Atherosclerotic coronary artery narrowings, which provoke myocardial ischemia are the most common cause of angina pectoris and lead to adverse cardiac events. Removing the ischemic potential of a stenosis decreases symptoms and improves outcomes. Invasive coronary angiography remains the primary method for identifying coronary artery stenoses, but its inability to diagnose lesions responsible for inducing myocardial ischemia, particularly those of intermediate diameter stenosis remains a major limitation. To address this issue, there has been a long-standing interest in coronary wire-based methods for assessing coronary artery physiology. The goal of this review is to describe past efforts, define current standards, and address remaining controversy in the area of the invasive functional assessment of intermediate coronary artery stenosis.

**Historical Perspective**

In the early 1970s, Gould et al performed seminal laboratory studies demonstrating that resting coronary flow remains unchanged with increasing epicardial coronary stenosis until the vessel lumen is >85% narrowed. They described the importance of inducing hyperemia to bring out the ischemic potential of more moderate coronary stenoses by measuring coronary flow reserve (CFR), defined as maximal coronary flow divided by resting flow. They showed that CFR had an inverse relationship to progressive coronary stenosis. However, it was not until the early 1990s, when a suitable Doppler wire became available to measure distal coronary flow velocity that invasive CFR and other velocity-based assessments could be performed readily in humans. Because coronary flow is proportional to coronary flow velocity, CFR can be estimated by measuring the coronary velocity at rest and during maximal vasodilation, typically after administration of adenosine.

Subsequently, several studies were performed demonstrating the ability of Doppler wire-derived CFR to identify physiologically important coronary narrowings and to guide percutaneous coronary intervention (PCI). These experiences, however, highlighted some important limitations of this technique, which hampered its widespread acceptance. The technical aspects of obtaining an acceptable Doppler signal challenged even experienced interventional cardiologists. The lack of an absolute normal value of CFR made interpretation more difficult. Although a CFR <2 is considered abnormal, a value of 3, for example, may also be abnormal in a diseased vessel, which normally has a CFR of 6. In addition, because resting flow is part of the definition of CFR, changes in heart rate, blood pressure, or left ventricular contractility, which alter resting flow significantly affect the reproducibility of CFR. Finally, CFR by definition interrogates the status of the entire coronary circulation, both the epicardial vessel and the microcirculation. In a patient with microvascular dysfunction, CFR in a vessel free of epicardial disease will be abnormal, limiting the use of CFR for separating ischemia-producing epicardial disease from concomitant microvascular dysfunction. To overcome this limitation, the concept of relative CFR was introduced, normalizing the CFR in a vessel with epicardial disease to another vessel without epicardial disease, assuming microvascular dysfunction is global. However, microvascular dysfunction may not be global and this index involves instrumenting 2 coronary arteries, adding to the time and complexity of measurement. For all these reasons, routine measurement of CFR or relative CFR to interrogate intermediate coronary lesions is no longer performed commonly, although it remains possible with dual pressure/flow guidewires.

The importance of measuring translesional pressure gradients to gain further insight into the hemodynamic consequences of an epicardial stenosis has also been recognized for many years. Grünzig et al assessed the adequacy of the first percutaneous transluminal coronary angioplasty by measuring the residual resting pressure gradient across the treated lesion. These initial efforts were hampered by the overestimation of pressure gradients because of the size of the end-hole catheters used to measure distal pressure and by the lack of greater appreciation for the importance of measuring the hyperemic ratio of distal to proximal pressure, as opposed to the absolute resting gradient. During the 1990s, the development of a 0.014" coronary pressure wire and the description and initial validation of myocardial fractional flow reserve (FFR) by Pijs et al and De Bruyne et al ushered in the modern era of the invasive assessment of coronary physiology.

**Fractional Flow Reserve**

FFR is defined as the maximum myocardial blood flow in the presence of an epicardial stenosis compared with the maximum flow in the hypothetical absence of the stenosis. Myocardial flow is equal to the change in pressure across
the microvasculature (distal coronary pressure minus venous pressure) divided by the resistance. Because venous pressure is generally negligible compared with coronary pressure, it is typically eliminated from the equation for FFR. After administration of nitroglycerin, the epicardial artery resistance is minimized, and after administration of a microcirculatory vasodilator, such as adenosine, the microvascular resistance is minimized, at which point coronary pressure becomes proportional to flow. In a normal epicardial vessel, there is little pressure loss along its course meaning proximal and distal pressure are equal; in a diseased vessel, proximal pressure is a reflection of what distal pressure or flow would be in the absence of a stenosis, assuming the minimal microvascular resistance is similar in the presence and the absence of a stenosis. Therefore, FFR can be calculated by dividing the mean distal coronary pressure (representative of maximal myocardial flow in the presence of a stenosis) measured with a pressure wire, by the mean proximal coronary pressure (representative of what the distal pressure or flow would be in the absence of a stenosis) measured simultaneously with a guide catheter, during maximal hyperemia. This ratio is a reflection of the fraction of normal flow reaching the region of myocardium subtended by the vessel being interrogated.

FFR has many unique attributes, which distinguish it from CFR and other invasive measures of coronary physiology and which have contributed to its widespread acceptance and use as the reference standard for assessing the physiological significance of epicardial coronary disease (Table 1). First, FFR can be measured relatively easily, safely, and with high reproducibility and low variability. In the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) trial, multivessel FFR assessment was performed in 496 patients without significant complication.16 When compared with angiography-guided PCI in this study, the procedure duration for FFR-guided PCI was identical. Recent studies have confirmed the high reproducibility of FFR on repeated measurements in the same vessel, with an r2=0.98 and a coefficient of variation of 3% (Figure 1).17 Because FFR is measured during maximal hyperemia, it is independent of the variability of resting flow. For example, 2 studies have shown that changes in heart rate, blood pressure, and left ventricular contractility do not significantly affect FFR.9,10

Other attributes of FFR include that it has a consistent normal value; it has been well-validated; and it has a narrow ischemic threshold. The normal FFR is 1.0 in every vessel and in every patient. In the landmark trial validating FFR, it was compared with the best available noninvasive reference standard for diagnosing ischemia.18 Because no single noninvasive stress test has a perfect accuracy for diagnosing ischemia, a combination of 3 different stress tests was used by the investigators to serve as the reference standard. According to sequential Bayesian analysis, if each of these tests has an accuracy of 80%, then the combination of all 3 will have an accuracy of >95%. In comparison with this noninvasive gold standard, an FFR cutoff of <0.75 to define significant ischemia had a sensitivity of 88%, specificity of 100%, and diagnostic accuracy of 93%. Subsequent studies and clinical experience have shown that incorporating a gray zone for FFR from 0.75 to ≤0.80 can improve the sensitivity, without dramatically affecting the specificity.19 If the FFR value is below 0.75, one can be certain myocardial ischemia can be induced in the territory subtended by the vessel being interrogated. If the FFR is >0.80 then one can be certain significant ischemia is not present. When the FFR falls in the gray zone, then one must use clinical judgment to decide whether revascularization is warranted.

The final and perhaps most important attribute of FFR is that it predicts outcomes and has been extensively validated in a wide variety of clinical settings and patient subsets both in multicenter, randomized, controlled trials and in real-world registries. Three large multicenter, randomized clinical trials have demonstrated the safety of deferring revascularization of vessels with a nonischemic FFR value (the DEFER trial),20 significantly improved clinical outcomes when using FFR to guide PCI in patients with multivessel coronary disease (the FAME trial),16 and significantly worse outcomes when deferring revascularization of vessels with an ischemic FFR value (the FAME 2 trial).2 FFR has been validated in a variety of patient populations and lesion subsets, including for assessing intermediate left main disease,21 serial lesions,22 bifurcation disease,23 diffuse disease,24 acute coronary syndrome patients,25,26 nonculprit vessels of patients with ST-segment–elevation myocardial infarction,27 and culprit vessels after remote myocardial infarction.28 Multiple large registries have also demonstrated improved outcomes when FFR is used to guide PCI and have shown improved decision

Table 1. Advantages of Fractional Flow Reserve

<table>
<thead>
<tr>
<th>Advantages of FFR</th>
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<tr>
<td>Normal value of 1.0 in every patient and vessel</td>
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<tr>
<td>Well-defined ischemic threshold of ≤0.80</td>
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<tr>
<td>Specific for the epicardial vessel</td>
</tr>
<tr>
<td>Independent of the microvasculature</td>
</tr>
<tr>
<td>Accounts for collateral flow</td>
</tr>
<tr>
<td>Independent of hemodynamic changes</td>
</tr>
<tr>
<td>Excellent reproducibility</td>
</tr>
<tr>
<td>Validated against a true noninvasive reference standard</td>
</tr>
<tr>
<td>Extensively validated against clinical outcomes in a variety of patient populations and lesion subsets</td>
</tr>
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</table>

FFR indicates fractional flow reserve.
making when FFR is used routinely during diagnostic angiography. Most recently, a large meta-analysis of >9000 patients confirmed that FFR demonstrates a continuous and independent relationship with clinical outcomes (Figure 2).

**Resting Measures of Coronary Physiology**

The earlier work by Gould et al stressed the importance of maximizing coronary flow by inducing hyperemia to best quantify the physiological effect of a stenosis. In the early 1990s, resting pressure gradients were compared with non-invasive reference standards and found to be inferior to FFR and, therefore, not pursued further. However, more recently, with the accumulation of data supporting the use of FFR, and as the application of FFR became more widespread, there has been growing interest in simplifying the technique. Because the requirement for achieving hyperemia when measuring FFR can add time, and when using intravenous adenosine, expense and patient discomfort, Mamas et al published their experience comparing resting distal pressure divided by proximal pressure (Pd/Pa) to FFR in 483 patients. They found a significant linear correlation between the two. To improve the accuracy of rest Pd/Pa, they proposed a hybrid approach of using rest Pd/Pa when it was ≤0.85, which had a positive predictive value of 95%, or ≥0.93, which had a negative predictive value of 96%, and measuring FFR if the rest Pd/Pa fell between these cutpoints. In their cohort, the Pd/Pa values fell above or below these cutpoints 66% of the time, meaning that adenosine would only be necessary in 34% of cases.

In 2012, Sen et al introduced a novel resting pressure-derived index called the instantaneous wave-free ratio (iFR). Using wave intensity analysis, these investigators proposed that during a portion of diastole, myocardial resistance is low and constant. By analyzing the Pd/Pa just during this period of diastole, they hypothesized that iFR might predict FFR without the need for adenosine. When comparing iFR with FFR across 157 stenoses, they found the optimal iFR cutoff of 0.83 had a sensitivity of 85% and a specificity of 91% for predicting FFR with a cutoff ≤0.80. In a subsequent registry of 312 patients with intermediate stenoses, these investigators found that the optimal iFR cutoff was 0.89 and it had a diagnostic accuracy of 80% for predicting an FFR≤0.80.

Other investigators, in an attempt to reproduce the above results with iFR, performed a prospective analysis comparing iFR with FFR across 206 lesions and found lower levels of agreement between the two. To resolve these discrepant findings, an independent core laboratory examined the diagnostic accuracy of iFR and rest Pd/Pa in comparison with FFR measured across 1593 lesions from 15 centers worldwide. This study found the optimal cutoff value for iFR was 0.90 for predicting an FFR≤0.80, with a diagnostic accuracy of 80.4%. The optimal cutoff value for rest Pd/Pa was 0.92, with a diagnostic accuracy of 81.5%. Because these results are not sufficient to allow iFR or rest Pd/Pa to replace FFR, the study also looked at a hybrid approach, in which case iFR or rest Pd/Pa would be relied on if they fell above or below certain thresholds and FFR would be measured if they fell between these cutpoints. For example, if one restricted the iFR range to ≤0.88 (to predict an FFR≤0.80) and ≥0.97 (to predict an FFR>0.80), one could achieve 90% agreement with FFR and avoid the need for adenosine in 65% of patients. If one desired a 95% agreement between iFR and FFR, one could avoid adenosine in 29% of cases. A similar pattern was found for rest Pd/Pa. A key question raised by this study is whether avoiding the need for adenosine is worth sacrificing the accuracy and data supporting lesion assessment with FFR.

**Other Proposed Indexes**

Recently, investigators have revisited measuring Pd/Pa after intracoronary contrast injection, contrast FFR. This index which does not require pharmacological hyperemia and which
can be performed quickly like resting indices, takes advantage of the modest hyperemia induced by contrast media and, therefore, may correlate more closely with FFR than resting indices. The hyperemic effect of contrast media has been appreciated for more than 50 years and was used in earlier coronary physiology studies. However, as contrast agents with lower osmolality which are less hyperemic became preferred for coronary angiography, and as studies showed the improved hyperemia achieved with agents like adenosine, the use of contrast media in coronary physiology studies declined. With the recent increase in enthusiasm to measure FFR as a result of the wealth of data supporting it and the desire to provide further justification for PCI, the urge to streamline FFR as much as possible has also increased. A small study reevaluating contrast FFR has found an improved correlation with FFR, as compared with what has been previously reported with resting indices, such as iFR and rest P/Pa. To prove that contrast FFR more accurately predicts FFR and can be measured as easily as resting indices, a large, multicenter, international study is now underway and will compare the correlations between contrast FFR, iFR, and rest P/Pa to FFR in 750 patients (www.clinicaltrials.gov NCT02184117).

Over the years, many other indices, such as translesional coronary flow velocity, slope of the instantaneous hyperemic diastolic coronary flow velocity-pressure relation, diastolic FFR, pulse transmission coefficient, diastolic flow velocity-pressure gradient relation, hyperemic stenosis resistance, coronary pressure notch, pressure drop coefficient, lesion flow coefficient, and basal stenosis resistance have been proposed for evaluating the physiological significance of intermediate coronary artery stenoses. However, none of these has gained widespread use either because of measurement complexity, lack of data supporting their use, or lack of any substantial advantage for FFR. The most recently proposed FFR-like indices are reviewed and compared with FFR in Table 2.

### Current Controversies

Although no invasive index for assessing the functional significance of an intermediate coronary stenosis is perfect, FFR is widely perceived to be the reference standard. There are some aspects related to the theory of FFR and to its actual measurement, which have created controversy. First, FFR theory states that during maximal hyperemia, when myocardial resistance is minimized and coronary autoregulation abolished, coronary pressure becomes proportional to flow, and therefore, myocardial flow in the presence of a stenosis can be determined by measuring distal coronary pressure. However, some have argued that this assumption is invalid because at low perfusion pressures the relationship between pressure and flow is no longer linear. In other words, coronary flow will stop before coronary pressure equals zero. This is because of the backpressure resulting from the myocardium and the coronary venous system. However, within the physiological range of pressures where FFR is measured, the linear relationship between pressure and flow exists and, therefore, this theoretical concern has not had clinical implications on the validity of FFR.

There has also been controversy over whether the minimal achievable microvascular resistance in the presence of a stenosis is equivalent to the resistance in the hypothetical absence of a stenosis. One study measuring microvascular resistance before and after uncomplicated PCI found lower levels of minimal resistance after PCI. This finding may be because of measurement error that occurred by not taking into account the contribution of collateral flow, which is greater in the presence of a stenosis and which when neglected leads to apparently higher levels of microvascular resistance. Earlier work and several follow-up studies performed by different investigators in both animals and humans have found that microvascular resistance is equivalent in both the presence and the absence of an epicardial stenosis when collateral flow is incorporated into the measurement.

Another concern about the actual measurement of FFR is its theoretical reliance on achieving maximal hyperemia. If maximal hyperemia does not occur, the flow across the stenosis may be less, the pressure gradient lower and the FFR overestimated. For these reasons, it is critical that when FFR is measured the hyperemic agent is administered correctly and in an adequate dosage (Table 3). If one is concerned that maximal hyperemia has not been achieved, an alternative pharmacological agent can be delivered. If there is still concern, microvascular resistance can be measured simultaneously with the same pressure wire, for example, by calculating the index of microcirculatory resistance using a thermodilution technique; in this manner, one can assess whether resistance is minimized and flow maximized. If the FFR is higher than expected based on the angiographic findings and the index of microcirculatory resistance is low, then one can be reassured that hyperemia has been achieved and the FFR result is valid. If FFR is high and index of microcirculatory resistance is high, then probably microvascular dysfunction is present, which may explain the presence of symptoms or ischemia. In this scenario, the use of intravenous adenosine is helpful because the symptoms and hemodynamic changes, which often occur are reassuring that hyperemia has been achieved. FFR is still valid in that it informs the operator that there is little to be gained by performing PCI; several studies demonstrate that PCI of the epicardial stenosis in this setting does not improve outcomes. To circumvent this requirement for maximal hyperemia, combined pressure and Doppler flow indices have been proposed. These require further validation and improvements in technology before they are used to augment FFR measurement.

Another issue raised about the need for maximal hyperemia concerns the fact that adenosine may not completely
abolish autoregulation and minimize microvascular resistance. Prolonged coronary occlusion probably produces the greatest degree of hyperemia, but is not practical in the clinical setting. The addition of other vasodilators on top of adenosine has been proposed and may further reduce FFR, however, in theory this would require recalibration of the FFR cutoff value for identifying lesions capable of causing myocardial ischemia. It is unlikely that an additional agent would create enough additional hyperemia such that an FFR with adenosine alone which is >0.80 would drop to <0.75. This may explain why measuring FFR with adenosine alone has proven to be so useful clinically, despite the theoretical possibility that in a small proportion of patients truly maximal hyperemia was not achieved.

Table 3. Hyperemic Agents Used for Coronary Physiology Assessment

<table>
<thead>
<tr>
<th>Agent</th>
<th>Route</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenosine</td>
<td>IV infusion</td>
<td>140 µg/kg per min</td>
<td>Reference standard. Side effects include dyspnea and chest pain. Prolonged hyperemia allows pressure wire pullback</td>
</tr>
<tr>
<td>Adenosine</td>
<td>IC bolus</td>
<td>&gt;100 µg</td>
<td>Easy to use, inexpensive, and no significant side effects. Transient heart block at high doses. Hyperemia lasts only 10–15 s</td>
</tr>
<tr>
<td>Adenosine</td>
<td>IC infusion</td>
<td>240–360 µg/min</td>
<td>Inconvenient set-up. Fewer side effects compared with IV infusion. Prolonged hyperemia allows pullback. Not well-validated</td>
</tr>
<tr>
<td>Regadenoson</td>
<td>IV bolus</td>
<td>400 µg</td>
<td>Convenient, single IV bolus. Expensive. Side effects similar to IV adenosine but less severe and briefer. Hyperemia lasts 20 s–10 min</td>
</tr>
<tr>
<td>Papaverine</td>
<td>IC bolus</td>
<td>10–20 mg</td>
<td>Easy to use, inexpensive. Rare, but significant side effect of polymorphic VT. Hyperemia lasts 30 s, allowing pullback</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>IC bolus</td>
<td>0.3–0.9 µg/kg</td>
<td>Easy to use, inexpensive. Major side effect is hypotension. Hyperemia lasts 50 s allowing pullback. Not well-validated</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>IV infusion</td>
<td>50 µg/kg/min</td>
<td>Inconvenient as it takes time for onset an offset. Side effects include palpitations and hypotension. Not well-validated for FFR</td>
</tr>
<tr>
<td>Nicorandil</td>
<td>IC bolus</td>
<td>2 mg</td>
<td>Not available in United States. Fewer side effects compared with IV adenosine. Hyperemia lasts 30 s. Not well-validated</td>
</tr>
</tbody>
</table>

FFR indicates fractional flow reserve; IC, intracoronary; IV, intravenous; and VT ventricular tachycardia.

A final issue with respect to measuring FFR that has created some controversy relates to whether it should be measured at the lowest level of $P_d/P_a$ or once stable hyperemia has occurred. This is only an issue with intravenous adenosine infusion because with intracoronary adenosine hyperemia is short-lasting and the hemodynamic effects much less pronounced. Even with intravenous adenosine, typically the lowest $P_d/P_a$ occurs during stable hyperemia. However, occasionally with the onset of the pharmacological action of intravenous adenosine complete microvascular dilation occurs before peripheral vasodilation and aortic pressure briefly rises, before falling. With complete microvascular dilation, coronary flow increases and is directly proportional to the aortic pressure. The greater aortic pressure can lead to greater flow and to a slightly lower $P_d/P_a$ compared with what is seen during stable hyperemia, which is typically marked by a lower aortic pressure.

Figure 3. Occasionally fractional flow reserve (FFR) tracing demonstrates the lowest distal coronary pressure/proximal coronary pressure ($P_d/P_a$) at the onset of hyperemia (A), before peripheral vasodilation has occurred, but after autoregulation has been abolished, such that coronary flow is proportion to aortic pressure and, therefore, slightly higher than after peripheral vasodilation has occurred. This brief period of slightly higher flow can lead to a lower $P_d/P_a$ compared with what is recorded when FFR is measured during stable hyperemia (B).
est Pd/Pa during stable hyperemia has also been highlighted. Flushing the guiding catheter, and checking for drift have been needed before advancing down the coronary pressure wire. Technical accuracy of FFR assessment depends on meticulous technique when measuring FFR. Technical factors that influence FFR include variable delivery, metabolism or effect of adenosine. These varied responses can lead to changing Pd/Pa during stable hyperemia (Figure 3). Fortunately, in the majority of cases, the differences in Pd/Pa are small and, therefore, they do not have a significant effect on determining lesion significance based on FFR.

Reports like these serve as a reminder about the importance of meticulous technique when measuring FFR. Technical issues such as the importance of equalizing the pressure wire to the guiding catheter pressure before advancing down the coronary, flushing the guiding catheter, and checking for drift have been discussed in more detail previously. Of note, advances in pressure wire technology, including current development of fiber-optic pressure sensor guidewires may further improve the accuracy of FFR assessment.

Conclusions
Identifying and revascularizing coronary lesions, which are responsible for producing myocardial ischemia improves symptoms and outcomes. Unfortunately, noninvasive stress imaging studies and coronary angiography alone have significant limitations, which make the invasive assessment of the physiological significance of an epicardial stenosis a critical component to guiding decisions about revascularization. According to current guidelines, FFR is the preferred method for achieving this important role.

Disclosures
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References
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Coronary Physiologic Indexes


Invasive Coronary Physiology for Assessing Intermediate Lesions

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