Three decades of research have repeatedly demonstrated the diagnostic and prognostic values of coronary flow reserve (CFR) in patients with coronary artery disease (CAD). Whether measured invasively or noninvasively, CFR has been shown to be able to identify patients with myocardial blood flow impairment, predict prognosis, and stratify which lesions may benefit from revascularization.1–7

In the cardiac catheterization laboratory, however, CFR has largely been replaced by a pressure-only measurement, fractional flow reserve (FFR), as the most common invasive tool to guide coronary revascularization. FFR uses a ratio between distal coronary and aortic pressures under conditions of maximal hyperemia8 to estimate the relative flow reduction.

Background—Coronary flow reserve has extensive validation as a prognostic marker in coronary disease. Although pressure-only fractional flow reserve (FFR) improves outcomes compared with angiography when guiding percutaneous coronary intervention, it disagrees with coronary flow reserve classification 30% of the time. We evaluated whether baseline instantaneous wave-free ratio (iFR) could provide an improved pressure-only estimation of underlying coronary flow reserve.

Methods and Results—Invasive pressure and flow velocity were measured in 216 stenoses from 186 patients with coronary disease. The diagnostic relationship between pressure-only indices (iFR and FFR) and coronary flow velocity reserve (CFVR) was compared using correlation coefficient and the area under the receiver operating characteristic curve. iFR showed a stronger correlation with underlying CFVR (iFR–CFVR, ρ=0.68 versus FFR–CFVR, ρ=0.50; P<0.001). iFR also agreed more closely with CFVR in stenosis classification (iFR area under the receiver operating characteristic curve, 0.82 versus FFR area under the receiver operating characteristic curve, 0.72; P<0.001, for a CFVR of 2). The closer relationship between iFR and CFVR was found for different CFVR cutoffs and was particularly marked in the 0.6 to 0.9 FFR range. Hyperemic FFR flow was similar to baseline iFR flow in functionally significant lesions (FFR ≤0.75; mean FFR flow, 25.8±13.7 cm/s versus mean iFR flow, 21.5±11.7 cm/s; P=0.13). FFR flow was higher than iFR flow in nonsignificant stenoses (FFR >0.75; mean FFR flow, 42.3±22.8 cm/s versus mean iFR flow, 26.1±15.5 cm/s; P<0.001).

Conclusions—When compared with FFR, iFR shows stronger correlation and better agreement with CFVR. These results provide physiological evidence that iFR could potentially be used as a functional index of disease severity, independently from its agreement with FFR. (Circ Cardiovasc Interv. 2014;7:492-502.)

Key Words: coronary disease ◼ fractional flow reserve, myocardial

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WHAT IS KNOWN

- Coronary flow reserve is a powerful predictor of outcomes in coronary artery disease.
- Recent studies have found that coronary flow reserve may be a better predictor of events when compared with fractional flow reserve.

WHAT THE STUDY ADDS

- Instantaneous wave-free ratio, a non-hyperemic pressure-only index of disease severity, relates more closely to underlying coronary flow than fractional flow reserve, particularly in the intermediate zone.
- In patients with coronary artery disease, adenosine only increases flow significantly above baseline in mild, fractional flow reserve–negative stenosis.
- Our results provide insight into the safety of using instantaneous wave-free ratio in clinical practice, finding which will need to be confirmed in large prospective clinical outcome trials.

causation by a stenosis. The development of pressure-only FFR has undoubtedly facilitated the clinical application of invasive physiology, and its role as a decision-making tool is supported by large clinical trials. There remain, however, 30% of cases in which information derived from pressure FFR conflicts with direct measurement of underlying CFR. These diagnostic disagreements are known not to be a result of measurement error but instead represent true biological differences between CFR and FFR: because both indices rely on the achievement of maximal coronary flow for their calculation, for any given stenosis their values move in opposite directions when hyperemic flow increases (Figure 1).

The instantaneous wave-free ratio (iFR) has recently been proposed as an index that uses pressure-only recordings to identify physiologically significant stenoses. Because iFR does not intend to estimate maximal myocardial blood flow with pressure, it differs from FFR as it does not require pharmacological induction of hyperemia for its calculation. Although early studies have reported a close relationship between iFR and FFR, it is not known which pressure-only index agrees more closely with the true flow reserve CFR.

In this study, we performed the first comparison between pressure indices iFR and FFR against coronary flow velocity reserve (CFVR) in patients undergoing invasive functional assessment of CAD. We sought to evaluate whether iFR, by avoiding hyperemia, would agree more closely with underlying CFVR. If confirmed, this would provide further physiological validation for iFR as a vasodilator-free index of coronary disease severity.

Methods

Study Sample

This study included 216 stenoses from 186 patients scheduled for coronary angiography or percutaneous coronary intervention at the Academic Medical Centre, Amsterdam, The Netherlands, and Imperial College, London, United Kingdom. The sample from Amsterdam included 141 stenoses from 2 substudies: 1 subsample of 56 lesions in which pressure and flow were measured simultaneously, collected between November 2001 and January 2012 and the other includes 85 stenoses with nonsimultaneous measurements of pressure and flow, from the basal stenosis resistance study data set, with data collected from April 1997 to September 2006. The sample from Imperial College consisted of 75 stenoses, all collected from 2010 to 2013, as part of the Adenosine Vasodilator Independent Stenosis Evaluation (ADVISE) study and subsequent studies from the group. Exclusion criteria were restricted to significant valvular pathology and prior coronary artery bypass graft surgery. The local ethical review boards approved the respective study protocols, and all subjects gave written informed consent.

Cardiac Catheterization and Hemodynamic Recording

Cardiac catheterization was performed according to standard practice. 5000 IU unfractionated intravenous (IV) heparin was given at the start of the procedure together with 300 to 600 mcg of intracoronary (IC) nitrates. Invasive physiological data were acquired after diagnostic angiography. In 131 stenoses, pressure and flow velocity were measured simultaneously with a 0.014-in combined pressure and Doppler sensor-tipped wire (CombiWire XT, Volcano Corporation, San Diego, CA). In the remaining 85 lesions, pressure and flow were measured sequentially with separate pressure and flow wires. Distal and proximal pressures were normalized at the tip of the catheter. Measurements were performed during baseline conditions and during hyperemia, induced by either IV infusion in 75 cases (140 μg/kg/min) or IC bolus injection (20–60 μg) of adenosine in the remaining 141 stenoses.

Hemodynamic Data Analysis

Data (ECG, pressure, and flow velocity) were extracted from a digital archive (CombiMap or personal computer). Pressure drift was identified either by returning the pressure sensor to the catheter tip at

Figure 1. How can a low fractional flow reserve (FFR) value be generated? Schematic representation of the relationship between pressure gradient and flow across a coronary stenosis. The same FFR value (in this example, 0.75, equivalent to a pressure drop of 25 mm Hg) can be generated via 2 different mechanisms. In (1), even a small magnitude of hyperemic flow is sufficient to generate a 25-mm Hg drop in a severe, flow-limiting lesion. In (2), much higher hyperemic flow rates are needed for the same 25 mm Hg to be created in a mild stenosis. Stenosis (1) is very likely causative of myocardial ischemia, whereas stenosis (2) is by definition not significantly flow limiting, despite displaying the same FFR classification.
the end of the procedure or by means of pressure drop-flow velocity curves, using the zero-flow pressure intercept as a measure of drift. Hemodynamic data analysis was performed off-line using a custom software package in MatLab (Mathworks Inc, Natick, MA). Pressure and flow data acquired simultaneously were aligned as previously described. The diastolic iFR window was identified using fully automated algorithms acting over ECG-gated, time-aligned pressure traces, as described previously. Quantitative coronary angiography was performed off-line in appropriate consoles.

Definition of Physiological Indices

\[
\begin{align*}
\text{Pa} &= \text{Proximal (aortic) pressure} \ (\text{mm Hg}) \\
\text{Pd} &= \text{Distal (coronary) pressure} \ (\text{mm Hg}) \\
\text{FFR} &= \frac{\text{Pd}}{\text{Pa}} \text{ at whole-cycle hyperemia} \\
i\text{FR} &= \frac{\text{Pd}}{\text{Pa}} \text{ at baseline iFR window} \\
i\text{FR during adenosine administration} (i\text{FRa}) &= \frac{\text{Pd}}{\text{Pa}} \text{ at hyperemic iFR window} \\
\text{Baseline flow} &= \text{Mean baseline whole-cycle coronary flow velocity} \ (\text{cm/s}) \\
\text{Flow}_{\text{FFR}} &= \text{Mean whole-cycle coronary flow} \\
\text{Flow}_{\text{gh}} &= \text{Mean coronary flow velocity during the baseline iFR window (mid-diastole)} \ (\text{cm/s})* \\
\text{CFVR} &= \frac{\text{Whole-cycle hyperemic flow velocity}}{\text{Whole-cycle baseline flow velocity}} \\
\text{HSR} &= \frac{\text{Whole-cycle hyperemic pressure gradient (mm Hg)}}{(\text{Whole-cycle hyperemic flow velocity} \ (\text{cm/s}))} \\
\end{align*}
\]

*Only calculated in stenoses in which pressure and flow velocity were measured simultaneously (n=131).

**CFVR refers to indices using a ratio of flow velocities (invasive Doppler and noninvasive stress echocardiography), and CFR refers to indices using a ratio of flow velocities (invasive and noninvasive thermodilution).

Statistical Analysis

Statistical analysis was performed using Stata 13.1 (Statacorp). Data are expressed as means±SD, unless stated otherwise. Correlations between pressure-only indices and CFVR were assessed by calculation of the Pearson correlation coefficient rho (ρ) by Greiner’s relation using the somersd routine in Stata, because this is more robust to outliers and can take account of clustering of data within patients. Receiver operating characteristic (ROC) curves were constructed for each pressure-only index against CFVR as the reference standard, using multiple CFVR cutoffs (1.7, 2.0, 2.5, and 3.0). The areas under the ROC curve (ROC_{AUC}) were compared using somersd to calculate Harrell c. An additional comparison of ROC curves was made with the comroc routine in Stata which uses percentile values derived from the empirical distribution of the test measure among controls with a correction for ties and taking account of clustering. A Wald test for comparisons based on bootstrap SEs (1000 replications) was performed, but because this analysis gave almost identical values to somersd, these results have not been presented below. The classification agreement (and sensitivity, specificity, negative predictive value, and positive predictive value) between pressure-only indices (iFR and FFR) and CFVR was calculated using ROC-derived cutoffs (highest sum of sensitivity and specificity for a CFVR of 2.0) and using clinically established cutoffs (CFVR 2.0; FFR 0.809; and the equivalent iFR cutoff of 0.900). When evaluating the underlying hemodynamics of large baseline–hyperemic pressure disagreements, we used an FFR cutoff of 0.75 for significance, because this has been demonstrated to be the optimal ischemic FFR cutoff across multiple studies. Comparison of means was performed using Student t test. A P value of <0.05 was considered statistically significant.

Results

Sample Characteristics

The 216 stenoses (186 patients) demonstrated unimodally distributed iFR, FFR, and CFVR values. Mean FFR was 0.74±0.17, mean iFR was 0.81±0.21, and mean CFVR was 2.1±0.77. Mean diameter stenosis was 56±16%. The majority of patients included in this study presented with stable symptoms (98%), with 52% demonstrating single-vessel disease. Fifty-six percent of all stenoses evaluated were in the left anterior descending coronary artery. Angiographic and demographic characteristics are summarized in Table 1.

Diagnostic Agreement Between Pressure-Only Indices and CFVR

iFR showed a stronger correlation with underlying CFVR (iFR–CFVR, ρ=0.68 [0.60–0.76]) than did FFR (FFR–CFVR, ρ=0.50 [0.39–0.62]; P<0.001 for comparison). Across the entire range of functional stenosis severities, iFR was found to be in closer diagnostic agreement with CFVR than FFR (iFR ROC_{AUC} 0.82 [confidence interval {CI}, 0.76–0.88] versus FFR ROC_{AUC}, 0.72 [CI, 0.65–0.79]; P<0.001, for a CFVR of 2; Figure 2). This was particularly evident within the intermediate 0.60 to 0.90 FFR range (iFR ROC_{AUC}, 0.78 [CI, 0.69–0.86] versus FFR ROC_{AUC}, 0.59 [CI, 0.48–0.69]; P<0.001, for a CFVR of 2). iFR also demonstrated better diagnostic discrimination over baseline Pd/Pa (Pd/Pa ROC_{AUC}, 0.78 [0.72–0.85]; P=0.004). The better agreement of iFR with CFVR was found for different CFVR cutoffs (Table 2). The iFR cutoff value with the highest diagnostic accuracy to identify stenosis with a CFVR ≤2 was 0.85. Although iFR values were significantly lower when measured at hyperemia (iFRa; mean iFRa, 0.63±0.22 versus mean iFR, 0.81±0.21 and mean FFR, 0.74±0.17; P<0.001), the agreement between iFRa and CFVR was significantly worse than baseline iFR (iFR ROC_{AUC} 0.82 [CI, 0.76–0.88] versus iFRa ROC_{AUC}, 0.74 [CI, 0.68–0.81]; P<0.001).

Pressure Indices and Discrimination Between Stenoses With Normal and Abnormal CFVR

Mean CFVR of stenoses with iFR value >0.9 was 2.51±0.7, whereas mean CFVR of stenoses with an iFR ≤0.9 was 1.69±0.6 (P<0.001). A lower iFR value of ≤0.85 identified a subgroup of stenoses with a particularly low CFVR (mean CFVR of 1.44±0.44 with a positive predictive value
to identify stenoses with CFVR of <2.0 and <2.5 of 83% and 99%, respectively).

Diagnostic discrimination was not improved by adenosine administration and FFR calculation (Figure 3). For instance, among stenoses with iFR ≤0.9, those with FFR >0.8 still had a mean CFVR <2. Also, among stenoses with iFR >0.9, a low FFR result paradoxically identified lesions with an even higher CFVR (Figure 3).

Magnitude of Coronary Flow Velocities During Baseline and Hyperemia
Flow \( f_{FFR} \) was significantly higher than flow \( f_{iFR} \) in mild stenoses, when FFR was >0.75 (mean flow \( f_{FFR} \) 42.3±22.8 cm/s versus mean flow \( f_{iFR} \) 26.1±15.5 cm/s; \( P<0.001 \); Figure 4). However, among FFR-significant lesions (≤0.75), flow \( f_{iFR} \) and flow \( f_{FFR} \) were not significantly different (mean flow \( f_{FFR} \) 25.8±13.7 cm/s versus mean flow \( f_{iFR} \) 21.5±11.7 cm/s; \( P=0.13 \); Figure 4). Both flow \( f_{FFR} \) and flow \( f_{iFR} \) were significantly higher than whole-cycle baseline flow (flow \( f_{PdPa} \)) across the whole spectrum of FFR values (flow \( f_{PdPa} \) 16.8±8.4 cm/s in lesions with FFR ≤0.75; and flow \( f_{PdPa} \) 19.8±8.4 in lesions with FFR >0.75; \( P<0.001 \) for comparisons with iFR–flow and FFR–flow).

Magnitudes of hyperemic flow velocities were not different between IC and IV adenosine administration. Among mild stenoses (with FFR >0.8) mean flow \( f_{FFR,IC} \) was 42.5±21.5 cm/s vs mean flow \( f_{iFR,IC} \) 44.5±21.1 cm/s (\( P=0.61 \)). Among functionally severe stenoses (FFR <0.6), mean flow \( f_{FFR,IV} \) was 20.8±11.6 cm/s versus mean flow \( f_{iFR,IV} \) 21.9±12 cm/s (\( P=0.82 \)). Among intermediate lesions (FFR, 0.6–0.9) mean flow \( f_{FFR,IV} \) was 38.6±15.3 cm/s versus mean flow \( f_{iFR,IC} \) 39.9±20.1 cm/s (\( P=0.70 \)).

Prevalence and Mechanisms Behind Large Trans-Stenotic Gradients Only Present at Hyperemia
High iFR values (iFR >0.90) that, after adenosine administration, demonstrated a significant drop in FFR (FFR ≤0.75) were observed only in 4.1% of cases (Figure 5).

Among stenoses with FFR values ≤0.75, the difference between iFR and FFR values was primarily driven by the magnitude of trans-stenotic flow velocity, with larger numeric differences being associated with significantly higher CFVR values (Figure 5). Analysis of absolute flow velocities in this subgroup of stenoses (FFR ≤0.75 and iFR >0.9) revealed that the high value of CFVR was caused by higher-than-average hyperemic flow velocities with normal values of baseline flow (Table 3). Furthermore, the magnitudes of hyperemic coronary flow velocities in this subgroup were similar to the ones observed in unobstructed lesions, with FFR >0.80 (Table 3). The underlying flow profile of stenoses with large gradients only present during hyperemia is similar to those of FFR-negative vessels, with high hyperemic flow velocity and higher-than-average CFVR. Examples of such cases are presented in Figure 6.

Therefore, among stenoses showing a definite abnormal FFR result (≤0.75), 2 distinct groups existed with respect to the underlying CFVR value: those with abnormal iFR (≤0.9), in which CFVR values were also abnormal, and those with normal iFR (>0.9), which demonstrated significantly higher hyperemic flow and CFVR values (Table 3).

### Discussion

In this study, we have found that (1) iFR provides better pressure-derived diagnostic agreement with CFVR than FFR; (2) the diagnostic conflicts between pressure-only indices and CFVR are at least partly caused by the induction of hyperemia, because iFR loses its better classification agreement with CFVR when calculated during adenosine administration (iFRA); (3) flow \( f_{iFR} \) is higher than flow \( f_{FFR} \) only in physiologically mild stenoses, when FFR is >0.75; and (4) large drops from high iFR values to low FFR values are driven by high CFVR and high magnitudes of hyperemic flow.

### iFR–FFR Disagreements: Comparison With Another Flow-Based Index

The classification agreement between iFR and FFR has already been extensively evaluated in >2000 stenoses.15,17,23,26 Multiple studies consistently showed the iFR–FFR classification match to be 80% to 90%, similar to the agreement reported between different invasive and noninvasive functional tests.2,19,27–31 FFR classification of stenoses is prognostically relevant because it is backed up by outcome trials. However, from the perspective of identification of flow-limiting stenoses or myocardial ischemia, direct comparisons between iFR and FFR are of limited value because, in individual cases, when disagreements occur it is not possible to infer which index more closely agrees with

<table>
<thead>
<tr>
<th>Table 1. Demographic and Angiographic Data</th>
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<tr>
<td>Age, y</td>
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<tr>
<td>Male %</td>
</tr>
<tr>
<td>Comorbidities, %</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
</tr>
<tr>
<td>Smoking history</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Chronic renal disease</td>
</tr>
<tr>
<td>Severe LV dysfunction (EF &lt;30%)</td>
</tr>
<tr>
<td>Clinical presentation, %</td>
</tr>
<tr>
<td>Stable angina</td>
</tr>
<tr>
<td>Unstable angina</td>
</tr>
<tr>
<td>Coronary anatomy, %</td>
</tr>
<tr>
<td>Single-vessel CAD</td>
</tr>
<tr>
<td>Multivessel CAD</td>
</tr>
<tr>
<td>LAD</td>
</tr>
<tr>
<td>LCx</td>
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<tr>
<td>RCA</td>
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<tr>
<td>Other</td>
</tr>
<tr>
<td>Proximal vessel</td>
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<tr>
<td>Diameter stenosis, %, ±SD</td>
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<tr>
<td>Adenosine route, %</td>
</tr>
<tr>
<td>Intravenous</td>
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<tr>
<td>Intracoronary</td>
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</table>

CAD indicates coronary artery disease; EF, ejection fraction; LAD, left anterior descending; LCx, left circumflex artery; LV, left ventricular; and RCA, right coronary artery.
measures of flow or perfusion without a third party discriminator. Simultaneous iFR and FFR comparisons against independent discriminators are essential to assess the diagnostic performance of both indices. In the present study, therefore, by evaluating iFR and FFR against CFVR, an established and extensively studied flow-based index, we provide further evidence to support iFR as an index capable of detecting flow-limiting coronary disease (Figure 2 and Table 2). The closer diagnostic agreement between iFR and CFVR was observed for different CFVR cutoffs (Table 2) and particularly marked within intermediate FFR values (Table 2), which suggests our results are not driven by the extremes of disease severity. Our findings are similar to those of the Classification Accuracy of Pressure-Only Ratios Against Indices Using Flow Study (CLARIFY) study\textsuperscript{18} and a study by van de Hoef et al,\textsuperscript{16} both of which found that iFR was noninferior to FFR to detect ischemia using invasive flow and myocardial perfusion imaging, respectively. Also, the present study identified 0.85 as the iFR

Figure 2. Diagnostic performance of pressure-only indices against coronary flow reserve. A, When compared with fractional flow reserve (FFR), instantaneous wave-free ratio (iFR) has better diagnostic agreement with coronary flow velocity reserve (CFVR). Scatter plots between FFR and CFVR (B) and between iFR and CFVR (C) are shown, with the dashed horizontal line demarcating a CFVR cutoff of 2.0. NPV indicates negative predictive value; Pa, proximal (aortic) pressure; Pd, distal (coronary) pressure; PPV, positive predictive value; and ROC\textsubscript{AUC}, area under the receiver operating characteristic curve.

Table 2. Diagnostic Agreement Between Pressure-Only Indices and Different Cutoffs of Coronary Flow Velocity Reserve

<table>
<thead>
<tr>
<th>CFR Cutoff</th>
<th>Whole Sample (186 Patients; 216 Observations)</th>
<th>0.6–0.9 FFR Range (113 Patients; 129 Observations)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>iFR AUC (0.84–0.93)</td>
<td>FFR AUC (0.73–0.87)</td>
</tr>
<tr>
<td>1.7</td>
<td>0.89 (0.84–0.93)</td>
<td>0.80 (0.73–0.87)</td>
</tr>
<tr>
<td>2.0</td>
<td>0.82 (0.76–0.88)</td>
<td>0.72 (0.65–0.79)</td>
</tr>
<tr>
<td>2.5</td>
<td>0.79 (0.74–0.85)</td>
<td>0.71 (0.64–0.78)</td>
</tr>
<tr>
<td>3.0</td>
<td>0.77 (0.70–0.84)</td>
<td>0.69 (0.59–0.79)</td>
</tr>
</tbody>
</table>

The closer relationship between iFR and underlying flow reserve could be observed for different coronary flow velocity reserve cutoffs. Also, iFR was markedly better than FFR within the intermediate 0.6 to 0.9 FFR region, demonstrating that the results were not driven by the extremes of stenosis severities. AUC indicates area under the curve; CFR, coronary flow reserve; FFR, fractional flow reserve; and iFR, instantaneous wave-free ratio.
cutoff with the maximal accuracy to identify flow-limiting stenoses by CFVR, value similar to 0.86 reported in CLARIFY study.18

Figure 3. Measurement of instantaneous wave-free ratio (iFR) and fractional flow reserve (FFR) for the identification of stenoses with abnormal coronary flow velocity reserve (CFVR). iFR measurement identifies lesions with low underlying CFVR (green). Adenosine administration and FFR calculation add no discrimination over baseline iFR results (red).

Our analysis also provides indirect insight into the safety and prognostic value of iFR. Patients with a CFR ≥2 are known to have lower rates of major cardiac events, particularly

Figure 4. Adenosine and coronary flow. Adenosine-induced augmentation of coronary flow is variable across the spectrum of disease severity (top, scatter plot). Whole-cycle hyperemic flow (fractional flow reserve [FFR] flow) is not higher than baseline mid-diastolic wave-free flow (instantaneous wave-free ratio [iFR] flow) in functionally ischemia-inducing stenoses, when FFR is ≤0.75 (A). FFR flow becomes higher than iFR flow only in mild, FFR-negative lesions (B).
myocardial infarction and death, regardless of whether CFR is measured with positron emission tomography,4 invasive flow (CFVR),3 or stress echocardiography (CFVR).5,32 Importantly, excellent 5-year survival with a normal CFVR is maintained even when FFR is abnormal in the same vessel.1 Similarly, a low value of CFVR is an independent marker of poorer outcomes, even in the absence of documented myocardial ischemia.4 Indeed, a low CFVR in the left anterior descending during stress echocardiography is a more powerful predictor of outcomes than is the presence of regional wall motion abnormalities.5 Therefore, the closer association between iFR and CFVR suggests that iFR could be useful as a tool to help clinical decision making.

Adenosine Does Not Significantly Increase Coronary Flow in Patients With Obstructive CAD

Although early FFR experiments elegantly demonstrated that hyperemic flow is significantly higher than baseline flow in healthy young animals with normal coronary arteries33 and in healthy young human subjects,12 we found that adenosine does not invariably increase coronary flow in patients with CAD (Figure 4). Previous studies have indeed suggested that direct extrapolation of coronary hemodynamic findings cannot be made from animals or healthy subjects to patients with vascular risk factors, CAD, and varying degrees of microvascular dysfunction. Uren et al34 demonstrated with positron emission tomography that in patients with CAD, hyperemic flow is on average only higher than baseline whole-cycle flow in lesions with <50% diameter stenosis. Similar results were recently reported by Sen et al18 in the CLARIFY study, which showed that FFR hyperemic distal coronary resistance is only significantly lower than baseline iFR resistance in vessels without flow-limiting disease. Finally, a large variability in microcirculatory resistance measured with thermodilution has recently been demonstrated in coronary vessels with intermediate stenoses35 supporting the idea that an inconsistent inter-patient response to adenosine is one of the main responsible for the variable magnitudes of hyperemic flow achieved during FFR calculation.18 In agreement with these studies, we found that hyperemic flow_{FFR} is on average only higher than the baseline flow_{iFR} in patients with FFR >0.75 (Figure 4). Therefore, in patients undergoing invasive functional assessment of coronary disease in clinical practice, adenosine administration (IV or IC) only significantly increases coronary flow above baseline diastole in nonobstructing, FFR-negative stenoses. In the remaining clinically relevant significant lesions, the baseline diastolic flow of autoregulatory vasodilatation seems to suffice.36

Pressure–Flow Diagnostic Conflicts

Our study also contributes to our understanding of the mechanisms behind pressure–flow diagnostic conflicts.37 Induction of maximal hyperemia is a prerequisite for the calculation of both FFR and CFVR.38 However, because their values move in opposite directions when hyperemic flow increases (Figure 1) for any given stenosis and fixed baseline flow, an improvement in hyperemic flow would paradoxically lead to a worse FFR result (and vice versa). Therefore, because the individual response to adenosine has been shown to vary significantly among patients with CAD,12,13,18,39 diagnostic disagreements between pressure indices and CFVR are expected to occur if both are measured during hyperemia. Our results support

Table 3. Underlying Coronary Flow in Different Subgroups of Stenoses

<table>
<thead>
<tr>
<th>Flow Parameters</th>
<th>Stenoses With iFR ≤0.9 and FFR ≤0.75 (Concordant Group, Gradient Present at Baseline and Hyperemia)</th>
<th>Stenoses With iFR &gt;0.9 and FFR ≤0.75 (Discordant Group, Gradient Only Present at Hyperemia)</th>
<th>Overall Stenoses With FFR &gt;0.80 (Reference Group, Unobstructed Arteries)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperemic CFV, cm/s</td>
<td>24.9±13.4 (P=0.016)</td>
<td>44.7±19.6</td>
<td>43.4±21.3</td>
</tr>
<tr>
<td>CFVR</td>
<td>1.59±0.58 (P&lt;0.001)</td>
<td>2.8±0.54</td>
<td>2.4±0.74</td>
</tr>
</tbody>
</table>

Stenoses in which a significant gradient is only present during hyperemia (mid panel) represent a subgroup of lesions with particularly high underlying flow reserve (CFVR). Importantly, the high CFV in such stenoses is driven by high magnitudes of hyperemic flow. CFV indicates coronary flow velocity; CFVR, coronary flow velocity reserve; and FFR, fractional flow reserve.
this concept, as we found that the closer relationship between iFR and CFVR is lost when iFR is measured during adenosine administration (iFRA), suggesting that the hyperemic response itself (and not the utilization of whole-cycle physiology) is the most likely cause of conflicts between pressure indices and CFVR.

Our findings also help to clarify the physiological mechanisms behind large iFR–FFR disagreements. In a small proportion of stenoses, ischemic FFR values (≤0.75) may be generated by high hyperemic flow rates and higher-than-average CFVR (Table 3 and Figures 5 and 6). Specifically, the generation of large hyperemic gradients in stenoses with normal iFR values (>0.9) identify a particular subgroup of patients with high CFVR (Figure 1, mechanism 2, and Figure 3). These lesions demonstrate, on average, magnitudes of hyperemic flow velocities equal to what is observed in stenoses with FFR >0.80, both significantly higher than flow velocities seen in the overall population of FFR-significant lesions (≤0.75; Table 3). Also, these cases have been shown to have 5-year outcome similar to vessels with concordant FFR and CFVR results (FFR >0.75; CFVR >2.0). Although uncommon (<5% of cases in this cohort), this phenomenon has been previously described in studies using positron emission tomography, Doppler,13 and thermodilution-derived CFR.39

The concept that a large coronary pressure gradient only present during hyperemia is a result of high CFVR has previously been identified and explored by independent groups. Akasaka et al40 and MacCarthy et al41 have independently demonstrated that a good correlation with CFVR can be obtained from pressure alone by measuring the changes in pressure gradients from baseline to hyperemia. Indeed, Johnson et al,12 using data derived from a large positron emission tomography data set, specifically warned against the universal application of a fixed FFR cutoff of 0.75 to 0.8 to detect ischemia in all patients, because this threshold could vary depending on the interindividual variability of CFVR and the extent of microvascular disease in any given population. Therefore, stenoses with a large discrepancy between high iFR and low FFR...
values represent, on average, a subgroup of lesions with high CFVR in which hyperemic coronary flow is not significantly limited. In such cases, care should be taken when interpreting the low FFR values as evidence of ischemia. Randomized clinical trials need to be performed to prospectively evaluate outcomes in such subgroup of stenoses.

Clinical Implications

Use of invasive functional evaluation of coronary disease has significantly increased with the development of FFR, largely because of the simplification brought by use of pressure-only methods. However, adoption of FFR remains low (6%–8%).42,43 The reasons are multifactorial and include difficult access to adenosine in some geographies and concerns over increased procedural time and costs, particularly in patients with 3-vessel disease.32 Therefore, the demonstration that iFR, a pressure-only index that does not require adenosine, has a close association with underlying CFVR, is supportive of its potential future role as a tool to guide decision making in CAD. By eliminating the need for hyperemia, iFR could make coronary functional assessment simpler and deliver the known benefits of physiology-guided revascularization to many more patients with CAD. Clinical trials will evaluate the impact of iFR-guided decisions on clinical outcomes (NCT 02053038).

Limitations

Our study has limitations. First, our analysis was performed retrospectively in previously recorded hemodynamic traces. However, our study represents the largest comparison of pressure-only indices against invasive flow in patients with CAD, meticulously recorded in centers dedicated to the measurement of coronary hemodynamics.

This study used CFVR as a reference comparison, an index that, despite its established diagnostic and prognostic value in coronary disease, is not widely used in the catheterization laboratory for clinical decision making. For the interrogation of intermediate stenoses, CFVR has been largely replaced by a simple pressure ratio (FFR) because of its easier applicability and demonstrated superiority over angiography.9,11 Clinical application of invasive CFVR is now largely limited to evaluation of coronary microvascular function9 and scientific research. These practical aspects of CFVR use, however, do not diminish its biological value as flow-based discriminator, especially when measurements are performed by experienced operators in high-volume centers which participated in this study. Both FFR and CFVR have demonstrated to be useful to guide revascularization, with similar rates of major adverse cardiac events,8 and equal ability to detect myocardial ischemia in the presence of coronary stenoses.19,28 Also, iFR and FFR were obtained from the same hemodynamic trace in which CFVR was measured. Therefore, technical limitations to CFVR should equally affect its relationship with both iFR and FFR. Finally, although a CFVR value of 2.0 is the most widely accepted cutoff and the majority of our analysis is based on such value, we have also performed comparisons with multiple CFVR cutoffs to reduce the potential bias of choosing a single dichotomous cutoff for the reference test.

We used a ratio of flow velocities to calculate flow reserve, which assumes the cross-sectional area of the vessel is maintained from baseline to hyperemia. This is achieved by the administration of IC nitrates at the start of the recordings. Significant changes in underlying flow rate are unlikely to occur as a result of changes in vessel diameter during adenosine administration.8

Different adenosine routes (IV versus IC) and doses were used to induce coronary hyperemia. Although this might be seen as a potential limitation, it better reflects the real-world use of FFR in clinical practice, making our results directly applicable to patients with CAD. Although larger doses of IC adenosine can be used, the dose used in this study (20–60 mcg) achieved the same magnitude of hyperemic flow velocity as 140 mcg/kg/min of IV adenosine infusion, regime used in FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) and FAME II (Fractional Flow Reserve [FFR] Guided Percutaneous Coronary Intervention [PCI] Plus Optimal Medical Treatment [OMT] Versus OMT). Also, recent large clinical cohorts have shown the clinical benefits of FFR when using such lower doses in clinical populations.44 A more detailed discussion on the optimal dose of vasodilators to achieve maximal coronary hyperemia has recently been provided by van de Hoef et al.24

We performed a specific ROC analysis on the performances of iFR and FFR against CFVR in the intermediate 0.6 to 0.9 FFR range. Whether such narrower range of FFR values represents a particularly important subgroup of lesions is debatable, considering that cardiac events are lower in this region when compared with more severe stenoses.11,14 Because recent reports suggested that such intermediate range is important,45 our analysis aimed to demonstrate that the diagnostic agreement between iFR and CFVR was maintained when FFR values fell between 0.6 and 0.9. However, we did not perform any correlation analysis in such restricted range, because this can artificially lower the relationship between any 2 tests.46

A word of caution is important when using pressure indices as an estimation of underlying coronary flow. Although different in many physiological aspects, both iFR and FFR use a transcoronary ratio of pressures as a means of estimating the underlying reduction in coronary flow. Although this pressure-only approach facilitates clinical application of physiology in the catheterization laboratory, it should not be seen as a biological equivalent of direct measurement of coronary flow.

Finally, the demonstration that, when compared with FFR, iFR has a closer relationship with underlying CFVR should not be interpreted as superiority of one index over another. In studies of coronary physiology and ischemic heart disease, all intertest comparisons are limited by the lack of a true gold standard for the detection of myocardial ischemia. Although extensively validated as a measure of myocardial perfusion, CFVR is only one of several available methods to measure it and is currently not the most commonly used tool in the catheterization laboratory. Therefore, our findings cannot infer any clinical benefits of iFR over FFR in clinical decision making. We have simply demonstrated a close diagnostic agreement between iFR and underlying coronary flow, which helps its validation as a potential test to detect flow-limiting stenoses. Our findings help set the physiological foundations for future studies with clinical outcomes, which will evaluate the merits of iFR as a clinical decision-making tool.
Conclusions
When compared with FFR, iFR agrees more closely with underlying CFR, a strong predictor of CFR for its calculation, iFR may simplify functional evaluation of coronary stenoses and enable expansion of physiology-guided revascularization to many more patients with CAD.

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Disclosures
Drs Davies and Mayet hold patents pertaining to iFR technology, which is under license to Volcano Corporation. Dr Davies is a consultant for Volcano Corporation. The other authors report no conflicts.

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Baseline Instantaneous Wave-Free Ratio as a Pressure-Only Estimation of Underlying Coronary Flow Reserve: Results of the JUSTIFY-CFR Study (Joined Coronary Pressure and Flow Analysis to Determine Diagnostic Characteristics of Basal and Hyperemic Indices of Functional Lesion Severity—Coronary Flow Reserve)

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