Journal of the American College of Cardiology Vol. 61, No. 15, 2013

Published by Elsevier Inc.
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2012.09.065

VERIFY (VERification of Instantaneous Wave-Free Ratio and Fractional Flow Reserve for the Assessment of Coronary Artery Stenosis Severity in EverydaY Practice)

A Multicenter Study in Consecutive Patients

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Objectives This study sought to compare fractional flow reserve (FFR) with the instantaneous wave-free ratio (iFR) in patients with coronary artery disease and also to determine whether the iFR is independent of hyperemia.

Background FFR is a validated index of coronary stenosis severity. FFR-guided percutaneous coronary intervention (PCI) improves clinical outcomes compared to angiographic guidance alone. iFR has been proposed as a new index of stenosis severity that can be measured without adenosine.

Methods We conducted a prospective, multicenter, international study of 206 consecutive patients referred for PCI and a retrospective analysis of 500 archived pressure recordings. Aortic and distal coronary pressures were measured in duplicate in patients under resting conditions and during intravenous adenosine infusion at 140 μg/kg/min.

Results Compared to the FFR cut-off value of ≤0.80, the diagnostic accuracy of the iFR value of ≤0.80 was 60% (95% confidence interval [CI]: 53% to 67%) for all vessels studied and 51% (95% CI: 43% to 59%) for those patients with FFR in the range of 0.60 to 0.90. iFR was significantly influenced by the induction of hyperemia: mean ± SD iFR at rest was 0.82 ± 0.16 versus 0.64 ± 0.18 with hyperemia ($p < 0.001$). Receiver operating characteristics confirmed that the diagnostic accuracy of iFR was similar to resting Pd/Pa and trans-stenotic pressure gradient and significantly inferior to hyperemic iFR. Analysis of our retrospectively acquired dataset showed similar results.

Conclusions iFR correlates weakly with FFR and is not independent of hyperemia. iFR cannot be recommended for clinical decision making in patients with coronary artery disease. (Comparison of Fractional Flow Reserve Versus Instant Wave-Free Ratio for Assessment of Coronary Artery Stenosis Severity in Routine Practice; NCT01559493) (J Am Coll Cardiol 2013;61:1421–7) © 2013 by the American College of Cardiology Foundation

Fractional flow reserve (FFR) is a pressure-derived index of coronary stenosis severity and represents the ratio of maximal blood flow in a stenotic artery to maximal flow in the same artery in the absence of any stenosis (1–4). It has been well validated (5–7), and in patients with multivessel coronary disease undergoing percutaneous intervention (PCI), FFR guidance improves health and economic outcomes

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Manuscript received March 20, 2012; revised manuscript received August 4, 2012, accepted September 11, 2012.

Abbreviations and Acronyms

ACC = American College of Cardiology

ESC = European Society of Cardiology

FFR = fractional flow reserve

iFR = instantaneous wave-free ratio

Pa = aortic pressure

Pd = distal coronary pressure

PCI = percutaneous coronary intervention

compared to treatment based on angiography alone (8–10). As a result, FFR guidance during PCI has received a class 1A recommendation from the European Society of Cardiology (11) and a class IIA recommendation from the American College of Cardiology (12). FFR measurements require that myocardial resistance is minimal and constant. In clinical practice, intravenous adenosine infusion is used to establish these conditions. Although most patients experience some breathlessness and chest tightness during adenosine infusion, these symptoms are generally well tolerated (13). The instantaneous wave-free ratio (iFR) has been proposed as an index of stenosis severity that is independent of hyperemia and can be measured without the need for adenosine (14). The concept of iFR is based on the hypothesis that there is a diastolic "wave-free" period (WFP) when microvascular resistance is already constant and minimal. An iFR value of ≤0.83 has been suggested as having diagnostic accuracy comparable to the commonly used FFR cutoff of ≤0.80. We studied consecutive unselected patients referred for angiography with or without PCI to compare FFR to iFR and to determine whether iFR is independent of hyperemia.

Methods

The study protocol was approved by the institutional review board or ethics committee at each participating center, and all patients provided written informed consent. This study is registered at the National Institutes of Health Clinical Trials website (NCT01559493). All consecutive patients referred for FFR-guided angiography with or without PCI during a 5-week period from January 4 to February 10, 2012,

Table 1 Baseline Characteristics (n = 206)

Age (yrs)	65.2 ± 10.2
Male	146 (71)
Mean body mass index (kg/m^2)	27.7 ± 4.6
Risk factors	
Cigarette smoker	64 (31)
Diabetes	50 (24)
Hypercholesterolemia	127 (62)
Treated hypertension	137 (67)
Family history	71 (35)
Mean % of left ventricular ejection fraction	56 ± 11
Stable angina	140 (68)
Unstable angina	46 (22)
No. of previous MIs in the culprit artery territory	28 (14)
Index artery	
LAD	133 (64)
Cx	28 (14)
RCA	45 (22)
No significant disease	16 (8)
Single-vessel disease	85 (41)
Two-vessel disease	64 (31)
Three-vessel disease	41 (20)
Medication	
Aspirin	181 (88)
Clopidogrel or ticagrelor or prasugrel	94 (46)
ACE inhibitor or ARB	139 (68)
Beta-blocker	161 (78)
Statin	169 (82)
Calcium antagonist	49 (24)
Long-acting nitrate	45 (22)
Insulin	19 (9)
Oral antidiabetes medication	33 (16)

Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; Cx = circumflex coronary artery; LAD = left anterior descending coronary artery; MI = myocardial infarction; RCA = right coronary artery.

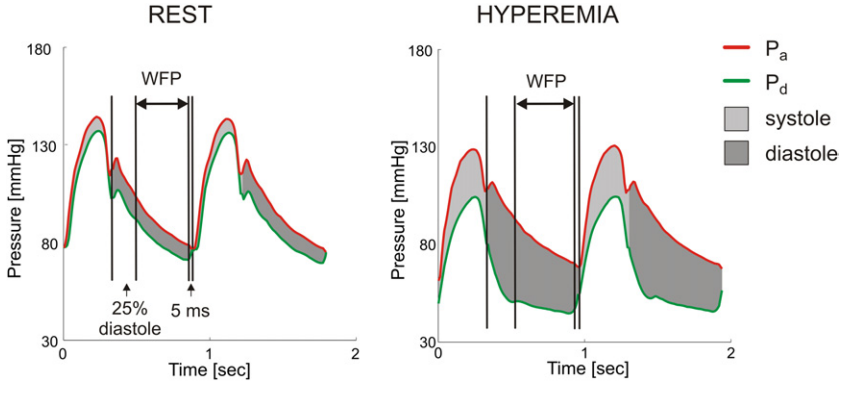

Figure 1 Pressure Tracings of 2 Sequential Heartbeats at Rest and During Hypermia Induced by Adenosine

The wave-free period (WFP) begins 25% into diastole and ends 5 ms before the end of diastole. Aortic pressure is in **red** and distal coronary artery pressure is in **green**. Both the systolic pressure gradient **(light shade)** and diastolic pressure gradient **(dark shade)** increase substantially during hyperemia.

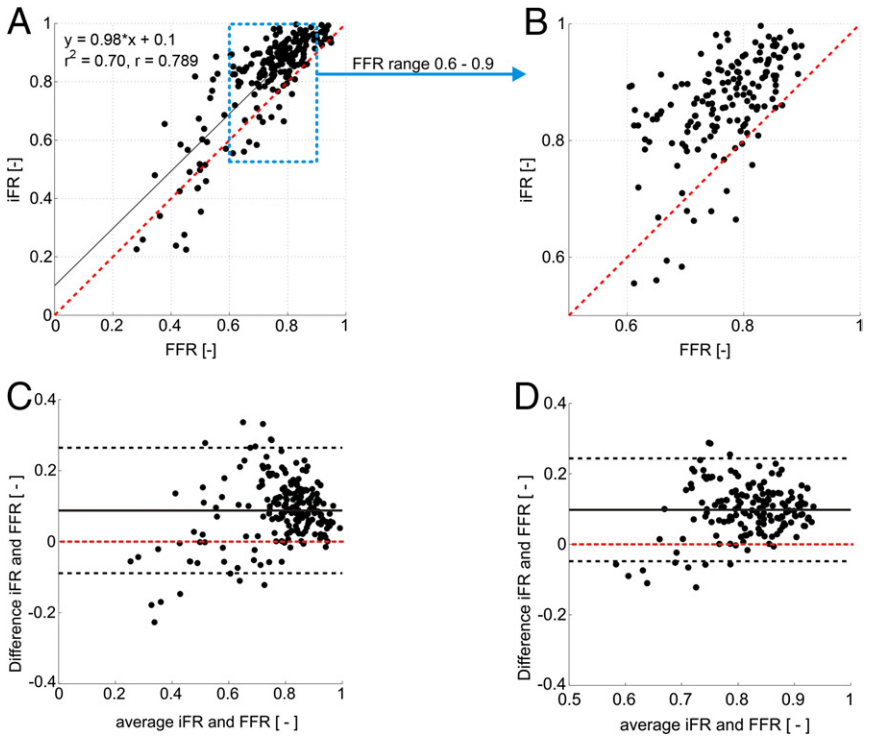

Figure 2 **Scatterplots and Bland-Altman Plots of FFR Versus iFR for the Prospective Dataset (n = 206)**

(A and C) All vessel; **(B and D)** vessels with FFR 0.60 to 0.90. Lines of identity are shown as **dashed red lines**. In addition to the linear regression shown **(A, solid black line)**, a hinged regression line (not shown) was fitted by least squares and gave a slope of 0.67 above the hinge point of FFR = 0.60 (x-axis) and 0.75 (**y-axis**) and a slope below it of 1.65; r is Spearman's correlation. Limits of agreement, −0.08 to 0.27 **(B)** and −0.05 to 0.24 **(D)**, are shown as **dashed lines,** and average differences are shown as **solid lines**. When FFR is low (<0.60), the 95% mean ± SD limits of agreement (±1.96) are wide (−0.36, 0.23).

were included. Exclusion criteria were a history of coronary artery bypass surgery, extremely tortuous coronary arteries, an occluded coronary artery, severely calcified lesions, or a history of acute myocardial infarction within 5 days. Retrospective analysis was conducted using archived pressure recordings from 500 unselected patients from three of the participating centers.

FFR was measured in one coronary artery in each patient after the operator had identified potential targets for PCI. The RadiAnalyzer Xpress instrument (St. Jude Medical, Uppsala, Sweden) and a coronary pressure wire (Certus, St Jude Medical, Uppsala, Sweden) were used in all cases. After the coronary angiogram was obtained, the pressure wire was zeroed, equalized, and positioned with the sensor in the distal third of the target artery. Two minutes after the last injection of contrast medium, pressure recording commenced. After approximately 10 cardiac cycles, an intravenous infusion of adenosine (140 μg/kg/min) was administered through a large antecubital or central vein. The response to adenosine was confirmed by changes in heart rate and blood pressure and development of typical symptoms. After a stable minimum value of FFR was established, the adenosine infusion and pressure recording were stopped. Following a 2-min rest period, the sequence was repeated to test reproducibility of all indices. Finally a pullback recording was performed to exclude wire drift.

iFR was measured as the ratio of mean distal coronary pressure to mean aortic pressure during the diastolic WFP

Table 2 **Diagnostic Performance and Accuracy of iFR ≤0.80**

Diagnosis	% of FFR ≤0.80 (n)	% of Sensitivity (95% CI)	% of Specificity (95% CI)	% of PPV (95% CI)	% of NPV (95% CI)	% of Accuracy (95% CI)
Prospective study						
All FFRs (n = 206)	65 (134)	40 (31–48)	99 (93–100)	98 (90–100)	47 (39–55)	60 (53–67)
FFRs 0.6–0.9 (n = 160)	64 (103)	25 (17–35)	98 (91–100)	96 (81–100)	42 (34–51)	51 (43–59)
Retrospective study						
All FFRs (n = 497)	68 (339)	40 (35–46)	99 (97–100)	99 (96–100)	44 (38–49)	59 (54–63)
FFRs 0.6–0.9 (n = 392)	70 (275)	28 (22–33)	99 (95–100)	99 (93–100)	37 (31–42)	49 (44–54)

CI = confidence interval; NPV = negative predictive value; PPV = positive predictive value.

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Table 3 Diagnostic Performance and Accuracy of iFR ≤0.83

Diagnosis	% of FFR ≤0.80 (n)	% of Sensitivity (95% CI)	% of Specificity (95% CI)	% of PPV (95% CI)	% of NPV (95% CI)	% of Accuracy (95% CI)
Prospective study						
All FFRs (n = 206)	65 (134)	54 (45–62)	96 (88–99)	96 (89–99)	53 (44–62)	68 (61–75)
FFRs 0.6–0.9 (n = 160)	64 (103)	41 (31–51)	95 (85–99)	93 (82–99)	47 (38–56)	60 (52–68)
Retrospective study						
All FFRs (n = 497)	68 (339)	55 (49–60)	98 (95–99)	98 (95–100)	50 (44–56)	68 (64–72)
FFRs 0.6–0.9 (n = 392)	70 (275)	45 (39–52)	97 (93–99)	98 (93–100)	43 (37–49)	61 (56–66)

CI = confidence interval; NPV = negative predictive value; PPV = positive predictive value.

as described by Sen et al. (14) (Fig. 1). In order to determine whether iFR was independent of hyperemia, mean Pd/Pa during this period was also measured during adenosine infusion ("hyperemic" iFR). All analyses were performed in a fully automated manner without manual selection of data time points.

Data management and statistics. For the prospective study, a sample size of 189 subjects provided 90% power at the 5% significance level to confirm a difference of 10% in the diagnostic accuracy of iFR compared to FFR from a null hypothesis value of 80%. We planned to recruit 200 patients to account for any missing data. Clinical data without patient identifiers and coronary pressure recordings were submitted to a core laboratory (Department of Biomedical Engineering, University of Technology, Eindhoven, the Netherlands). Coronary pressure recordings were exported from RadiView software (version 2.2, St Jude Medical, Uppsala, Sweden) and analyzed using Matlab (Mathworks, Inc., Natick, Massachusetts). The relationship between FFR and iFR was quantified with a coefficient of determination (r^2). Agreement between the methods was assessed by Bland-Altman plots and 95% limits of agreement. The performance of iFR was assessed using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy (the percentage of patients correctly diagnosed by iFR), together with their 95% confidence intervals (CIs). iFR was compared to hyperemic iFR and other measures by using receiver operating characteristics (ROC) area under the curve (AUC) analysis using the method described by DeLong et al. (15). Analyses were performed with the entire dataset and with the subgroup of patients with an FFR in the range 0.60 to 0.90. Statistical analysis was performed by an independent statistician (J.M.) with IBM SPSS version 19.0 (IBM Corp., Armonk, New York), Minitab version 16.0

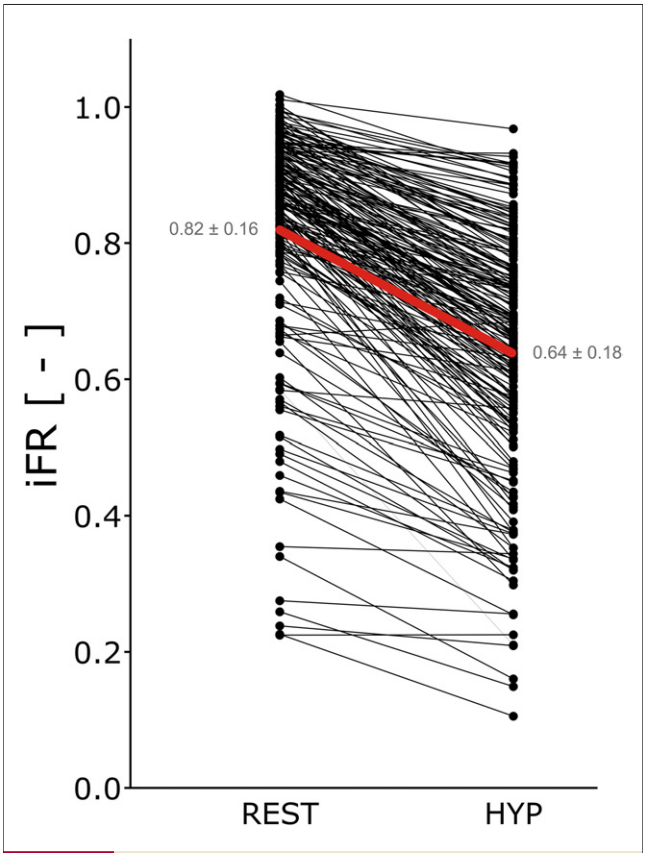

Figure 3 iFR During Rest and Hypermia With Mean ± SD for Each Group

Mean difference: 0.18 (95% CI: 0.17 to 0.20), p < 0.0001.

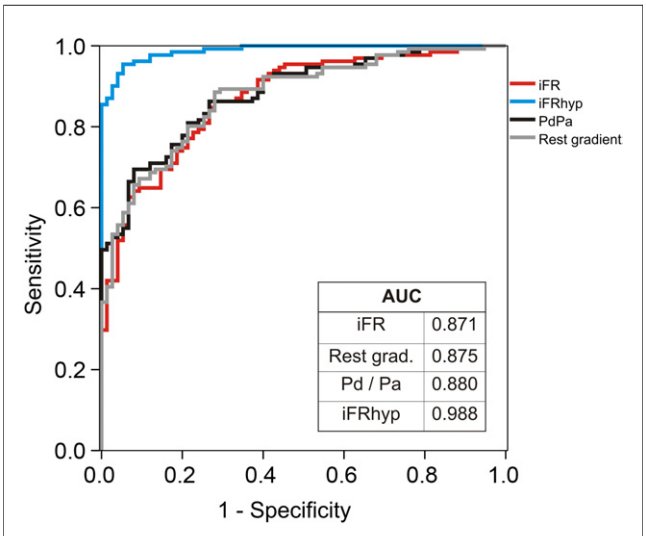

Figure 4 ROC Curves for iFR (AUC = 0.87), Hyperemic iFR (iFRhyp; AUC = 0.99, p < 0.000001), Distal Coronary/Aortic Pressure Ratio at Rest (Pd/Pa; AUC = 0.88, p = 0.52), and Resting Gradient Between Aortic and Distal Coronary Pressures (AUC = 0.87, p = 0.77)

All p values are comparisons with iFR.

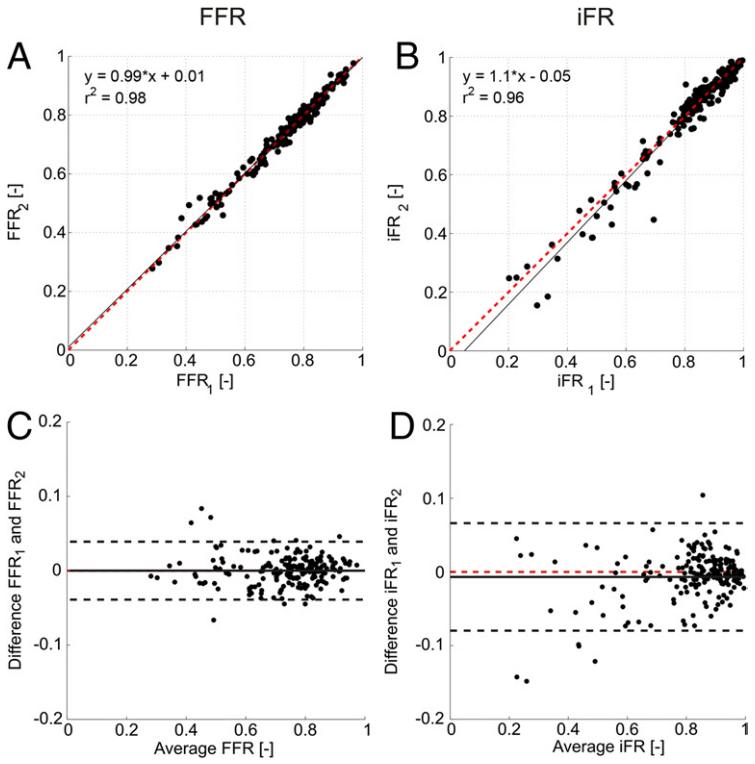

Figure 5 **Scatterplots and Bland-Altman Plots Showing the Reproducibility of FFR and iFR**

Line of identity is in **red (dashed)**. **(A and B)** Linear regression equation line is shown in **solid black.** **(C and D)** Mean differences **(solid black line)** and 95% limits of agreement **(dashed black lines)** are shown.

(Minitab Inc., State College, Pennsylvania), and R (R Foundation, Vienna, Austria) software.

Results

The clinical characteristics of the patients in the prospective study are shown in Table 1. The relationships between FFR and iFR are shown in Figure 2. Compared to the commonly used FFR cut-off value of ≤0.80, the diagnostic performance of iFR of ≤0.80 is shown in Table 2. Overall accuracy was 60% (95% CI: 53% to 67%) for all vessels studied and 51% (95% CI: 43% to 59%) for those with FFR in the range of 0.60 to 0.90. Sen et al. (14) proposed that iFR of ≤0.83 has diagnostic performance equivalent to an FFR of ≤0.80. The diagnostic performance of iFR at ≤0.83 in our prospectively acquired dataset is shown in Table 3. Overall accuracy was 68% (95% CI: 61% to 75%) for all vessels studied and 60% (95% CI: 52% to 68%) for those with FFR in the range of 0.60 to 0.90. iFR decreased significantly with hyperemia: mean ± SD iFR at rest 0.82 ± 0.16 versus 0.64 ± 0.18 with hyperemia (95% CI for difference 0.17 to 0.20; p<0.0001) (Fig. 3). ROC confirmed that the diagnostic performance of iFR was similar to that of resting Pd/Pa (p = 0.52) and trans-stenotic pressure gradient (p = 0.77) and inferior to that of hyperemic iFR (p < 0.0001) (Fig. 4). Both iFR and FFR showed excellent reproducibility (Fig. 5). However, FFR had significantly better reproducibility (p < 0.000) with the iFR differences having between 2.5 and 4.4 times larger variance than FFR differences (95% CI and F-test to compare two variances). The FFR 95% limits of agreement were −0.04 to 0.04; iFR 95% limits of agreement were wider (−0.07 to 0.08), particularly when iFR <0.8 (−0.08 to 0.14). The relative error (iFR − FFR/FFR) for heart rate (p = 0.032) and pressure rate product (p = 0.032) indicated that iFR was susceptible to variations in heart rate and blood pressure during resting conditions. This is illustrated by the wider spread of points in the iFR scatter plot than in the FFR scatter plot (Fig. 5). Results of the analysis of our retrospectively acquired dataset were consistent with those of the prospective study (Table 2 and 3, Fig. 6). In Figure 6A (as in Fig. 2A), in addition to the simple linear regression shown (solid black line), a hinged regression line was fitted by least squares and gave a slope of 0.62 above the hinge point of FFR = 0.63 (x-axis) and 0.78 (y-axis), and a slope below it of 1.19.

Discussion

Our results show a moderate overall correlation between FFR and iFR but only a weak correlation in the clinically important range for decision making of 0.60 to 0.90. Sen et

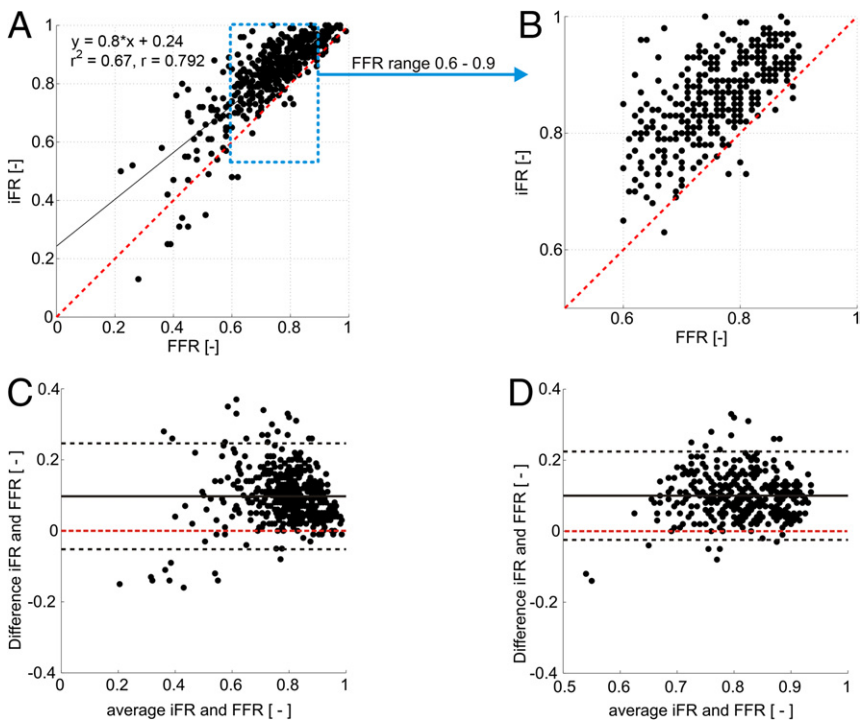

Figure 6 **Scatterplots and Bland-Altman Plots of FFR Versus iFR for the Retrospective Dataset (n = 500)**

(A and C) All vessels; **(B and D)** vessels with FFR 0.60 to 0.90. Lines of identity are shown as **dashed red lines** (r is Spearman's correlation). **(B and D)** Limits of agreement are shown as **dashed lines** (**B**: −0.05 to 0.25; **D**: −0.02 to 0.22), and average differences are shown as **solid lines** (0.10 for each).

al. (14) suggested that an iFR value of ≤0.83 was equivalent to the widely used and validated FFR cut-off value of ≤0.80. However, in our prospective study, the diagnostic accuracy of iFR was unacceptably low using a cut-off value of either 0.80 or 0.83. Almost identical results were found in the retrospective study. We also found that iFR, which is by definition a resting parameter and said to be independent of hyperemia, did in fact change markedly during adenosine-induced hyperemia, a finding which challenges the underlying concept and clinical applicability of iFR. Finally, we found that FFR and iFR had comparable reproducibility.

Multiple experimental models and preclinical and clinical studies have established that neither blood flow nor trans-stenotic pressure gradient at rest can determine whether a stenosis in a coronary artery will limit myocardial perfusion under conditions of increasing demand. Only when hyperemia is induced and coronary flow reserve is measured can a relationship between stenosis severity and the presence of ischemia be demonstrated (16–19). The hypothesis underlying iFR depends on accepting that mean resting myocardial resistance during the WFP of diastole is minimal and equivalent to mean resistance during maximal hyperemia over the complete cardiac cycle. However, this is clearly not the case. Minimal diastolic resistance at rest (whether measured during the whole of diastole or only during the WFP) is generally 50% to 100% higher than the average resistance over the complete heart cycle during hyperemia, as is apparent from our observation of an average decrease in iFR from rest to hyperemia of more than 100% relative to the reduction of iFR from its normal value of 1.0. The concept of iFR also depends on accepting that adenosine exerts its predominant effect on coronary flow during systole and does not influence mean resistance during the WFP in diastole. This is also incorrect. Blood flow at rest in a normal coronary artery is low during systole (because of high resistance) and occurs primarily in diastole. During adenosine-induced maximal hyperemia, coronary blood flow and trans-stenotic pressure gradient increase in both phases of the cardiac cycle but much more so during diastole than systole (Fig. 1). Indeed the correlation between FFR measured over the complete cardiac cycle and diastolic Pd/Pa measured during hyperemia is much closer than the correlation between iFR and FFR (20). In addition to these considerations, the geometry of a stenosis determines the relative magnitude of the friction coefficient (f) and the separation coefficient (s), as described by the equation $\Delta P = fQ + sQ^2$, where P = pressure and Q = flow (21, 22). In short, minimal resting gradients of severe lesions can increase substantially during hyperemia, whereas in long moderate lesions, large resting gradients may increase only minimally

during hyperemia. Therefore, two different stenoses with identical resting gradients (and therefore identical iFRs) can generate completely different hyperemic gradients (and therefore different FFRs).

Ultimately, the sole justification for replacing FFR with iFR is the belief that removing the need to administer adenosine will facilitate the use of pressure wire-guided decision making. However, notwithstanding the poor diagnostic accuracy of iFR, intravenous adenosine infusions are generally well tolerated particularly given the duration of infusion for the measurement of FFR is only 30 to 120 s. Any adverse reactions that do occur are short lived and harmless, with severe asthma being the only absolute contraindication. In addition, when for practical reasons, intravenous adenosine is difficult to administer, it can be replaced by intracoronary adenosine with similar results in most clinical situations (13).

Conclusions

In summary, iFR is not independent of hyperemia, correlates poorly with FFR, and has not been validated experimentally or relative to any of the established noninvasive techniques for identifying reversible myocardial ischemia, including the true gold standard of repeat testing before and after revascularisation (4). Consequently, we believe that iFR cannot be recommended for clinical decision making in patients with coronary artery disease.

Acknowledgment
The authors gratefully acknowledge the support of clinical colleagues and technicians who helped us to perform this study.

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Key Words: adenosine ■ angina ■ FFR ■ hyperemia ■ iFR.