International Journal of Cardiology 168 (2013) 4070–4075

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Clinical validation of the resting pressure parameters in the assessment of functionally significant coronary stenosis; results of an independent, blinded comparison with fractional flow reserve

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ARTICLE INFO

Article history:
Received 9 January 2013
Received in revised form 27 June 2013
Accepted 2 July 2013
Available online 26 July 2013

Keywords:
iFR
FFR
Resting whole-cycle Pd/Pa
Diagnostic performance

ABSTRACT

Background: The role of resting pressure parameters, i.e. instantaneous wave-free ratio (iFR), and resting distal coronary pressure/aortic pressure (Pd/Pa) in assessing functionally significant stenosis remains controversial. We sought to assess the diagnostic performance of iFR and resting whole-cycle Pd/Pa in Asian patients.
Methods: In this study, 238 consecutive lesions (no total occlusions) in which fractional flow reserve (FFR) was measured with both intravenous and intracoronary adenosine administration were included. Coded resting pressure data were sent to the core laboratory in which iFR was calculated in a blinded fashion.
Results: FFR and iFR had unimodal distributions and the correlation was $r = 0.77$ (95% confidence interval, 0.71 to 0.82). In a receiver-operating-characteristic curve analysis, iFR had an area under the curve (AUC) of 0.9 at FFR $\leq$ 0.80. The best cut-off value for iFR was 0.90 with a sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy of 76%, 86%, 82% and 80%, and 82%, respectively. The resting whole-cycle Pd/Pa cut-off of 0.91 demonstrated a diagnostic accuracy of 82% (AUC 0.9). However, iFR had higher discriminatory power than the resting whole-cycle Pd/Pa.
Conclusion: Both iFR and resting whole-cycle Pd/Pa showed good diagnostic performance to define the functionally significant stenosis in an independent Asian cohort distributed unimodally and without total occlusions. However, further validation is needed to explore the areas of disagreement between different physiologic parameters prior to adoption of resting pressure parameters into routine clinical practice.

1. Introduction

The revascularization of patients with objective evidence of ischemia can improve functional status and outcomes [1–3], and fractional flow reserve (FFR) is a proven physiologic tool for assessment of lesion specific ischemia. FFR-guided percutaneous coronary intervention (PCI) can improve the event free survival, and reduce health care costs [3–5]. FFR calculation requires the administration of potent coronary vasodilator such as adenosine, a process which aims to minimize coronary resistance to allow a linear relationship between pressure and flow [6].

Recently, Sen et al. proposed a new pressure-derived physiologic index from coronary wave-intensity analysis, the instantaneous wave-free ratio (iFR), which does not require adenosine for its calculation [7]. iFR relies on the identification of a wave free period in diastole when distal coronary resistance is intrinsically stable within the cardiac cycle. In the ADVISE study, iFR demonstrated diagnostic accuracy of 88% in defining the presence of myocardial ischemia. However, there has been debate on the accuracy and clinical usefulness of this novel index [8,9]. Moreover, its relationship with resting pressure ratio has not been clearly defined yet.

In the present study, we aim to test the diagnostic performance of iFR in an independent cohort of Asian patients with intermediate stenosis whose FFR was measured with at least 2 different methods of

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http://dx.doi.org/10.1016/j.ijcard.2013.07.030

hyperemia and to investigate the relationship between the resting whole-cycle Pd/Pa ratio and iFR.

2. Methods

2.1. Study population

FFR had been measured in consecutive patients at Seoul National University Hospital and Keimyung University Dongsan Medical Center, which are university hospitals with large PCI volumes. For the current analysis, 243 consecutive, predominantly intermediate lesions on coronary angiogram with FFR measurement with both intracoronary bolus and intravenous adenosine were selected from the FFR database. Patients were excluded if any of the following was present: in-stent restenosis, acute ST-segment elevation myocardial infarction, chronic total occlusion lesions, vessels with collateral feeders, regional wall motion abnormalities of a target vessel segment, left ventricular ejection fraction < 40%, primary myocardial or valvular disease, contraindication to adenosine, or angiographically visible thrombus at a target lesion. In patients with acute coronary syndrome, only the non-culprit vessels were interrogated after treatment of the infarct related artery. The study complied with the Declaration of Helsinki and was approved by the Institutional Review Board of each participating hospital. The authors comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

We excluded 3 lesions with inadequate data acquisition, 1 lesion with frequent premature ventricular beats, and 1 lesion with complete atrioventricular block, leaving 238 lesions available for the final analysis.

2.2. Hemodynamic recording and FFR measurement

Target vessel engagement was performed via radial or femoral approach using 5- to 7-French guiding catheters. Angiographic images were acquired after intracoronary nitroglycerin (100 to 200 μg) administration. FFR was measured using a 0.014-inch pressure guide wire (St. Jude Medical, Minneapolis, Minnesota) as previously described [4] and hyperemia was induced by both the continuous intravenous infusion of adenosine (140 μg/kg/min) and intracoronary bolus administration (40 μg for the right coronary artery and 80 μg for the left coronary artery). FFR was calculated as the mean distal coronary pressure (Pd) divided by the mean aortic pressure (Pa) during maximal hyperemia and functional significance was defined with the threshold of FFR ≤ 0.80 as suggested in the FAME study [10]. If there was discrepancy between intracoronary bolus and intravenous infusions the lower value was used for the final analysis.

2.3. Quantitative coronary angiography

Quantitative coronary angiography (QCA) was performed by experienced observers who were unaware of the FFR findings. Using the guiding catheter for calibration and an edge detection system (CAAS 5.7 QCA system, Pie Medical, Maastricht, Netherlands), the reference diameter, minimal lumen diameter and lesion length were measured, and the percent diameter stenosis was calculated.

2.4. Calculation of iFR and resting whole-cycle Pd/Pa

iFR calculation was performed in a blinded fashion. The baseline tracing data with a duration of 5 heart beats or longer were extracted from the FFR console platforms. The data were then anonymized and coded as ASCII text file and sent to the iFR core lab, where iFR was calculated using fully automated algorithms acting over the wave-free period over a minimum of 5 beats.

iFR was calculated as the mean pressure distal to the stenosis during the diastolic wave-free period divided by the mean aortic pressure during the diastolic wave-free period. The onset of diastole was identified from the dicrotic notch, and the diastolic window was calculated beginning 25% of the way into diastole and ending 5 ms before the end of diastole. This time was chosen to reflect the wave-free period in diastole when resistance is naturally minimized (Fig. 1). All analyses were performed in a fully automated manner without the need for manual selection of data time points.

The ratio of mean distal coronary pressure to mean aortic pressure was used for calculation of resting whole-cycle Pd/Pa values.

2.5. Sample size calculation and statistical analyses

A total sample size of 243 achieves 81% power to detect a change in sensitivity from 0.8 to 0.9 using a one-sided binomial test and 95% power to detect a change in specificity from 0.8 to 0.9 using a one-sided binomial test with an estimated rate of 4% for inadequate data for iFR calculation. The target significance level is 0.05. The actual significance level achieved by the sensitivity test is 0.0458 and that achieved by the specificity test is 0.0315. The assumed prevalence of the disease is 0.35.

Data were expressed as mean ± standard deviation for continuous variables and percentages for categorical variables. Comparison of continuous variables was performed using the Student *t*-test or paired *t*-test. Pearson's correlation was used to calculate the association between iFR and FFR. A receiver-operating-characteristic (ROC) curve analysis was used to determine the optimal cut-offs for iFR and resting whole-cycle Pd/Pa to agree with an FFR ≤ 0.8 using maximizing classification match. Two-sided p-values of less than 0.05 were considered statistically significant. Statistical tests were performed using SPSS version 17 (SPSS Inc., Chicago, Illinois, USA) and Matlab (Mathworks, Inc., Natick, Massachusetts). Sample size calculation was performed with PASS 11 (NCSS Statistical Software, Kaysville, Utah, USA).

3. Results

3.1. Population characteristics

The study population was formed predominantly by physiologically intermediate stenosis (Fig. 2). Mean FFR was 0.81, with 72% of the FFR values falling between 0.7 and 0.9. Only 26% of the stenoses had an FFR value ≤0.75. The baseline clinical characteristics and angiographic findings are summarized in Table 1. The mean age of the study population was 63 years, 68% were male, 28% had diabetes mellitus and 63% had dyslipidemia. Most patients presented with stable angina (63%), and most lesions were located in the left anterior descending artery (73%). The mean percent diameter stenosis was 53%.

3.2. FFR vs. iFR

FFR with intracoronary adenosine administration was higher than that with intravenous adenosine administration by 0.007 (0.82 ± 0.10 vs. 0.81 ± 0.10, $p < 0.001$) and there was a very strong correlation between both FFRs with 2 different methods of hyperemia ($r = 0.98$; 95% CI, 0.975 to 0.984) (Fig. 3A). Each FFR with different methods of hyperemia had a strong correlation with iFR (FFR with intracoronary bolus adenosine administration and iFR: $r = 0.78$, 95% CI 0.72 to 0.83; FFR with intravenous continuous adenosine administration and iFR: $r = 0.77$, 95% CI 0.71 to 0.82). However, in 38 patients (16%), FFR with intravenous adenosine administration was lower than that with intracoronary bolus administration. A Bland–Altman agreement plot showed the 95% limits of agreement between −0.033 and 0.048 (Fig. 3B).

iFR was higher than FFR (0.89 ± 0.10 vs. 0.82 ± 0.10, $p < 0.001$) (Fig. 4A) and iFR was found to closely correlate with FFR ($r = 0.77$, 95% CI 0.71 to 0.82) (Fig. 4B). A Bland–Altman agreement plot showed the 95% limits of agreement between −0.04 and 0.22 (Fig. 4C). There were no differences in clinical and angiographic characteristics between iFR–FFR concordance (upper right and lower left quadrants in Fig. 4B) and discordance (upper left and lower right quadrants in Fig. 4B) groups.

Using an FFR cut-off of ≤0.80 to define a significant stenosis, a ROC curve analysis identified an ideal iFR cut-off of 0.90, with an area under the ROC curve of 0.90. The optimal 0.90 iFR cut-off demonstrated a diagnostic accuracy of 82%, with sensitivity, specificity, and positive and negative predictive values of 76%, 86%, and 80% and 82%, respectively (Table 2). The iFR area under the ROC curve remained unchanged for the hypertensive and diabetic sub-populations (0.90 and 0.91, respectively).

3.3. Relationship between iFR, resting whole-cycle Pd/Pa and FFR

Mean iFR was lower than the resting whole-cycle Pd/Pa (0.89 ± 0.10 vs. 0.93 ± 0.06, $p < 0.001$). The resting whole-cycle Pd/Pa values were spread over a narrower range of values when compared to iFR and FFR (95% of the Pd/Pa data fell within 0.19 points [0.82–1] vs. 0.31 for iFR [0.7–1] and 0.36 for FFR [0.6–0.95]) (Fig. 5).

Diagnostic categorization of stenoses by resting whole-cycle Pd/Pa was good, with an area under the ROC curve of 0.9. The optimally identified Pd/Pa cut-off of 0.91 demonstrated a diagnostic accuracy of 82%. However, this was principally driven by a specificity of 96%, as the same cut-off demonstrated a sensitivity of only 63% (Table 2).

As the resting whole-cycle Pd/Pa data was distributed within a narrow range of values, small deviations away from its optimal cut-off significantly affected its diagnostic performance. The overall

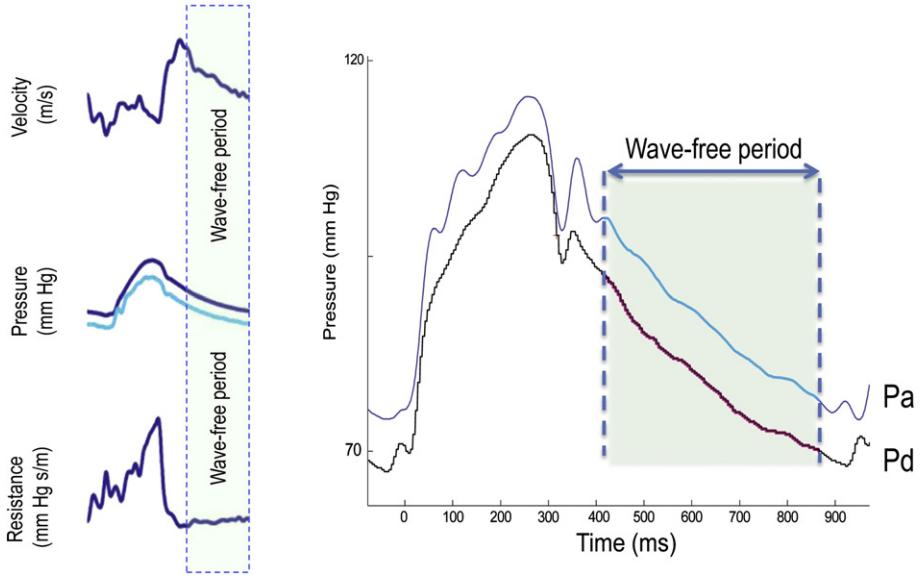

Fig. 1. Measurement of instantaneous wave-free ratio (iFR) in cardiac cycle. iFR was calculated as the mean distal pressure divided by the mean aortic pressure during the diastolic wave-free period. The diastolic window was calculated beginning 25% of the way into diastole and ending 5 ms before the end of diastole. This time was chosen to reflect the wave-free period in diastole when resistance is naturally minimized.

Pd/Pa diagnostic accuracy fell below 80% within 0.01 from its cut-off point. In contrast, iFR diagnostic accuracy remained stable in a region of values which spread up to 0.04 points away from its optimal cut-off (Fig. 6A). This difference was driven by an improved sensitivity of iFR to detect FFR-positive stenoses (Fig. 6B).

4. Discussion

In this study, we evaluated the diagnostic performance of iFR and resting whole-cycle Pd/Pa in an independent cohort of Asian patients with intermediate stenoses in whom FFR was measured by both intracoronary bolus administration and intravenous continuous infusion of adenosine. There are several strengths in this study. First, we performed the FFR measurement with at least two different methods of hyperemia. Second, the whole analysis was performed in a blinded fashion and iFR was calculated using the established algorithms of ADVISE, so that the concept of iFR can be directly proved in an independent cohort. Third, our study population comprised the 'real-world' patients with intermediate stenoses where the functional assessment of ischemic lesion is crucial. The distribution of FFR in our study population was unimodal (Fig. 2) [8]. We also excluded CTO lesions to minimize the bias caused by the collateral feeders.

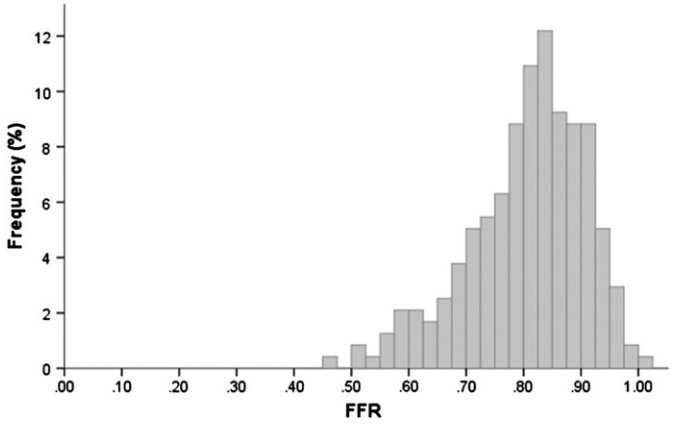

Fig. 2. Distribution of fractional flow reserve (FFR).

4.1. Evaluation of iFR in clinical practice

In this validation study, the optimal cut-off value for iFR to identify stenoses with an FFR of 0.80 was 0.90. This value is higher than the optimal iFR cut-off observed in the ADVISE study which was 0.83, but similar to that in the ADVISE registry, 0.89 [8]. A possible explanation for the different cut-off values may be accounted as follows: as these cut-offs were identified using ROC-curves, the cut-offs are sample specific. Choosing dichotomies on the basis of their maximal significance often leads to selection of approximately the median of the distribution of the population being studied. In the ADVISE study, the mean iFR was 0.76 with a median of 0.84, whereas in the current study, the mean iFR was 0.89 with a median

Table 1
Baseline characteristics of 238 consecutive patients.

Age, years	62.8 ± 0.6
Male	161 (68%)
Hypertension	133 (56%)
Diabetes mellitus	66 (28%)
Hypercholesterolemia	148 (63%)
Current smoking	64 (27%)
Diagnosis	
Stable angina	151 (63%)
Acute coronary syndrome	84 (36%)
Left anterior descending artery lesions	173 (73%)
Left ventricular ejection fraction	61.6 ± 0.4%
Fractional flow reserve	0.81 ± 0.01
Fractional flow reserve ≤ 0.80	103 (43.3%)
Quantitative coronary angiography (n = 233)	
Lesion length, mm	16.8 ± 11.3
Minimal lumen diameter, mm	1.29 ± 0.46
Reference diameter, mm	2.78 ± 0.47
Percent diameter stenosis, %	53.4 ± 13.8
Distribution of lesion severity	
Mild stenosis (diameter stenosis < 40%)	15%
Intermediate stenosis (diameter stenosis 40–70%)	71%
Severe stenosis (diameter stenosis >70%)	14%

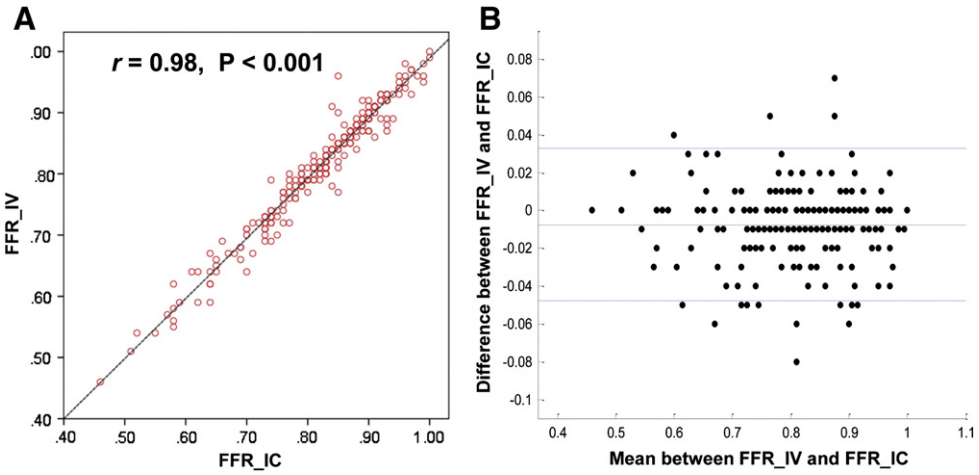

Fig. 3. Comparison between fractional flow reserve measurements with intravenous and intracoronary administration of adenosine. A. There was a strong correlation between fractional flow reserve (FFR) with intravenous administration (FFR_IV) and intracoronary bolus adenosine administration (FFR_IC) ($r = 0.98$, 95% CI, 0.975 to 0.984, $r^2 = 0.96$). The mean of the FFRs with intravenous adenosine administration was 0.81 ± 0.10, and that of FFRs with intracoronary adenosine administration was 0.82 ± 0.10. B. Agreement between FFR_IV and FFR_IC: Bland–Altman plot showed the 95% limits of agreement between −0.033 and 0.048 (blue lines).

of 0.91. Both this study and the ADVISE registry predominantly included patients with intermediate stenosis. Patients from this study were a representative sample of individuals undergoing pressure-wire interrogation of intermediate stenoses in day to day clinical practice. This was reflected in the distribution of FFR values, with a mean FFR of 0.81 ± 0.10, and 72% of the stenoses falling within the intermediate range of 0.7–0.9. This difference is of importance because diagnostic indices of disease severity need to be evaluated in populations similar to which they will be applied in practice, such as this clinical cohort. However, further studies with larger population are needed to define the adequate cut-off value of iFR.

4.2. Incremental benefits of iFR over Pd/Pa

A similar accuracy and area under the ROC curve were demonstrated by resting whole-cycle Pd/Pa compared with iFR. Mamas et al. [11] showed a strong correlation between resting whole-cycle Pd/Pa and FFR: a resting whole-cycle Pd/Pa of ≤0.85 had a positive predictive value of 95%, while a resting whole-cycle Pd/Pa of ≥0.93 had a negative predictive value of 95.7%. However, several aspects of its underlying physiology limit its applicability as a potential diagnostic tool. Resting whole-cycle Pd/Pa values are concentrated within a much narrower range of possible values, when compared to iFR. In this study, 95% of the overall population of stenoses had Pd/Pa ranging from 0.82 to 1. As all indices are displayed in 0.01 increments, 19 possible Pd/Pa results can represent 95% of all possible stenosis severities. That compares to 31 for iFR (0.7 to 1) and 36 for FFR (0.6–0.95). This is in agreement with a previous FFR cohort, which demonstrated that over 95% of patients had Pd/Pa values above 0.86 [11]. In practice, this limited range of results for Pd/Pa means that resting whole-cycle Pd/Pa may have lower discriminatory power around its cut-off value compared with iFR and be more easily affected by the artificial changes in pressure traces, such as those caused by noise, drift or any other source of measurement error.

4.3. Clinical implications of our findings

There has been debate on the accuracy and clinical usefulness of iFR. In a correspondence of Rudzinski and colleagues [9], they calculated iFR in a large number of FFR tracings with appropriate resting and hyperemic pressure recordings (n = 555) and showed only a

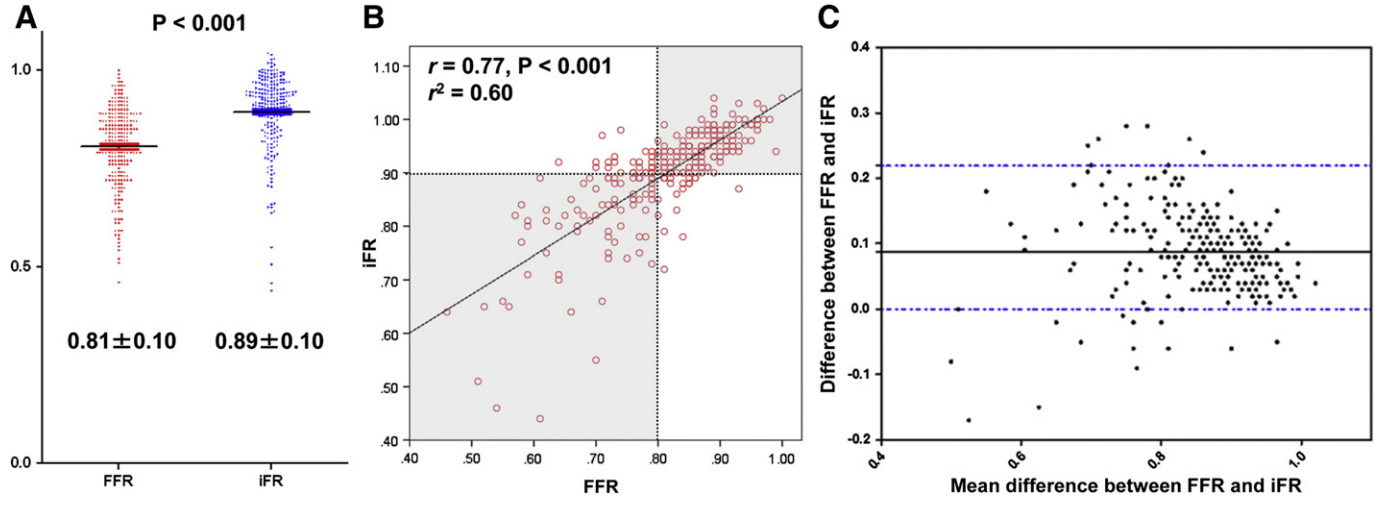

Fig. 4. Comparison of instantaneous wave-free ratio (iFR) with fractional flow reserve (FFR). The mean iFR was higher than the mean FFR (0.89 ± 0.10 vs. 0.81 ± 0.10, P < 0.001) (A) and iFR showed a good correlation with FFR ($r = 0.77$, 95% CI 0.71 to 0.82, $r^2 = 0.60$). The discrepancy between iFR and FFR was found in 49 (20.6%) cases (B). A Bland–Altman agreement plot showed the 95% limits of agreement between −0.04 and 0.22 (C).

Table 2
Diagnostic performance of iFR and resting whole-cycle Pd/Pa in 238 consecutive patients.

	FFR ≤ 0.80	
	Resting whole-cycle Pd/Pa	iFR
Best cut-off value	0.91	0.90
Area under the curve	0.90	0.90
Sensitivity	0.63	0.76
Specificity	0.96	0.86
PPV	0.93	0.80
NPV	0.77	0.82
Diagnostic accuracy	0.82	0.82

iFR = instantaneous wave-free ratio; FFR = fractional flow reserve; NPV = negative predictive value; PPV = positive predictive value; Pd/Pa = distal coronary pressure/aortic pressure.

weak correlation between iFR and FFR. The reported diagnostic accuracy was 69% for all data and 60% in the FFR range between 0.60 and 0.90, which is lower compared with our study results.

Our study is a further step towards the validation of a new index, iFR, as a diagnostic tool to assess the physiological significance of angiographically intermediate coronary stenoses in a catheterization laboratory. The establishment of iFR as an invasive diagnostic method would potentially permit an increase in physiology-guided revascularization, especially in circumstances in which administration of adenosine is not possible. Nonetheless, iFR needs to be validated in its ability to predict adverse cardiovascular outcome in future clinical trials.

5. Conclusions

In an independent clinical cohort of patients with intermediate coronary stenoses, both iFR and resting whole-cycle Pd/Pa demonstrated a good diagnostic agreement with FFR, when calculated in a blinded fashion and using the same algorithm applied to the ADVISE studies. However, iFR had higher discriminatory power than resting whole-cycle Pd/Pa. Further validation is needed to explore the areas of disagreement between different physiologic parameters prior to adoption of iFR into routine clinical practice.

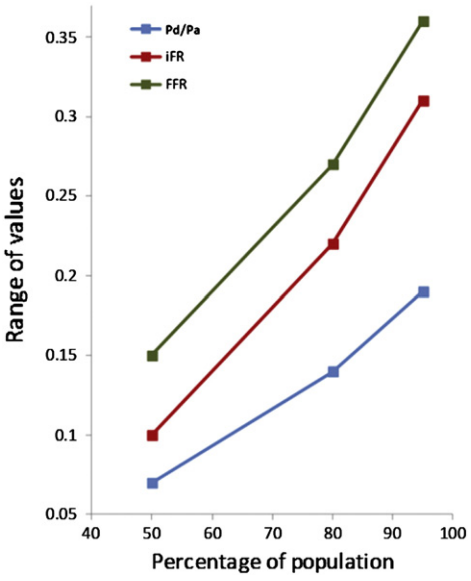

Fig. 5. Distribution of fractional flow reserve, instantaneous wave-free ratio and resting pressure gradient values. Values of fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) were spread more widely compared to resting whole-cycle Pd/Pa. Pd/Pa = distal coronary pressure/aortic pressure.

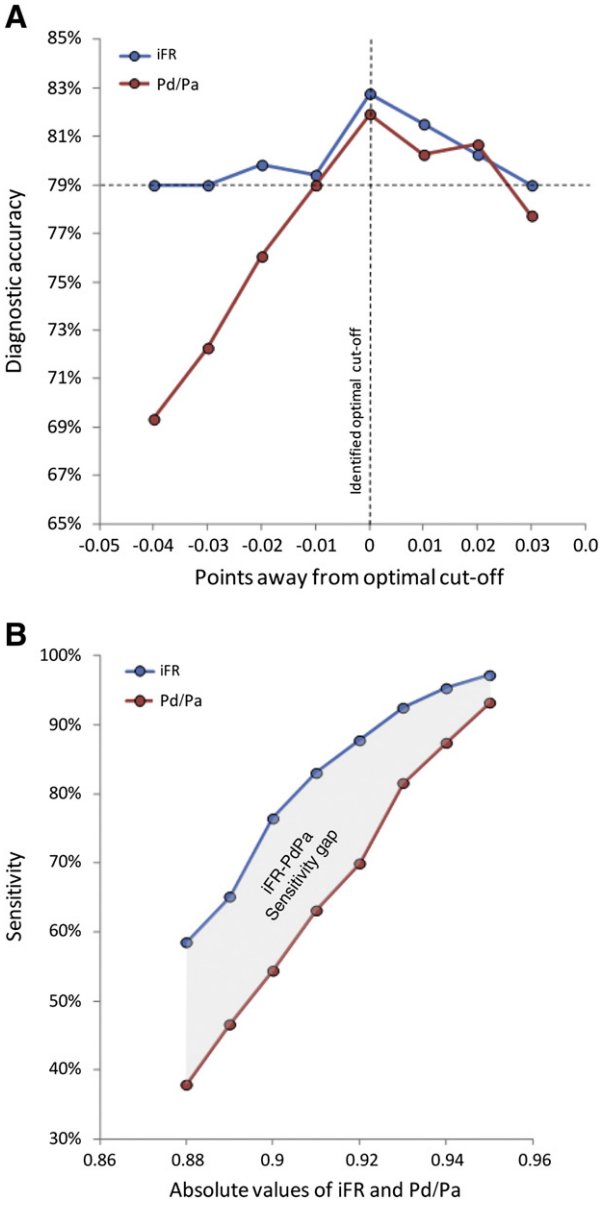

Fig. 6. Comparison of stability between instantaneous wave-free ratio and resting pressure gradient. The diagnostic accuracy of resting Pd/Pa to identify FFR-significant stenoses falls immediately around its optimal cut-off (A). In contrast, instantaneous wave-free ratio (iFR) demonstrates stable accuracy, which can be explained by its superior sensitivity (B).

Disclosures

Dr. Davies holds patents pertaining to this technology.

Acknowledgment

This study was supported by a grant from the Innovative Research Institute for Cell Therapy and the Korea Healthcare Technology R&D Project, Ministry of Health and Welfare, Republic of Korea (A062260).

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