable)</td>
<td>661 (698)</td>
<td>N/A</td>
<td>0.74</td>
<td>81</td>
<td>N/A</td>
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<td>Total or average (as applicable) for all studies</td>
<td>1545 (1701)</td>
<td>N/A</td>
<td>0.74</td>
<td>83</td>
<td>N/A</td>
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</tbody>
</table>

*Data overlap with Chamuleau et al.127 and include all data from Meuwissen et al.67 †n = 26 for MPS. §n = 98 for MPS. Abbreviations: DSE, dobutamine stress echocardiogram; ISR, in-stent restenosis; LCA, left coronary artery; MI, myocardial infarction; MPS, myocardial perfusion scintigraphy; MVD, multivessel disease; NA, not applicable; RCA, right coronary artery; SVD, single vessel disease; VD, vessel disease; X-ECG, exercise electrocardiography.
≤0.80 was associated with a significantly lower rate of major adverse cardiac events than medical therapy at 1-year follow-up (4.3% versus 12.7%; HR 0.32, 95% CI 0.19–0.53, P <0.001). However, approximately 80% of patients with a stenosis with an FFR ≤0.80 in whom revascularization was deferred did not have associated major adverse cardiac events, and approximately 70% did not require revascularization at all within the first year of follow-up. These data indicate that strict adherence to the 0.80 FFR cut-off value might not provide optimal discrimination between functionally relevant and nonrelevant coronary stenoses in all patients with stable CAD. FFR versus noninvasive testing

Myocardial ischaemia results not only from obstructive epicardial CAD, but also from endothelial dysfunction, structural microcirculatory remodelling, and extravascular compression of the collapsible elements of the microcirculation. The proposed use of FFR as a surrogate for noninvasive testing to detect reversible myocardial ischaemia has led to some misunderstanding of the characteristics of this diagnostic tool. To state that FFR is the invasive ‘gold standard’ for the detection of inducible myocardial ischaemia, as is becoming customary, is conceptually inaccurate, as discussed below.

Noninvasive imaging techniques, either radionuclide-based or ultrasound-based, identify the presence of ischaemic myocardium on the basis of cellular or myocardial dysfunction—altered K+ permeability of cell membranes, or decreased myocardial contractility, respectively. These modalities can be used to determine the presence and extent of myocardial ischaemia, and also allow the identification of necrotic myocardium. Nonetheless, noninvasive detection of myocardial ischaemia is sensitive to the additive effect of concomitant triggers of ischaemia, such as tachycardia, high left ventricular filling pressures, increased wall stress, and enhanced myocardial contractility. Likewise, ischaemia generated by conditions other than obstructive epicardial CAD, such as microvascular disease, results in similar abnormalities as seen by noninvasive imaging and is, therefore, undistinguishable from ischaemia originating exclusively from epicardial CAD. In addition, noninvasive imaging techniques can isolate ischaemia at the level of myocardial territory, but cannot necessarily define the causal vessel or lesion, especially in patients with multivessel CAD.

Physiological techniques, in which intracoronary guidewires are used, do not provide insight into the consequences of CAD, but only into the flow-limiting characteristics of the epicardial stenosis. Moreover, myocardial ischaemia generated by increased myocardial oxygen demand cannot be directly detected by intracoronary physiological measurements. FFR has been validated against noninvasive stress testing to determine a cut-off value that, in general, can be expected to relate to inducible myocardial ischaemia. However, such a direct relationship with myocardial ischaemia depends on the effects of abnormalities throughout the coronary circulation and microcirculation and, therefore, differs between individual patients. Moreover, increased myocardial oxygen demand is assumed to be mirrored by a physiological increase in coronary flow, which
can supposedly be mimicked pharmacologically, for example by the administration of a potent arteriolar vasodilator, such as adenosine. However, no direct comparison of noninvasive and intracoronary functional testing to determine coronary flow, increased physiologically or pharmacologically, has been reported.

Quantifying the extent of ischaemic myocardium is important. The identification of stenoses causing impairment in blood supply to a large area of myocardium is of paramount importance because, in such patients, revascularization improves not only symptoms, but also prognosis. The extent of the ischaemic myocardium cannot be derived from FFR alone, but requires additional assessment of the subtended myocardium using objective noninvasive assessment or subjective estimates made on the basis of the distribution of the main epicardial vessel and its branches. Nonetheless, by definition, FFR provides a more-accurate insight into the functional severity of epicardial disease than visual estimation on coronary angiography. As such, appropriate use of FFR yields a favourable long-term prognosis for patients in the clinical setting by limiting revascularization to stenoses that are likely to cause myocardial ischaemia, rather than all stenoses deemed to be important by angiography.

In the absence of a true clinical gold standard for defining inducible myocardial ischaemia, emphasizing the synergistic value of noninvasive and intracoronary functional testing is important because, in many situations, assigning noninvasively identified ischaemic myocardium to a specific coronary stenosis can be challenging. Under such circumstances, intracoronary physiological testing allows selective assessment of the haemodynamic repercussions of coronary stenoses on myocardial perfusion and, thereby, identifies the stenosis most likely to be ischaemia-generating.

**ASSUMPTIONS AND LIMITATIONS OF FFR**

The simplified theoretical framework of FFR is based on two important assumptions about the characteristics of coronary physiology relevant to the relationship between coronary pressure and flow, and coronary microvascular resistance. These assumptions are not necessarily valid, as outlined in the following sections, and fundamentally limit the diagnostic accuracy of FFR.

**Assumed linearity between pressure and flow**

The concept of FFR is based on the assumption that the relationship between coronary perfusion pressure and flow during maximal coronary vasodilatation is proportional-linear; a given stenosis affects distal coronary pressure to the same proportion as it affects distal coronary flow. However, such a true linear relationship between these two variables does not exist, even during maximal vasodilatation. The actual pres-
sure–flow relationship is curvilinear; it is incremental–linear in the physiological range of perfusion pressures and has a nonzero pressure intercept—coronary blood flow ceases at a perfusion pressure of approximately 20 mmHg. Venous backpressure, collateral flow, epicardial capacitance (which describes the effect of blood storage in epicardial vessels during systole and its subsequent discharge into subendocardial vessels during diastole), and intramyocardial compliance also contribute to the intercept pressure (Figure 1). Venous pressure was subtracted from both aortic and distal coronary pressure in the experimental validation of FFR. However, this correction is not often performed in daily clinical practice as venous pressure is usually very low, and its influence is consequently considered negligible in comparison with the other determinants of the nonzero pressure intercept. Moreover, measurement of venous pressure requires an additional venous puncture, which adds to the inconvenience and discomfort associated with the physiological assessment.

**Minimal and stable microvascular resistance**

In addition to the nonzero pressure intercept that interferes with the linearity assumption in the concept of FFR, a linear relationship between coronary pressure and flow during coronary vasodilatation can be assumed only if coronary resistance during this condition is minimal and stable. The actual resistance values cannot be obtained by pressure measurements alone; therefore, coronary resistance must be assumed to be constant and minimal to be able to rely on pressure measurements alone. Before discussing the difficulties with, and implausibility of, achieving absolute minimal microvascular resistance during pharmacological vasodilatation, we shall first discuss the fundamental limitation of the necessity for this assumption.

FFR is a pressure-based estimate of the ratio between coronary blood flow in the presence of a stenosis and coronary blood flow in the absence of a stenosis, so the assumption of linearity, and thus the assumption of minimal and stable microvascular resistance, has to hold true in both the presence and the absence of an epicardial stenosis. Perfusion pressures in the presence or absence of a stenosis (distal pressure and aortic pressure, respectively), however, are different. Therefore, the assumption that coronary microvascular resistance is minimal and stable in both the absence and the presence of an epicardial stenosis implies that distal coronary resistance vessels are rigid tubes that do not change in diameter with changes in perfusion pressure. However, abundant evidence in the physiological literature indicates that, like epicardial coronary arteries, coronary resistance vessels are pressure-distensible and that their resistance to flow increases with decreasing distal perfusion pressure, and vice versa. Verhoeff et al. reported a fall in minimal microvascular resistance in response to restoration of coronary perfusion pressure by PCI, which yielded values below that of minimal microvascular resistance in the reference vessel. Such findings are in accordance with the results from
the experimental validation of FFR, in which a progressive overestimation of true coronary blood flow by the pressure-based FFR was noted with increasing stenosis severity.\textsuperscript{32} Therefore, the necessity to assume a stable and minimal resistance rather than actually measuring its status is a potential source of error in the assessment of FFR.

The use of an empirically determined FFR cut-off value could compensate in part for the relative error induced by the inaccuracy of assumptions underlying the concept of FFR. However, as previously discussed, the relationship between coronary pressure and flow is heavily dependent on external factors (Figure 1), whose degree of interference differs from patient to patient, and even within a single patient when haemodynamic conditions or myocardial contractility change. In addition, minimal microvascular resistance was shown to be highly variable between patients, and even between adjacent perfusion territories (discussed below), adding variability within as well as between patients.\textsuperscript{62-64} The relative error induced by the inaccuracy of these assumptions, therefore, differs for each patient, and even for each lesion, and this variable error cannot be accounted for by an empirically determined cut-off value.

**MEASURING PRESSURE AND FLOW TOGETHER**

A full interrogation of the physiological severity of a coronary lesion can be performed only by the simultaneous assessment of intracoronary pressure and flow, which enables the relative contributions of epicardial and microvascular resistance to the impairment of coronary flow to be identified. The potential to evaluate the magnitude of microvascular resistance is of great importance, because the position along the pressure–flow curve where the physiological measurement is performed during pharmacological vasodilatation is determined by the flow through the stenosis, which changes with microvascular resistance (Figure 5). As such, microvascular resistance is the critical determinant of the magnitude of pressure and flow that can be achieved at maximal vasodilatation for a specific stenosis, and is, therefore, an important determinant of FFR (Figures 5 and 6).

A guidewire equipped with both a pressure and a Doppler flow velocity sensor is now available, allowing simultaneous assessment of intracoronary pressure and flow velocity in daily practice.\textsuperscript{65} This device has enabled detailed studies of coronary haemodynamics, and physiological indices derived from such combined measurements are highly accurate surrogates for inducible myocardial ischaemia.\textsuperscript{66-68} Nonetheless, the use of these guidewires has not been extensively adopted in daily clinical practice owing to its complexity and the low level of interest from industrial partners to improve the technical features of the combined measurement system. Moreover, the concept of FFR is attractive because of its simplicity, which is endorsed by the perception of clinical cardiologists and industrial partners that coronary pressure alone is sufficient for diagnostic purposes in
Figure 5 | Effect of changes in hyperaemic microvascular resistance on FFR and CFVR. Variability in minimal MR changes the achievable CFVR and FFR in opposite directions: increased minimal microvascular resistance reduces hyperaemic blood flow (lower CFVR), and consequently decreases the pressure gradient across the stenosis, thereby increasing FFR. The dashed lines indicate clinically applicable cut-off values. Abbreviations: CFVR, coronary flow velocity reserve; FFR, fractional flow reserve; MR, microvascular resistance.

Figure 6 | Relationship between coronary flow velocity and the distal:aortic pressure ratio during the vasodilatory response to adenosine. FFR, expressed as distal to aortic pressure ratio (Pd/Pa), decreases when microvascular resistance is reduced by administration of adenosine. Conversely, CFVR (hyperaemic velocity/basal velocity) increases with decreasing microvascular resistance. For a mild stenosis, dilatation of resistance vessels has little effect on FFR, but a large effect on CFVR. By contrast, for a severe stenosis, the decrease in microvascular resistance has a large effect on FFR, whereas the effect on CFVR is small.
routine coronary interventional practice. At present, assessment of optimal intracoronary haemodynamic signals with the currently available combined system is dependent on operator experience with this specific device. Universal adoption will depend on technical advancements to improve the simplicity and, therefore, the clinical applicability of simultaneous measurements of coronary pressure and flow.

**Pharmacological maximal vasodilatation**

The achievement of maximal hyperaemia, which requires reaching minimal microvascular resistance, is believed to be essential for the application of FFR, but is less attainable than is currently acknowledged. Two factors are required for pharmacological maximal vasodilatation—an appropriate pharmacological mediator and administration of that mediator at a dose that allows for maximal vasodilatation, but does not cause insurmountable adverse effects. Adenosine is the most widely used vasodilatory agent in FFR-validation studies, and is the agent recommended for use in contemporary clinical studies. However, the complex physiological mediation of vascular tone would need to be abolished completely by adenosine alone in order for maximal vasodilatation to be induced in this manner. Moreover, the vasodilatory response to a standardized dose of adenosine would have to be similar in character and magnitude in all patients.

**Adenosine: pharmacology and function**

Adenosine is a naturally occurring nucleoside that is formed within the myocytes as a catabolite of ATP, cyclic AMP, and S-adenosyl homocysteine. Adenosine is released with increases in heart rate, or enhanced ventricular function during sympathetic activation, and is rapidly removed from the circulation by high-affinity uptake by red blood cells and direct deamination. Adenosine increases the level of cytosolic cyclic AMP, as the second messenger for vasomotion, by directly interacting with the purinergic subclass A2 receptors. The vasodilatory effects of adenosine occur primarily through effects on the microcirculation, whereas the nucleoside has very little effect on the epicardial conduit arteries. Originally, owing to its position within ATP metabolism, adenosine was thought to be the only substance mediating metabolic regulation of coronary blood flow during both stress and ischaemia. Currently, adenosine is seen as just one of numerous mechanisms that provide metabolic regulation of coronary blood flow, including nitric oxide and activation of ATP-dependent K+ channels. Endogenous adenosine has a role in cardioprotection and pain sensation during myocardial ischaemia, and attenuates left ventricular hypertrophy. Clearly, adenosine is a general cardiac mediator, and has a pivotal role in the physiological response in numerous circumstances.
Adenosine and coronary vasodilatation

The assumption that the administration of adenosine in a standardized dose induces complete elimination of vascular tone in all patients is challenged by several well-known mechanisms that have an important role in daily clinical practice. First, $\alpha$-adrenergic vasoconstriction, which limits the increment in coronary flow, has an important role in the coronary circulation, particularly in patients with atherosclerosis and during PCI. Both phentolamine (which blocks the $\alpha_1$ and $\alpha_2$ adrenergic receptors) and urapidil (a blocker of the $\alpha_1$ adrenergic receptor) can cause substantial reductions in the FFR value. Furthermore, the extent to which adenosine can counteract other mediators of coronary vasoconstriction, such as angiotensin, endothelin, serotonin, thromboxane A2, and vasopressin, is unknown. For example, angiotensin-converting-enzyme inhibition by enalaprilat was shown to cause substantial increases in coronary flow and reductions in FFR values; the investigators hypothesized that these observations occurred partially through a reduction in the level of endothelin-1. Nevertheless, and contrary to common belief, adenosine could be intrinsically unable to induce true maximal vasodilatation of the coronary vascular bed and, therefore, to induce a true maximal hyperaemic state in the coronary circulation. Consistent with this theory, hyperaemic microvascular resistance during vasodilatation induced by a standardized dose of adenosine is highly variable between patients, and even between adjacent perfusion territories within the same patient. Ultimately, the extent of the hyperaemic response during assessment of FFR is likely to depend on the equilibrium of all mediators of coronary vascular tone within an individual patient.

As discussed, the measured FFR value depends on the extent of the hyperaemic response achieved during pharmacologically induced vasodilatation, which is reflected in the achieved minimal microvascular resistance. Therefore, any unaccounted variability in minimal microvascular resistance will influence the FFR value (Figure 5). Moreover, the effect of this variability is much more pertinent in lesions within a clinically relevant range of stenosis severity than for minimally obstructed coronary arteries (Figure 6). Clearly, the variable reaction to adenosine influences the validity of the FFR concept and, therefore, the accuracy of FFR to determine the true functional consequences of a lesion. These uncertainties are not taken into consideration in current clinical practice, in which clinical decision-making is driven by rigid FFR cut-off values, and are another potential source of variability in FFR.

Increasing the dose of adenosine

Inadvertently, the lowest achievable FFR value is frequently used to determine 'maximal hyperaemia' or 'maximal vasodilatation'. Assuming that any patient will achieve a maximal hyperaemic state with the appropriate adenosine dose, several investigators have evaluated the effect of increasing doses of adenosine on the obtained FFR value. In-
cremental doses of adenosine of up to 720 µg (intracoronary administration) were found to induce substantially lower FFR values than routine intracoronary doses up to 60 µg or intravenous doses of 140 µg/kg/min. A high-dose intracoronary bolus of adenosine in addition to intravenous adenosine infusion was found to result in the lowest obtainable FFR values. These findings led the investigators incorrectly to conclude that increasing doses of adenosine increase the sensitivity of FFR to detect functionally important coronary lesions, ignoring the implications of the numerous FFR validation studies that have defined the association between FFR and myocardial ischaemia.

FFR has been validated against noninvasive stress testing with hyperaemia induced by adenosine at intracoronary doses of a maximum of 40–60 µg, or 140 µg/kg/min by intravenous infusion, yielding an optimal cut-off value for myocardial ischaemia of approximately 0.75 (Table 1 and Box 1).37

**Box 1 | Vasodilatation to determine fractional flow reserve**

*Epicardial vasodilatation:*
- Isosorbide dinitrate (≥200 µg, ≥30 s before measurement)

*Microvascular vasodilatation:*
- Intracoronary administration of adenosine (40–60 µg bolus injection)
- Intravenous infusion of adenosine (140 µg/kg/min for 2–3 min or until stable hyperaemia)
- Intracoronary papaverine* (10–12 mg for right coronary artery, 15–20 mg for left coronary artery)

*If adenosine is not available.

With the use of increasing doses of adenosine, reduced FFR values are unequivocally obtained, but to what extent can these FFR values be used as a surrogate to identify the presence of stenosis-related inducible myocardial ischaemia? For a given coronary stenosis, FFR generally decreases with increasing adenosine dose, which implies that FFR determined with high-dose adenosine results in a lower optimal cut-off value for inducible myocardial ischaemia than when FFR is determined with routine-dose adenosine in the same population. Increasing the dose of adenosine in the presence of borderline FFR values while adhering to routine cut-off values can, therefore, overestimate the functional repercussions of the coronary stenosis, and inadvertently lead to treatment of functionally unimportant coronary lesions. In daily practice, the adenosine doses that were used to define FFR thresholds for inducible myocardial ischaemia should be adhered to, and increasing adenosine doses or using unconventional vasodilatation strategies (for example, combining intravenous and intracoronary administration) should be avoided altogether.

**Route of adenosine administration**

Conflicting evidence exists on the appropriateness of intracoronary compared with intravenous administration of adenosine. Both techniques were used in the validation studies.
of FFR compared with noninvasive imaging modalities, and both have been associated with equivalent outcomes with respect to the diagnostic accuracy of FFR to identify stenoses associated with inducible myocardial ischaemia, and the optimal FFR cut-off value to do so (Table 1). Some reports show minor differences in FFR values between intracoronary and intravenous administration of adenosine. However, these differences are well within the repeatability range of subsequent FFR values, determined using separate intravenous adenosine infusions, 10 min apart (Table 2). The clinical outcomes of FFR-guided revascularization using low-dose intracoronary adenosine have been excellent, consistent with the interchangeability of intracoronary and intravenous administration to determine optimal cut-off values and ensure diagnostic accuracy. Consequently, intracoronary adenosine in doses of 40–60 µg can be considered an adequate and thoroughly validated alternative to intravenous adenosine.

Despite the equivalence of intracoronary and intravenous adenosine to determine FFR, these methods have different practical considerations. The intracoronary route is easy to use and is less time-consuming than intravenous administration. Therefore, intracoronary adenosine can be used easily for repeated evaluation of a single coronary lesion (for

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients (lesions)</th>
<th>Adenosine dose</th>
<th>Minimal FFR</th>
<th>P value</th>
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<td></td>
<td></td>
<td>Intravenous (µg/kg/min)</td>
<td>Intracoronary (µg)</td>
<td>Intravenous</td>
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<td>Jeremias (2000)99</td>
<td>53 (61)</td>
<td>140</td>
<td>15–20 (RCA), 18–24 (LCA)</td>
<td>0.78 ± 0.15</td>
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<td>De Bruyne (2003)100</td>
<td>21 (21)</td>
<td>140</td>
<td>40</td>
<td>0.61 ± 0.19</td>
</tr>
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<td>Casella (2004)105</td>
<td>50 (50)</td>
<td>140</td>
<td>Incremental doses of 60, 90, 120, and 150</td>
<td>NR</td>
</tr>
<tr>
<td>Koo (2005)101</td>
<td>20 (20)</td>
<td>140</td>
<td>40 (RCA), 80 (LCA)</td>
<td>0.78 ± 0.09</td>
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<tr>
<td>Yoon (2009)102</td>
<td>43 (44)</td>
<td>140</td>
<td>36–60 (RCA), 48–80 (LCA)</td>
<td>0.77 ± 0.10</td>
</tr>
<tr>
<td>Leone (2012)98</td>
<td>45 (50)</td>
<td>140</td>
<td>60</td>
<td>0.87 ± 0.07</td>
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<tr>
<td>Seo (2012)103</td>
<td>68 (68)</td>
<td>140</td>
<td>40 (RCA), 80 (LCA)</td>
<td>0.81 ± 0.10</td>
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<tr>
<td>López-Palop (2013)97</td>
<td>102 (108)</td>
<td>140</td>
<td>Incremental doses of 60, 180, 300, and 600</td>
<td>NR</td>
</tr>
</tbody>
</table>

Table 2 | Studies of intravenous versus intracoronary adenosine to induce maximal hyperaemia

Abbreviations: FFR, fractional flow reserve; LCA, left coronary artery; NR, not reported; NS, not significant; RCA, right coronary artery.
example, before and after PCI), or for multivessel interrogations. However, recording of the aortic pressure signal has to be interrupted for intracoronary administration and, therefore, the administration must be rapid, followed by a short saline flush, after which the stopcock should be switched back to record the aortic pressure signal. Importantly, care should be taken to start the FFR measurement only when the aortic pressure is accurately recording again.69 In addition, optimal engagement of the guiding catheter into the coronary ostium is critical to ensure accurate delivery of adenosine in the target artery.

Intracoronary administration of adenosine does not have the adverse effects associated with intravenous infusion, such as headache, blood-pressure drop, dyspnoea, and coughing. Aside from the issue of patient comfort, the substantial effects of intravenous adenosine on a patient’s haemodynamic state can inadvertently influence the results of the FFR measurement.106 By contrast, intravenous administration of adenosine, which results in a prolonged hyperaemic state, increases the amount of time available to obtain the FFR measurement. When using intravenous adenosine, care should be taken to obtain FFR measurements only after establishing a stable, hyperaemic state.7,40 Additionally, intravenous infusion enables a pressure pullback, a technique used to determine the precise location of haemodynamically important abnormalities in the presence of diffuse epicardial disease or serial coronary stenoses. A pressure pullback cannot be performed with intracoronary administration of adenosine because the hyperaemic reaction induced using this method is too short. Furthermore, for practical reasons, assessment of equivocal left main CAD can be performed more accurately with hyperaemia induced by intravenous adenosine than by intracoronary adenosine. Recommendations for the use of adenosine for vasodilatation in FFR in daily clinical practice are outlined in Box 1.

ADENOSINE-FREE LESION EVALUATION

Maximal vasodilatation is critical to the physiological assessment of functional lesion severity, but has a number of associated ambiguities. The interest in the assessment of functional lesion severity using parameters that do not require maximal vasodilatation using pharmacological agents, such as adenosine, has been piqued by two novel indices. Although several other vasodilator-free parameters derived from coronary flow or pressure have been evaluated over the past decade, none has been adopted into daily clinical practice owing to their limited diagnostic accuracy, or difficult acquisition method.68,107-112

Two novel indices that can be obtained during resting conditions—the basal stenosis resistance index (BSR)66 and the instantaneous wave-free ratio (iFR)106,113—have been proposed as alternatives to FFR in the past year. Whereas FFR requires adequate hyperaemia,
accurate discrimination of ischaemia-generating and nonischaemia-generating stenoses using BSR can be achieved by measuring both coronary pressure and flow velocity under resting conditions, and calculating the ratio of pressure gradient to distal flow velocity (the stenosis resistance index). The main advantage of the stenosis resistance index is that it is, by definition, less dependent than FFR on the extent of hyperaemia achieved. Furthermore, the stenosis resistance index calculated from measurements taken during hyperaemic conditions has a distinctly high diagnostic accuracy to determine lesion-related inducible myocardial ischaemia, indicating the high diagnostic potential of the stenosis resistance index in general. In iFR, discrimination between lesions that generate ischaemia and those that do not is based on the ratio of the distal coronary pressure to aortic pressure during a specific period in diastole, termed the wave-free period, during which time coronary flow is intrinsically at its highest. iFR can, therefore, be used effectively to identify ischaemia-producing lesions during resting conditions.

In the initial BSR validation study, the power of BSR to discriminate between ischaemia-generating and nonischaemia-generating stenoses identified through noninvasive stress testing was equivalent to that of FFR. iFR was evaluated in the ADVISE studies, in which favourable correlations between iFR and FFR were found, and the diagnostic accuracy of iFR to identify stenoses with an FFR ≤0.80 was high. In a subsequent study of iFR by other investigators, using a distinctly different algorithm to determine the wave-free period, a substantially lower diagnostic accuracy was found. However, a large meta-analysis including >1,500 stenoses confirmed the original findings on iFR diagnostic accuracy for FFR-identified relevant coronary stenoses, emphasizing the importance of appropriate iFR calculation. Although the results of the initial evaluation of these comprehensive novel techniques are favourable, they still require more-extensive validation and clinical evaluation before BSR and iFR can be considered true alternatives to FFR.

**CONCLUSIONS**

FFR is a surrogate for the noninvasive assessment of inducible myocardial ischaemia, and is of unequivocal clinical benefit in determining the need for revascularization in patients with stable CAD. The capacity of FFR to distinguish between ischaemia-generating and nonischaemia-generating lesions is supported by abundant evidence from large clinical outcomes studies. Nonetheless, clinical benefit does not prove that the assumptions underlying the concept of FFR are correct. This technique should, therefore, be interpreted as a surrogate measure with inherent assumptions and limitations. In this context, the ambiguities in achieving maximal vasodilatation, and the appropriate use of adenosine for FFR in daily clinical practice, should be acknowledged. When used appropriately by
experienced operators, FFR is currently the most-useful surrogate diagnostic tool for the assessment of inducible myocardial ischaemia available in cardiac catheterization, and is a valuable adjunct to coronary angiography to determine the need for revascularization. The use of FFR should be considered in the evaluation of any potentially equivocal coronary artery lesion.
REFERENCES


