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Diagnostic Classification of the Instantaneous Wave-Free Ratio Is Equivalent to Fractional Flow Reserve and Is Not Improved With Adenosine Administration

Results of CLARIFY (Classification Accuracy of Pressure-Only Ratios Against Indices Using Flow Study)

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Objectives This study sought to determine if adenosine administration is required for the pressure-only assessment of coronary stenoses.

Background The instantaneous wave-free ratio (iFR) is a vasodilator-free pressure-only measure of the hemodynamic severity of a coronary stenosis comparable to fractional flow reserve (FFR) in diagnostic categorization. In this study, we used hyperemic stenosis resistance (HSR), a combined pressure-and-flow index, as an arbiter to determine when iFR and FFR disagree which index is most representative of the hemodynamic significance of the stenosis. We then test whether administering adenosine significantly improves diagnostic performance of iFR.

Methods In 51 vessels, intracoronary pressure and flow velocity was measured distal to the stenosis at rest and during adenosine-mediated hyperemia. The iFR (at rest and during adenosine administration [iFRa]), FFR, HSR, baseline, and hyperemic microvascular resistance were calculated using automated algorithms.

Results When iFR and FFR disagreed (4 cases, or 7.7% of the study population), HSR agreed with iFR in 50% of cases and with FFR in 50% of cases. Differences in magnitude of microvascular resistance did not influence diagnostic categorization; iFR, iFRa, and FFR had equally good diagnostic agreement with HSR (receiver-operating characteristic area under the curve 0.93 iFR vs. 0.94 iFRa and 0.96 FFR, $p = 0.48$).

Conclusions iFR and FFR had equivalent agreement with classification of coronary stenosis severity by HSR. Further reduction in resistance by the administration of adenosine did not improve diagnostic categorization, indicating that iFR can be used as an adenosine-free alternative to FFR. (Classification Accuracy of Pressure-Only Ratios Against Indices Using Flow Study [CLARIFY]; NCT01118481) (J Am Coll Cardiol 2013;61:1409–20) © 2013 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

AUC = area under the curve
FFR = fractional flow reserve
HSR = hyperemic stenosis resistance
iFR = instantaneous wave-free ratio
iFRa = instantaneous wave-free ratio during adenosine
ROC = receiver-operating characteristic

Use of intracoronary physiological indices to guide revascularization improves clinical outcomes and reduces procedural costs (1,2). Because of the simplicity of measuring intracoronary pressure and the wealth of outcome data, fractional flow reserve (FFR) is the most frequently used measure of stenosis severity. However, intracoronary pressure distal to a stenosis reflects not only the severity of the stenosis but also pressure generated from the microcirculation (3). FFR is calculated as a ratio of mean distal to aortic coronary pressures over the entire cardiac cycle. To separate the hemodynamics of the stenosis from that of the microcirculation, FFR is calculated under conditions of constant (and minimal) microvascular resistance (4). This is achieved with the administration of vasodilators, such as adenosine (5).

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The instantaneous wave-free ratio (iFR) is a pressure-only index that takes an alternative approach to the isolation of the hemodynamics of a stenosis from the microcirculation (6). It does not use vasodilators; instead, it samples intracoronary pressure during the diastolic "wave-free" period—a period in the cardiac cycle when intrabeat microvascular resistance is inherently stable and minimized. This wave-free window provides a phase in which microvascular resistance is significantly lower than that over the whole cardiac cycle, and coronary hemodynamics are most suited for assessment of the hemodynamic effects of a stenosis (6,7). However, it is possible that microvascular resistance during the wave-free period can be lowered even further with the administration of adenosine, and it has been suggested that calculating iFR during adenosine administration may improve its ability to accurately discriminate flow-limiting stenoses (8).

In the ADVISE (Adenosine Vasodilator Independent Stenosis Evaluation) study, the classification of stenosis severity was good between iFR and FFR, but in the absence of a true gold standard, where differences in classification occurred, it was difficult to know which index was correct.

The absence of a true ischemic gold standard has hampered the development of new indices in the past. Previously, noninvasive imaging modalities have been used to further evaluate new intracoronary physiological tools. However, these techniques have limitations in multivessel disease and can only isolate ischemia at the level of a territory rather than a specific vessel (9). Therefore, in this study, we use the hyperemic stenosis resistance (HSR) index, an invasive pressure- and flow-based index, as the reference standard to determine which of the pressure-based indices most accurately represents the hemodynamic severity of the stenosis. HSR falls back to the fundamental importance of simultaneously measuring pressure and flow as first described by Gould (7), and in doing so, circumvents many of the limitations of a pressure-only index. It is recognized to be more stenosis specific, and less dependent on adenosine-mediated hyperemia than pressure-only indices (10–14).

In the first part of this study, we compared the diagnostic classification of iFR, iFRa, and FFR to HSR. We then assessed the changes in resistance that occur during the 3 pressure-derived indices to determine how adenosine administration influences diagnostic categorization.

Methods

Study population. This study included 51 stenoses (subjects 66.2 ± 9.2 years of age; 82.4% male) (Table 1) scheduled for coronary angiography or percutaneous coronary intervention at Guys and St. Thomas' NHS Trust or Imperial College London, UK. In addition to new data, patients were included from part 1 of the ADVISE study (6). Exclusion criteria were limited to significant valvular pathology, previous coronary artery bypass surgery, and weight >200 kg. All subjects gave written informed consent in accordance with the protocol approved by the local ethics committee (NRES 09/H0712/102; NCT01118481).

Study protocol. Pressure and flow velocity recordings were made distal to the target vessel coronary stenosis in 51 vessels at rest and during adenosine-induced hyperemia (76.5% intravenous [140 μg/kg/min] and 23.5% intracoronary [120 μg]).

Cardiac catheterization. Cardiac catheterization was undertaken through the femoral approach. After diagnostic angiography, a 0.014-inch pressure and Doppler sensor-

Table 1 Demographics

	Stenoses, n (%)
Male	42 (82.4)
Age, yrs	66.2 ± 9.2
Risk factors	
Smoker	15 (29.4)
Diabetic	14 (27.4)
Hypertension	18 (35.2)
Family history of ischemic heart disease	13 (25.5)
Vessel	
LAD	28 (54.9)
Cx	12 (23.5)
RCA	11 (21.6)
Adenosine route	
IV	39 (76.5)
IC	12 (23.5)

Cx = circumflex; HSR = hyperemic stenosis resistance; IC = intracoronary; IV = intravenous; LAD = left anterior descending artery; RCA = right coronary artery.

tipped wire (ComboWire XT, Volcano Corporation, San Diego, California) was passed into the target vessel through a guiding catheter. Pressure equalization was performed at the tip of the catheter prior to its advancement into the distal vessel. Unfractionated intravenous heparin, 5,000 IU, was given at the start of the procedure with 300 μg intracoronary glyceryltrinitrate.

Hemodynamic recordings. The electrocardiogram, pressures, and flow velocity signals were directly extracted from the digital archive of the device console (ComboMap, Volcano Corporation). At the end of each recording, the pressure sensor was returned to the catheter tip to ensure there was no pressure drift. Where drift was identified, the measurements were repeated. An adequate flow envelope was obtained in all patients, permitting the calculation of flow-based indices. Data were analyzed off-line, using a custom software package designed with Matlab (Mathworks, Natick, Massachusetts).

Data analysis. Processing of digital data (pressure, flow velocity, electrocardiogram) for the calculation of the various indices was performed at a workstation using Matlab (Mathworks). iFR was calculated as the ratio of distal to proximal pressures over the diastolic wave-free period using a fully automated pressure-only algorithm, as previously described (6). This period corresponds to a time in the cardiac cycle when waves are absent from the coronary artery (6) (Fig. 1). An instantaneous wave-free ratio during adenosine administration (iFRa) was also calculated using the same algorithm. FFR, HSR, and basal and hyperemic microvascular resistance were calculated in all patients, as previously described (14,15,16).

Definition of flow-based intracoronary indices was as follows:

$$\text{HSR} = \frac{Pa - Pd}{v}$$

$$\text{Hyperemic microvascular resistance (HMR)} = \frac{Pd}{v}$$

$$\text{Basal microvascular resistance (BMR)} = \frac{Pd_b}{v_b}$$

$$\text{Wave-free microvascular resistance (wfMVR)} = \frac{Pd_{wfp}}{v_{wfp}}$$

Where Pa = mean aortic pressure; Pd = mean intracoronary pressure distal to stenosis; v = mean flow velocity distal to stenosis during hyperemia; Pd_b = mean intracoronary pressure distal to stenosis at baseline; v_b = mean flow velocity distal to stenosis at baseline; and Pd_{wfp}/v_{wfp} = distal pressure over the wave-free period/flow velocity over the wave-free period.

Statistical analysis. All data are expressed as mean ± SD or median (25th and 75th quartiles), as appropriate. Receiver-operating characteristic curves (ROC) were constructed for each index, and the agreement in diagnostic categorization was compared between the indices by comparing the areas under the ROC using the *roccomp* command in STATA, version 11 (StataCorp, College Station, Texas) based on DeLong et al. (17). The optimal cut-off for each of the pressure only indices of iFR, iFRa, and FFR were selected to be that which maximized the sum of sensitivity and specificity, using HSR as the reference standard. The comparison of FFR to HSR was performed at the 0.75 and 0.8 FFR cut-off.

We determined the sample variance (probability distribution) of the observed microvascular resistance values, of each index, as an estimate of true variance of the entire patient population (STATA). The variance of the reduction in resistance for each of the 3 indices was compared using the F test. A value of $p < 0.05$ was deemed significant. Changes in microvascular resistance for each index are compared to cycle averaged resting resistance.

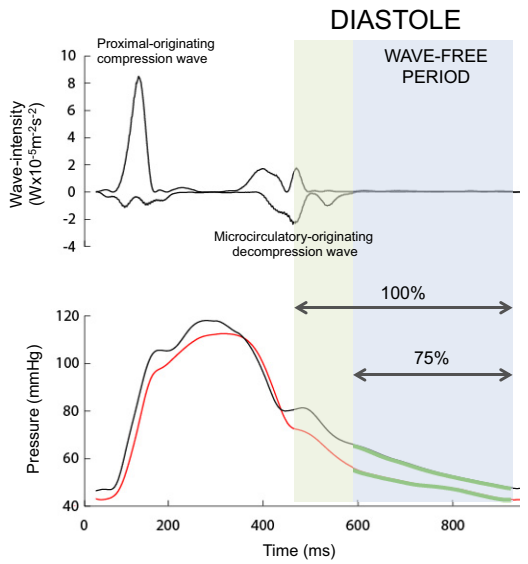

Figure 1 **Wave Intensity During the Diastolic Wave-Free Period**

Representative traces showing coronary artery wave intensity **(upper panel)** and corresponding pressure waveform **(lower panel)**. The duration of diastole and the diastolic wave-free period are indicated with **dashed vertical lines**. The portion of the pressure waveform used to calculate the instantaneous wave-free ratio (iFR) in this study is highlighted in **blue**.

Results

Patient distribution. There was a unimodal left skewed distribution of stenosis severity with 84.3% of stenoses in the 0.6 to 1.0 FFR range; 62.7% of stenoses were in the 0.6 to 0.9 FFR range (Fig. 2).

iFR and FFR. There was agreement in diagnostic classification between iFR and FFR in 47 of 51 lesions (92.3%). In the 4 lesions in which there was disagreement, in 2, iFR was negative and FFR positive, and in the other 2, iFR was positive and FFR negative (Fig. 3). When iFR was negative and FFR positive, HSR agreed with FFR in 1 case and with iFR in the other. In the 2 cases in which iFR was positive and FFR negative, again, HSR agreed with FFR in 1 patient and with iFR in the

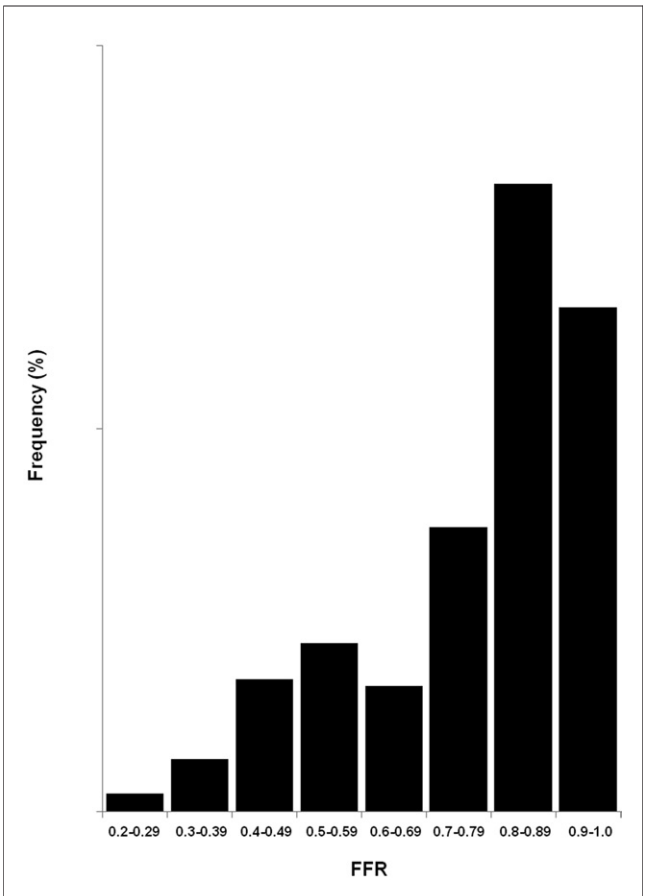

Figure 2 Frequency Distribution of FFR Values in Study

The severity of the range of stenoses was calculated using fractional flow reserve (FFR), and the frequency plotted for each range. This distribution is typical for a clinical population, where a significant proportion (62.7%) of the FFR values fall between the 0.6 to 0.9 range.

other. In both these cases, microvascular resistance during iFR was lower than that during adenosine-meditated FFR.

iFRa had significantly lower values than FFR and iFR (median iFRa 0.74 [0.58, 0.85] versus median FFR 0.84 [0.70, 0.89] and median iFR 0.93 [0.83, 0.98], $p < 0.001$ for both). Furthermore, this was true for both intracoronary and intravenous adenosine administration. Despite numerical differences, there was no significance difference in the ROC area under the curve (AUC) for either iFR or iFRa when compared to FFR ($p = 0.15$).

Of the adenosine-based indices, iFRa provided significantly greater trans-stenotic pressure gradients than FFR (iFRa 19.4 mm Hg [11.2 to 39.2] versus 12.2 mm Hg [7.2 to 27.9], $p < 0.001$). However, iFR produced statistically equivalent trans-stenotic pressure gradients to FFR (iFR 8.2 mm Hg [3.1 to 21.6] versus 12.2 mm Hg [7.2 to 27.9], $p = 0.48$).

FFR, iFR, and iFRa compared to HSR. The relationship of iFR, FFR, and iFRa to HSR was similar (Fig. 4). Median HSR was 0.35 (0.19, 1.08) mm Hg/cm·s. Using the established ischemic cut-off point of >0.8 mm Hg/cm·s for HSR (9), a 0.75 cut-off point for FFR was found to have the optimal diagnostic efficiency (ROC AUC) of 0.96 (95% CI: 0.89 to 1.00) with a sensitivity of 0.86, a specificity of 0.95, and in this population, a positive and negative predictive value of 0.86 and 0.95, respectively (Fig. 5, right panel). This compared to the 0.8 FFR cut-off point, which had a sensitivity of 0.87, a specificity of 0.84, and positive and negative predictive value of 0.68 and 0.94, respectively.

IFRa had an equivalent diagnostic performance to FFR, against HSR as the reference standard (ROC AUC 0.94, 95% CI: 0.85 to 1.00, $p = 0.45$ vs. FFR) (Fig. 5). Corresponding to its numerically smaller values, the classification cutpoint for iFRa was also lower, with a cutpoint of 0.66 found to have the highest diagnostic efficiency. With this cutpoint, iFRa had a sensitivity of 0.86, specificity of 0.92, and in this population, positive and negative predictive values of 0.8 and 0.94, respectively.

iFR without adenosine had a diagnostic performance (ROC AUC) of 0.93 (95% CI: 0.85 to 1.00) against HSR as the reference standard. An iFR cutpoint of 0.86 was found to be equivalent of HSR 0.8. iFR had a sensitivity of 0.86, specificity of 0.95, and in this population, positive and negative predictive values of 0.86 and 0.95, respectively (Fig. 4). The relationship of iFR to FFR and HSR was independent of heart rate (Fig. 6).

There was no significant difference among iFR, iFRa, and FFR in terms of agreement with HSR-guided treatment classification ($p = 0.48$) (Fig. 5).

Magnitude of microvascular resistance reduction according to epicardial stenosis severity. Intracoronary microvascular resistance was significantly lower during the diastolic wave-free period than averaged values over the whole cardiac cycle at rest (microvascular resistance 3.30 (2.07 to 4.38) mm Hg/cm·s vs. 5.30 (3.68 to 7.04) mm Hg/cm·s, $p < 0.001$) (Fig. 7).

The relationship between resting diastolic wave-free microvascular resistance and hyperemic whole cycle microvascular resistance varied according to stenosis severity. In patients with physiologically unobstructed arteries, defined as HSR ≤0.8 mm Hg/cm.s (36 stenoses, 70.6% of the study

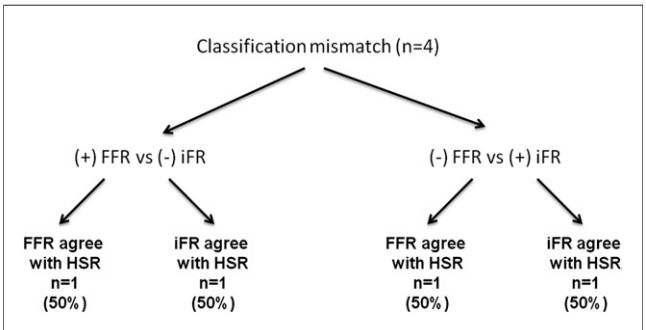

Figure 3 Disagreements of iFR and FFR

Instantaneous wave-free ratio (iFR) and fractional flow reserve (FFR) disagreed in 4 stenoses in terms of treatment categorization. When this occurred, hyperemic stenosis resistance (HSR) agreed with iFR in 50% of cases and FFR in 50% of cases.

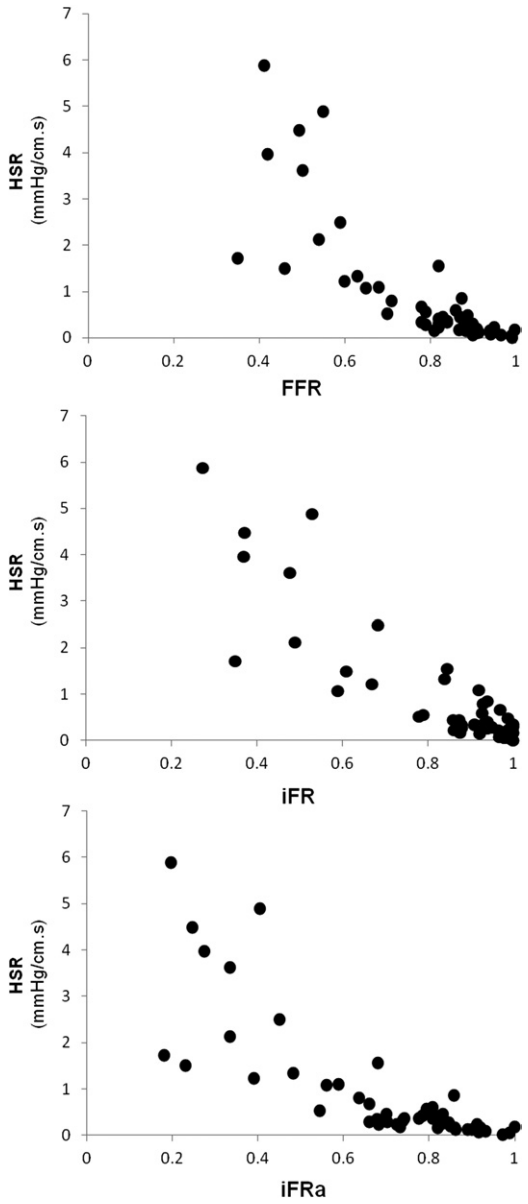

Figure 4 Relationship of iFR, FFR, and iFRa to HSR

All 3 pressure-derived indices—fractional flow reserve (FFR) **(top panel)**, instantaneous wave-free ratio (iFR) **(middle panel)**, and instantaneous wave-free ratio during adenosine administration (iFRa) **(bottom panel)**—have an inverse numerical relationship with hyperemic stenosis resistance (HSR). As stenosis resistance increases the pressure-derived indices decrease numerically.

population), the adenosine-based indices of iFRa and FFR demonstrated a greater reduction in intracoronary microvascular resistance (from baseline whole cycle resistance) than that achieved by iFR (FFR 57.0% [39.7% to 66.4%] and iFRa 76.6% [70.3% to 80.3] versus iFR 35.8% [30.3% to 40.6%], $p < 0.001$ for both) (Fig. 8A). Despite the lower magnitude of resistance observed with iFRa and FFR, in this group, agreement in diagnostic categorization to HSR was equivalent between the 3 pressure-derived indices (diagnostic accuracy = 86.7%).

In patients with physiologically obstructed arteries (HSR >0.8 mm Hg/cm·s), the fall in microvascular resistance was similar for FFR and iFR (FFR 34.6% [21.0% to 52.7%] and iFR 46.4% [32.6% to 54.3%], $p = 0.16$) (Figs. 8A and 8B, right panel), but larger with iFRa (69.2% [64.5% to 80.3%], $p < 0.001$ compared to both FFR and iFR).

iFR microvascular resistance can be lower than FFR microvascular resistance. In 39% of stenoses (20 stenoses, range 0.35 to 0.99 FFR), over both physiologically unobstructed and obstructed vessels, microvascular resistance was not lower during adenosine-mediated FFR compared to the baseline iFR wave-free period (Fig. 8B). In this group, median FFR was 0.79 (interquartile range [IQR]: 0.28) compared to a median iFR of 0.84 (IQR: 0.35). This phenomenon of lower microvascular resistance compared to FFR with iFR occurred in 34.4% (11 stenoses) in the 0.6 to 0.9 FFR range.

Comparison of iFR and FFR in the 0.6 to 0.9 FFR range. Of all stenoses, 62.7% fell within the 0.6 to 0.9 FFR range. In this range, both iFR and FFR had identical diagnostic agreement with HSR, 87.5%. Diagnostic agreement of iFRa to HSR was 84.4%. The sensitivity of iFR, FFR, and iFRa was 66.7% for all. The specificity of iFR, FFR, and iFRa was 92.3%, 92.3%, and 88.5%, respectively (Fig. 9).

When resistance reduction (compared to baseline whole cycle resistance) is plotted according to stenosis severity (Fig. 10), it can be seen that the reduction in resistance during the wave-free period increases with increasing epicardial stenosis severity (Fig. 10, right panel). The opposite was true with FFR, where the magnitude of reduction in microvascular resistance was lower in vessels with more severe stenoses (Fig. 10, left panel).

Consistency of microvascular resistance reduction achieved by iFR, FFR, and iFRa. Across the entire stenosis range, adenosine-mediated FFR had a more heterogenous effect on microvascular resistance than the wave-free period (iFR microvascular resistance reduction 37.2% [IQR: 15.8%] vs. FFR microvascular resistance reduction 53.9% [IQR: 29.0%], F test, $p < 0.001$) (Fig. 10, upper panel). This was particularly true of the 0.6 to 0.9 range (iFR microvascular resistance reduction 37.2% [IQR: 12.6%] vs. FFR microvascular resistance reduction 55.7% [IQR: 34.9%], F test, $p < 0.001$) (Fig. 10, upper panels, red dots).

iFRa had a more consistent reduction in microvascular resistance than FFR (iFRa microvascular resistance reduction 75.6% [IQR: 12.3%] vs. median FFR microvascular resistance reduction 53.9% [IQR: 29.0%], F test, $p < 0.001$). Despite microvascular resistance reduction during iFRa being numerically greater than that during iFR (iFRa resistance reduction 75.6% [IQR: 12.3%] vs. iFR microvascular resistance reduction 37.2% [IQR: 15.8%], $p < 0.001$), resistance reduction during iFR was just as consistent as that during iFRa (F test, $p = 0.73$). Furthermore, this was true

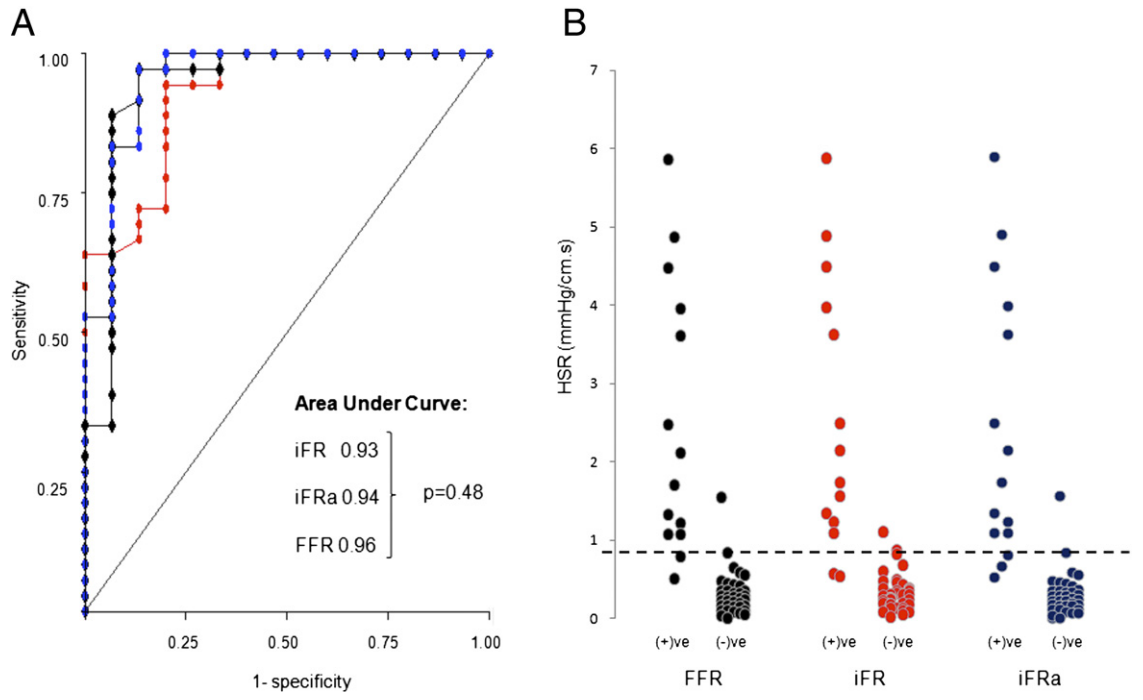

Figure 5 Diagnostic Characteristics of iFR, iFRa, and FFR Using HSR as Reference Standard

(A) Receiver-operating characteristic curves for instantaneous wave-free ratio (iFR), instantaneous wave-free ratio during adenosine administration (iFRa), and fractional flow reserve (FFR) versus hyperemic stenosis resistance (HSR). **(B)** Individual values of iFR, iFRa, and FFR categorized into positive ([+]ve) and negative ([−]ve) according to the parameter's own cutpoint plotted in relation to HSR. The cutpoint for HSR (0.8) is shown as a **horizontal dotted line**. Areas under the receiver-operating characteristic curve were compared as described by DeLong et al. (17).

in the 0.6 to 0.9 FFR range (iFR IQR: 12.6%, versus iFRa IQR: 11.8%, F test, p = 0.10).

Discussion

In this study we found that: 1) iFR and FFR have equal diagnostic classification agreement with HSR; 2) reduction in microvascular resistance during iFR is more consistent than that achieved during adenosine-mediated FFR; 3) microvascular resistance reduction during iFR is higher with increasing stenosis severity whereas the opposite is true for FFR; and 4) despite microvascular resistance being lower when iFR is measured after administration of adenosine

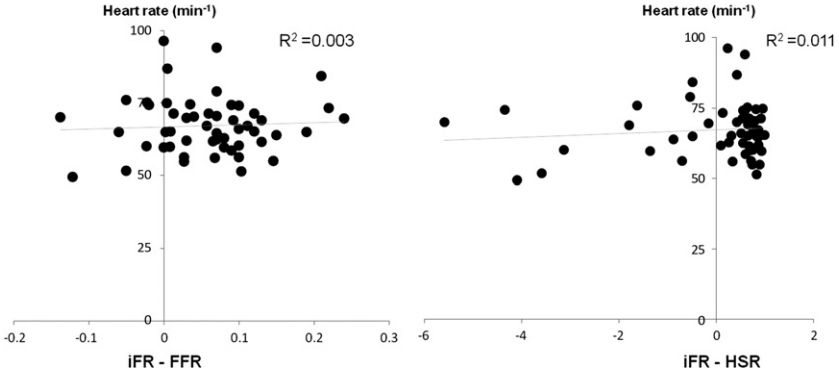

Figure 6 Influence on Heart Rate on Agreement of iFR With FFR and HSR

Heart rate was calculated for each patient. It can be seen that the difference between instantaneous wave-free ratio (iFR) and fractional flow reserve (FFR) or hyperemic stenosis resistance (HSR) cannot be explained by heart rate.

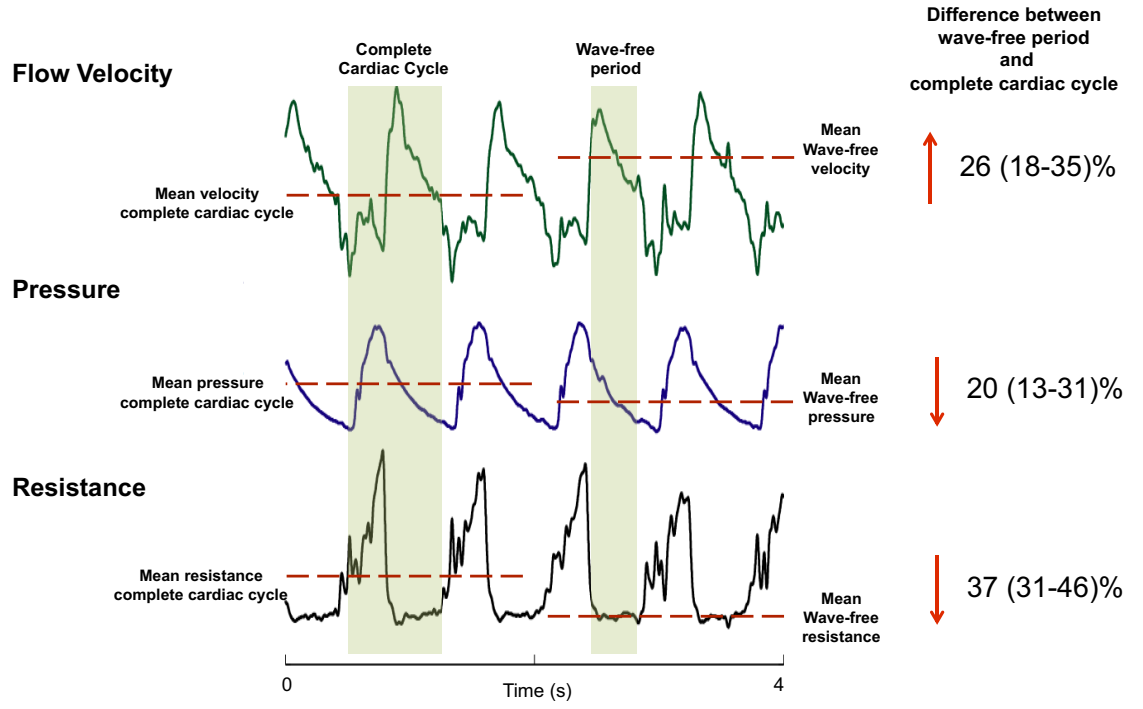

Figure 7 **Schematic Demonstrating Improved Discriminatory Conditions of Wave-Free Period Compared to Complete Cardiac Cycle**

The flow velocity, pressure, and instantaneous microvascular resistance were calculated over the wave-free period and during that of the complete cardiac cycle. Flow velocity is higher, and pressure is lower over the wave-free period. This results in lower microvascular resistance during the wave-free period in comparison to the complete cardiac cycle. Values are expressed as median ± interquartile range.

(iFRa), this does not improve classification agreement with HSR.

iFR and FFR have equivalent agreement with HSR across the entire stenosis range. The equivalent diagnostic performance of iFR and FFR are consistent with the findings of 3 other studies, including >700 stenoses: ADVISE (6), ADVISE Registry (18), and the South Korean prospective blinded study (19). Importantly, in all these studies the same automated algorithm for calculation of iFR was used. However, when iFR was calculated using a different investigator-designed algorithm, in the VERIFY (Verification of instantaneous wave-free ratio and fractional flow reserve for the assessment of coronary artery stenosis severity in every day practice) study, a weaker correlation between iFR and FFR was reported (8). Furthermore, the VERIFY study suggested that resistance could be lower over the wave-free period after adenosine administration, perhaps leading to improvement in stenosis discrimination.

It has been accepted that iFR and FFR have excellent agreement at the extremes of stenosis severity. However, since the publication of the ADVISE study results, there has been much speculation with regard to the scatter in correlation plot between iFR and FFR in the 0.6 to 0.9 range. Although FFR itself has not been validated extensively in this intermediate range (18,20,21), this disagreement has been attributed by some as a limitation of iFR (9).

Our findings suggest that hyperemic whole cycle resistance is far more variable than resting wave-free resistance and that this variability is maximal in the intermediate range of stenosis severity (Fig. 10), a finding consistent with those of others (22). This finding suggests that this biological intrinsic FFR variability may be the principle driver of differences between iFR and FFR. This variability in microvascular resistance during adenosine administration is likely to occur due to variability in adenosine-mediated responses of the myocardium and microvasculature (23–25). The more consistent reduction in microvascular resistance during iFR and iFRa compared to FFR suggests the predominant cause of the variable effect of adenosine on coronary microvascular resistance occurs during systole and early diastole—active phases of the cardiac cycle that are excluded by the wave-free window (6). This is consistent with the seminal work of Sen et al. (6) and Gould (7) that demonstrated that the pressure drop across a stenosis can be assessed most reproducibly during a period in the cardiac cycle free of the confounding effect of active contraction and relaxation of the myocardium on intracoronary pressure (systole and early diastole).

In terms of FFR, this manifests clinically as the cause of disagreement in repeated measures of FFR in the same lesion. Consequently the test-retest agreement of FFR in the 0.6 to 0.90 range, based on the DEFER reproducibility dataset

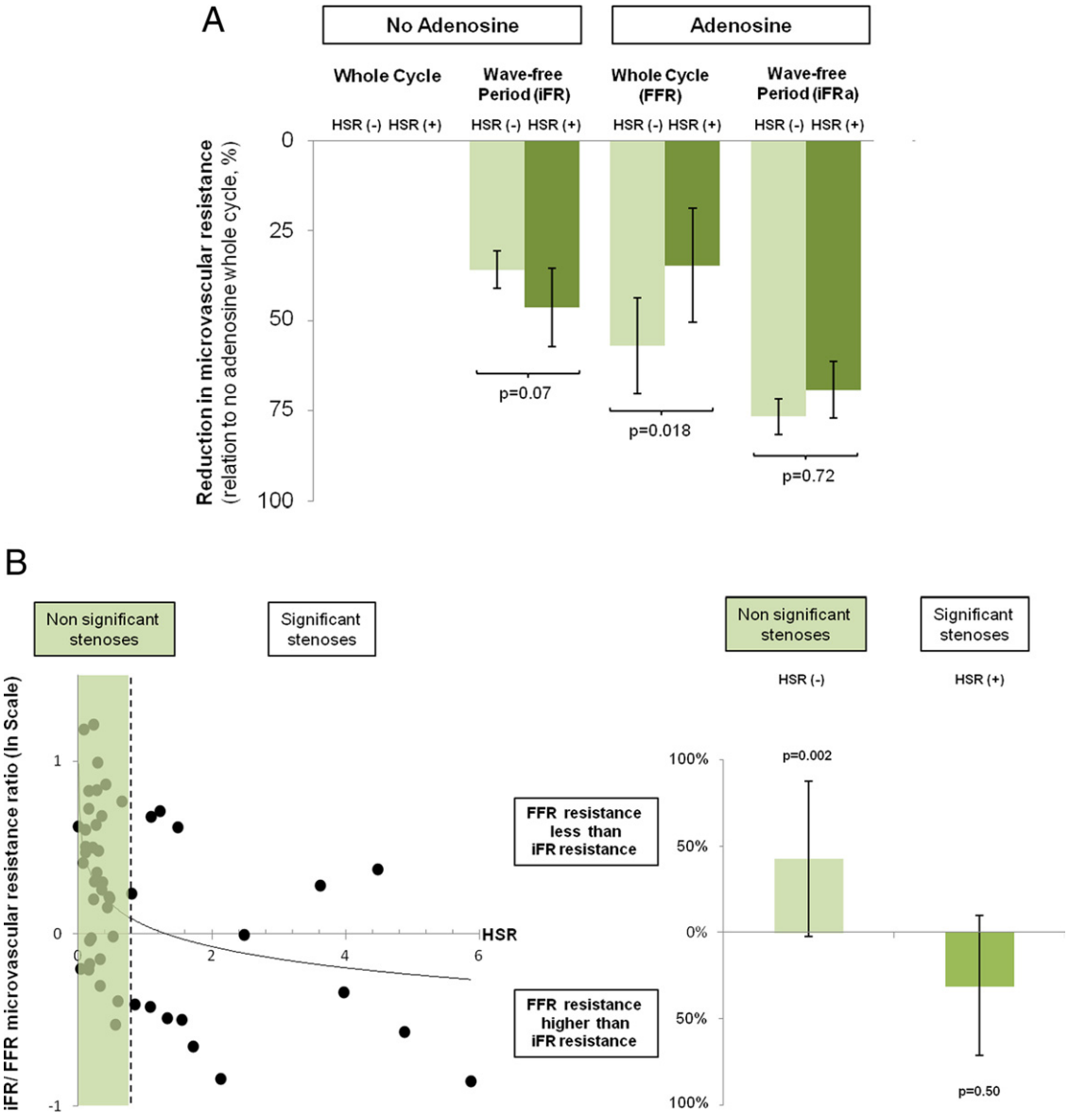

Figure 8 Reduction in Microvascular Resistance According to Epicardial Stenosis Severity

(A) A histogram comparing the magnitude of microvascular resistance reduction in each of the 3 pressure-based indices to that of the complete cardiac cycle under resting conditions. Microvascular resistance reduction is consistent with instantaneous wave-free ratio (iFR) and instantaneous wave-free ratio during adenosine administration (iFRa) in vessels with significant and nonsignificant stenosis. However, with fractional flow reserve (FFR) microvascular resistance reduction is significantly lower in vessels with non-significant stenoses. **(B)** A plot of difference in microvascular resistance between iFR and FFR against stenosis severity according to hyperemic stenosis resistance (HSR) **(left panel)**. It can be seen that when FFR microvascular resistance is significantly lower than that during iFR, it invariably occurs in vessels with nonsignificant stenoses **(left panel)**. As stenosis severity increases, this difference falls, such that microvascular resistance during iFR and FFR in vessls with significant stenoses are equivalent (p = 0.50). In 39% of stenoses, iFR microvascular resistance was lower than that during FFR, and this was not confined to severe lesions. (**Gray bar** = negative HSR).

where FFR was measured twice 10 min apart, is not 100% but only 81% (26). Therefore, when iFR and FFR disagree in this range, it is not certain that a repeated measure of FFR will even agree with itself. Indeed, stenoses in this range were never explored with the same power as those at the extremities of severity in the ischemia validation studies of FFR. As a result, it is possible that this may be an inherent limitation of using FFR as a reference standard in this range (20,21).

By measuring both pressure and flow HSR is less susceptible to the heterogenous response to adenosine (10,11). When used as the reference standard in this range, our results demonstrate equivalent diagnostic categorization of iFR and FFR (Fig. 9). Given these findings, it is reasonable to speculate that FFR,

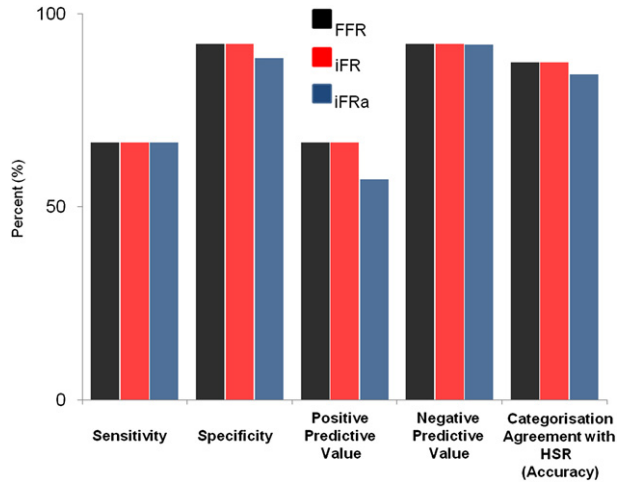

Figure 9 **Comparison of Diagnostic Characteristics of iFR, FFR, and iFRa in Stenoses in 0.6 to 0.9 FFR Range**

Instantaneous wave-free ratio (iFR) and fractional flow reserve (FFR) have equivalent diagnostic characteristics when compared to hyperemic stenosis resistance (HSR) diagnostic categorization in the 0.6 to 0.9 FFR range.

with its significantly more variable microvascular resistance reduction in the 0.6 to 0.9 range, is the predominant contributor to the scatter in this region (Fig. 10).

A simple post-hoc restricted correlation analysis between iFR and FFR in a limited range of FFR values (such as 0.6 to 0.9) can be misleading, especially when the intrinsic variability of FFR is not taken into account (18,27). A more robust method of further characterizing the diagnostic accuracy of iFR in this range is to prospectively identify a study population rich in lesions around this range. To this end, the ADVISE Registry (339 patients) and the South Korean Registry (238 patients) were designed to answer this question (18,19). These were the first studies to ever assess FFR in a distribution similar to that seen in routine clinical setting (80% lesions in 0.6 to 0.9 range). Reassuringly, when accounting for the inherent variability of FFR in this range, these studies also demonstrated close categorization match between iFR and FFR.

How can greater reduction of intracoronary microvascular resistance not give greater diagnostic value? Pressure-derived indices rely on Ohm's law, which demonstrates that a pressure gradient (ΔP) is equal to the product of flow (Q) and resistance (R) ($\Delta P = QR$). Therefore, for a pressure gradient to be used as a surrogate for flow, intracoronary microvascular resistance simply needs to be stable. However, to provide a clinically useful index, microvascular resistance also needs to be low enough, and flow high enough, to discriminate between trans-stenotic pressure gradients and therefore permit the index to differentiate between stenoses of differing severity. This has led to the current dogma that ever greater reductions in microvascular resistance should lead to an improvement in classification agreement (20). However, our results indicate that iFR, FFR, and iFRa had equivalent agreement in diagnostic classification with HSR. This observation is in keeping with other recent independent studies, which have also shown that diagnostic categorization agreement is not necessarily improved after the administration of pharmacological vasodilators (28).

From our results, the lack of incremental diagnostic benefit of the hyperemic indices of iFRa and FFR is because of 2 principle reasons, as follows.

Resistance reduction during FFR varies according to stenosis severity. During FFR, adenosine-mediated reduction in microvascular resistance was most marked in patients with physiologically unobstructed arteries as defined by HSR (Fig. 8). In these patients, the reduction in microvascular resistance was significantly greater than that during iFR (Fig. 8B, shaded area, left panel). This is simply a reflection of the effect of autoregulation that keeps coronary flow constant (23); as stenoses get progressively more severe, the microvasculature dilates to ensure adequate flow to the myocardium. Consequently, the effect of adenosine in arteries with severe lesions is limited as the microcirculation has little scope to dilate further when adenosine is administered—they have limited vasodilator reserve. However, the effect of adenosine in arteries with mild lesions is much greater as the microcirculation is relatively vasoconstricted, and as a result, the vasodilator reserve of these arteries is much larger. These findings are consistent with previous observations demonstrating an inverse relationship between adenosine-mediated vasodilator reserve of a coronary artery and epicardial stenosis severity (23,25).

As a result, when there is a significantly greater reduction in microvascular resistance during FFR, as compared to iFR, it does not impact on diagnostic accuracy because it occurs in the physiologically least obstructive cases (which are so far from the ischemic cut-off point that they are anyway correctly classified). These cases of physiologically unobstructed arteries contrast markedly with those patients with significant obstructive coronary disease. In cases of physiologically significant coronary disease (HSR >0.8), the magnitude of resistance reduction achieved by adenosine during FFR is far lower (Fig. 8A, "whole cycle adenosine"), and iFR microvascular resistance is equivalent to FFR microvascular resistance, and in some cases, even lower (Fig. 8B, left panel, unshaded area).

Reduction in microvascular resistance during the wave-free period is sufficient to differentiate between stenosis severities. Microvascular resistance reduction during iFRa was consistently greater than that possible during iFR and FFR. Despite this, diagnostic accuracy of iFRa was not improved even in the clinically relevant 0.6 to 0.9 FFR range. This suggests that the natural increase in coronary flow velocity and reduction in microvascular resistance during iFR is sufficient in magnitude to assess the fluid dynamics of a stenosis and to accurately differentiate according to severity without the need for adenosine.

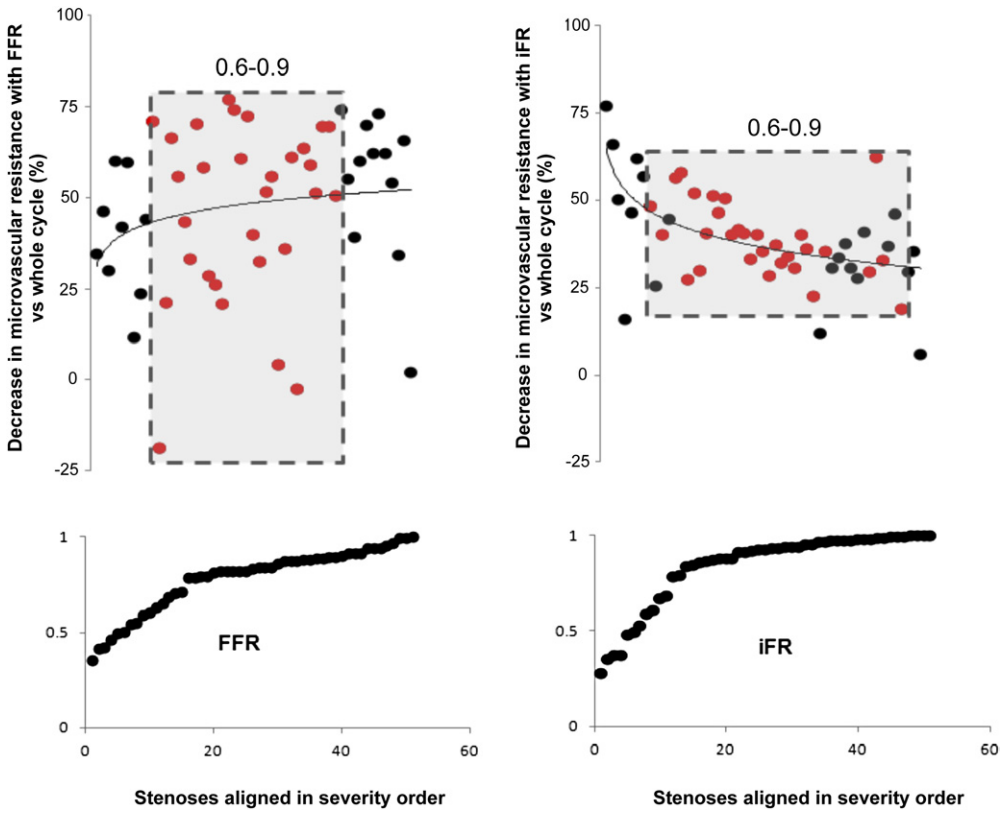

Figure 10 **Variability of Microvascular Resistance Reduction According to Stenosis Severity for Both iFR and FFR**

When instantaneous wave-free ratio (iFR) is close to a value of 1, the resistance over the wave-free period is consistently lower than that during the whole cycle at rest. As stenosis severity increases, the reduction in resistance during the wave-free period increases, suggesting that the autonomics of the epicardial artery are increasing flow during the wave-free period according to epicardial stenosis severity. In contrast, adenosine-mediated fractional flow reserve (FFR) has a more variable effect on resistance. For a similar grade in stenosis, its effects on resistance are far more varied. Furthermore, as stenosis severity increases, its ability to increase flow is reduced.

These 2 observations question the need for "maximal flow" in stenosis assessment. Indeed, for any apparent-maximal flow achieved with 1 dose of 1 vasodilator, that with another dose or drug might be different (29). Moreover, even setting aside pharmacological considerations, for any maximal flow achieved over the whole cardiac cycle, the flow in diastole may be higher and that during the wave-free period higher still. Because the increases in flow will not be exactly identical between methods, the pressure drops will also not be identical, and the methods will have some degree of numerical disagreement reflected in their different cutpoints. But, as this study finds, the indices will not necessarily differ in their diagnostic discrimination, provided the increase in flow is sufficient, consistent and microvascular resistance remains stable. Thus, instead of chasing the potentially unachievable state of "maximal" hyperemia, isolating an intrinsically stable resistance phase of the cardiac cycle, the diastolic wave-free period, provides a mechanism to obtain a flow that is consistently high enough for the accurate assessment of a stenosis.

Why microvascular resistance during iFR can be lower than that during FFR. In approximately 40% of stenoses, microvascular resistance during iFR was lower than that during adenosine-mediated FFR. This phenomenon occurred across the entire range of stenosis severities, including approximately one-third of stenoses in the 0.6 to 0.9 FFR range. In practice, this means that in a significant proportion of patients, adenosine-mediated FFR fails to increase flow greater than that already present at baseline during the diastolic wave-free period. This has previously only been described in a small minority of cases when comparing resting whole cycle microvascular resistance to hyperemic whole-cycle microvascular resistance (FFR) (30).

There are several potential reasons why the proportion of stenoses in this study demonstrating this phenomenon is larger than that previously described. First, in contrast to previous studies documenting this phenomenon, this study used predominantly intravenous adenosine. This enables measurements to be made in more severe lesions, where the operator has more time to attain a good Doppler trace. That is often far harder using intracoronary adenosine, where the increase in flow velocity following adenosine administration is more transient and, therefore, the time window to achieve a good Doppler envelope is far shorter. Second, the larger proportion of stenoses with this paradoxical response may

also reflect the unique hemodynamics of the wave-free period. Phasic analysis of coronary pressure, flow, and microvascular resistance demonstrates that microvascular resistance is approximately 30% to 40% lower during the wave-free period when compared to whole-cycle microvascular resistance. Consequently, adenosine-mediated FFR microvascular resistance is required to be consistently lower to surpass the reduction in microvascular resistance already achieved by simply selecting the wave-free period. Unfortunately, the variable reduction in microvascular resistance during FFR (20) prevents this from being consistently achieved and it is not possible to predict in which patients this will occur. By obviating the need for vasodilator administration, iFR is not subject to the natural variability associated with drug administration between patients, and therefore provides a more consistent assessment across lesions of similar severity (Fig. 10).

The next step for iFR. Physiologic-guided revascularization has been demonstrated to improve clinical outcomes and reduce procedural costs (1,2). However, adoption into clinical practice has been limited (31). One of the reasons for this is the requirement of adenosine (29–32). As a vasodilator-free index, iFR has been proposed as a possible solution to this problem. Given the good categorization match with FFR in >700 stenoses to date, it can be argued that there is little to gain from further comparisons with FFR. Furthermore, by measuring flow we identify a physiological reason that questions the use of FFR as the reference standard, particularly in the 0.6 to 0.9 range—the variable response to adenosine. Although we find that iFR is equivalent to FFR at detecting hemodynamic significant stenoses (as defined by HSR >0.8), the true measure of the clinical utility of the index will be determined by outcome studies. To this end, a systematic appraisal of iFR-guided deferral of therapy would allow clinicians to begin to assess its place in the clinical domain.

Study limitations. Although we use HSR as the reference standard in this study, it should be noted that there is no gold standard ischemia test. Despite being an inherent limitation to the establishment of any new ischemic test, we chose HSR as the reference standard because it measures both pressure and flow and is, therefore, less susceptible to the heterogenous effect of adenosine and because of its high specificity for ischemia (10–14).

The iFR cutpoint of 0.86 in this study is different from that in the ADVISE study (6). That is because in this study we compare iFR to the ischemic cut-off points of HSR (0.8) and FFR (0.75). It should be noted that this is different from the ADVISE Registry (18) and the Korean study (19), which were both highly powered to assess the cutpoint relating to the clinical (nonischemic) FFR cut-off of 0.8. Their findings were consistent with 0.89 being equivalent to FFR 0.8. In this study, the HSR 0.8 cut off is equivalent to FFR 0.75, and as such, it was necessary to obtain the iFR value (0.86) pertaining to these values.

This is a small study compared to the larger pressure-only studies in this field. As with all mechanistic studies, interpretation of our findings should be done in the context of the study size. However, this remains 1 of the largest pressure and flow studies using intravenous adenosine, and the only study comparing FFR, iFR, and HSR in the 0.6 to 0.9 range. The number of patients in which iFR and FFR disagree with each other is small, and their significance should be interpreted with caution. However, it should be noted that the proportion (7.7%) is consistent with clinical populations, the ADVISE Registry (6%), and South Korean Study (6%), suggesting that the study findings are consistent with other, larger datasets (18,19).

The distribution of stenoses in this study is unimodal with leftward skew, which is more reflective of the distribution seen in routine clinical practice (18,19). It may be argued that this may have masked any potential differences between iFR and the hyperemic indices. However, rather than acting in favor of iFR, such a skew is more likely to place iFR at a disadvantage, particularly if the magnitude of microvascular resistance is a key discriminator between the diagnostic accuracy of iFR and FFR as is assumed. This is because in a population such as this, the predominance of stenoses in the 0.6–1.0 FFR range identifies a population with marked differences in microvascular resistance between iFR and FFR. Given that reductions in microvascular resistance with hyperemia are most marked in patients with less obstructive lesions, one would expect the agreement of iFR to FFR and HSR to be weak in such a population and therefore biased against iFR. That the level of agreement between indices is good (including the 0.6 to 0.9 range) suggests that our conclusions that the flow velocity achieved during the wave-free period is sufficient to assess a stenosis and that pharmacologically induced greater flow is surplus to requirement are valid. Therefore, rather than introducing bias, the good level of agreement in this data distribution should reassure clinicians that the principal physiological findings of this study are applicable to the patients they see in the catheterization laboratory.

The ability to measure flow velocity accurately is challenging and has the potential to introduce a source of error. However, this was limited as measurements were predominantly made with intravenous adenosine to ensure adequate time was available to achieve the best possible flow velocity envelope and performed by experienced operators well practiced at making flow measurements. To this end, it is reassuring that our resistance findings are consistent with that reported by others (23).

Conclusions

iFR and FFR have equivalent levels of agreement with HSR classification of coronary stenoses severity. Adenosine administration did not improve the diagnostic performance of iFR, indicating that iFR can used as an adenosine-free alternative to FFR.

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