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ORIGINAL ARTICLE

Evaluation of the cut-off value for the instantaneous wave-free ratio of patients with aortic valve stenosis

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Abstract

The aim of this study was to examine the clinical value of iFR for AS patients. Functional evaluation of coronary stenosis in patients with aortic valve stenosis (AS) is challenging because the stress-induced test is often thought to be a contraindication. AS patients have a unique coronary flow pattern dependent on the diastolic phase. The instantaneous wave-free ratio (iFR) is a vasodilator-free, invasive pressure wire index of the functional severity of coronary stenosis and is calculated under resting conditions. And iFR calculated during a specific period of diastole may have the potential benefit to assess the functional severity of coronary stenosis in AS patients. We examined 158 consecutive patients (217 stenoses) whose iFR and fractional flow reserve (FFR) were measured simultaneously. Among the 158 patients, AS was observed in 13 (8.2%). The iFR showed good correlation with FFR in AS patients. The best cut-off value of iFR for the receiver-operator curve analysis to predict FFR of 0.8 was 0.9 for non-AS patients. However, it was 0.73 for AS patients. The present study demonstrated good correlation between iFR and FFR for AS patients. Vasodilator-free assessment using iFR may provide potential benefits when evaluating coronary stenosis in patients with AS. In AS patients, the best cut-off of iFR value predicting FFR value of 0.8 was lower than 0.9 that is the standard predictive value of iFR.

Keywords Instantaneous wave-free ratio · Aortic valve stenosis · Fractional flow reserve · Diastolic coronary flow

Introduction

Several studies have revealed that reducing myocardial ischemia with percutaneous coronary intervention improves functional status and clinical outcomes [1, 2]. The instantaneous wave-free ratio (iFR) is a new index of the functional

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severity of coronary stenosis [3–8]. Recently, several clinical studies reported that FFR and iFR are similar and closely correlated, but that they also differ in a few key aspects [9]. FFR is the pressure ratio during the whole cardiac cycle under hyperemia. In contrast, iFR is the index calculated using the trans-lesional pressure ratio during a specific period of diastole that is called the "wave-free period" and does not require vasodilators such as adenosine for its calculation.

Some registries have reported high comorbidity with coronary artery disease in aortic valve stenosis (AS) [10–12]. In patients with severe AS, there is no true gold standard test of coronary functional ischemia. A previous report suggested that a revascularization strategy guiding FFR is beneficial and has acceptable outcomes for patients with severe AS [13]. However, there is certain risk in evaluating FFR under hyperemia using vasodilators in AS patients. In these situations, the vasodilator-free index of iFR may have an advantage in assessing coronary functional severity in patients with AS. Previous studies reported a unique coronary flow pattern during the diastolic phase in patients with AS [14, 15]. In AS patients, resting coronary flow increases gradually when aortic valve area becomes < 1.0 cm^2 (cut off value generally used for the definition of moderate AS) [14]. In contrast to diastolic coronary flow, the systolic coronary flow decreases with increasing aortic valve stenosis severity, and almost all coronary blood flow is dependent on the diastolic phase in severe AS patients. The unique coronary flow pattern in AS patients may influence the relation between FFR and iFR. To date, there has been no report claiming a correlation between iFR and FFR in this population. The purpose of the present study was to examine the clinical value of iFR in patients with AS using FFR as the standard of evaluation for coronary functional severity.

Methods

Study design and patient population

In this retrospective study, we screened patients who had coronary artery stenosis of at least one target lesion with > 50% angiographic diameter stenosis (DS) as determined by quantitative coronary angiography (QCA) at a single centre (Tokyo Women's Medical University, Japan) between September 2013 and February 2015. We enrolled patients undergoing physiological assessment of coronary artery stenosis with both iFR and FFR. We excluded lesions that needed primary or emergent percutaneous coronary intervention for acute coronary syndrome. AS was defined as a valve area < 1.0 cm^2 and mean aortic valve pressure gradient > 40 mmHg.

Coronary angiography and quantitative coronary angiography

Coronary angiography was performed according to standard clinical practice using the radial or femoral artery approach. QCA was performed using a computer-assisted, automated, edge-detection algorithm (AWOS, Siemens) by an independent physician who was blinded to the results of FFR. The external diameter of the contrast-filled catheter (5-Fr or 6-Fr) was used as the calibration standard. The percentage of DS at end diastole was measured from the worst-view trace.

Standard iFR and FFR measurements

Both iFR and FFR examinations were performed using either diagnostic or interventional guiding catheters. After administration of an intracoronary bolus of nitroglycerin, the pressure wire (Prime Wire Prestige; Volcano Corporation, San Diego, CA) was advanced up to the tip of the catheter and pressure was equalized against that measured through the guiding catheter. After pressure equalization at the tip of the guide catheter was complete, the guidewire was advanced distal to the coronary artery stenosis. First, iFR was directly and automatically measured online using the Volcano Core system (Volcano Corporation). Second, FFR was measured during maximal hyperemia. Hyperemia for the target coronary artery was achieved using either an intracoronary bolus injection of 8–12 mg papaverine or continuous intravenous administration of adenosine at 150 μg/kg/min. At the end of each measurement, the pressure sensor was retracted to the tip of the guide catheter to avoid pressure drift.

Echocardiography

Conventional transthoracic echocardiographic examinations were performed using a commercially available ultrasound transducer and equipment. All images were stored digitally for playback and analysis. Echocardiography measurements were performed according to the guidelines of the American Society of Echocardiography [16]. We estimated left ventricular ejection fraction using the biplane Simpson method. Continuous-wave Doppler recordings were obtained from multiple views, including apical, right parasternal or clavicular, and subcostal views; the peak and mean aortic valve velocity profiles were also measured. Aortic valve area was calculated using the continuity equation according to standard protocol.

Statistical analysis

Categorical variables were compared using the X^2 test. Continuous variables were expressed as mean ± standard deviation and were compared using Student's t test based

on the distributions. A two-sided p value < 0.05 was considered statistically significant. Correlation between FFR and mean iFR was assessed by Spearman rank correlation. Receiver-operating characteristic (ROC) curves were used to evaluate the diagnostic performance of iFR when identifying a positive FFR measurement using the area under the curve. Statistical analyses were performed by a physician using statistical software (JMP Pro 12; SAS Institute Inc., Cary, NC).

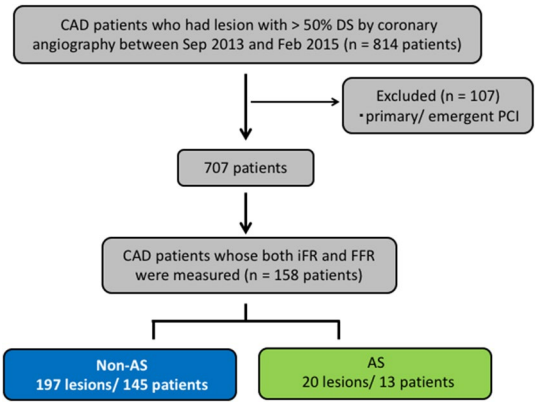

Fig. 1 Flow chart of study patients. *CAD* coronary artery disease, *DS* diameter stenosis, *Sep* September, *Feb* February, *iFR* instantaneous wave-free ratio, *FFR* fractional flow reserve, *AS* aortic valve stenosis

Compliance with ethical standards

The study protocol was based on the regulations of the hospital's ethics committee. All participating patients provided their written informed consent. Patient enrolment was performed according to the principles of the Declaration of Helsinki.

Results

Eight hundred fourteen patients who had % DS > 50% of coronary artery stenosis according to CAG were screened. We excluded patients who needed emergent PCI. A total of 158 patients with 217 lesions who underwent both iFR and FFR were finally included (Fig. 1). Among the 158 patients, AS was observed in 13 (8.2%).

Characteristics of the entire study population, separated according to the presence or absence of AS, are shown in Table 1. The severity of AS was consistent with that similarly found in previous registries of severe AS, with mean aortic valve area of 0.73 ± 0.28 cm^2 and mean aortic valve gradient of 44.0 ± 14.6 mmHg. Patients with AS were older and had undergone less previous revascularization therapy than patients without AS. The iFR showed an excellent correlation with FFR regardless of the prevalence of AS (non-AS: $r = 0.71$, $p < 0.0001$; AS: $r = 0.83$, $p < 0.0001$) (Fig. 2). Table 2 shows lesion characteristics for AS patients and non-AS patients. Lesion location was not significantly different between AS patients and

Table 1 Baseline characteristics in patients with AS and without AS

	All patients ($n = 158$)	Non-AS ($n = 145$)	AS ($n = 13$)	p value
Age* (years)	68.0 ± 11.6	67.0 ± 11.5	79.9 ± 5.6	< 0.0001
Men	118 (74.7%)	110 (75.9%)	8 (61.5%)	0.32
BMI*	23.8 ± 3.7	23.8 ± 3.7	23.3 ± 3.9	0.65
Diabetes mellitus	86 (54.4%)	77 (53.1%)	9 (69.2%)	0.39
Hypertension	126 (79.7%)	113 (77.9%)	13 (100%)	0.07
Hyperlipidemia	103 (65.2%)	96 (66.2%)	7 (53.9%)	0.38
Smoking	83 (52.5%)	77 (53.1%)	6 (46.1%)	0.77
Family history of CAD	51 (32.2%)	49 (37.9%)	2 (15.4%)	0.23
Prior myocardial infarction	49 (31.0%)	47 (32.4%)	2 (15.4%)	0.35
Previous PCI/CABG	86 (54.4%)	83 (57.2%)	3 (23.1%)	0.02
LVEF* (%)	50.1 ± 10.7	50.4 ± 10.9	46.6 ± 8.0	0.22
CKD	88 (55.7%)	80 (55.1%)	8 (61.5%)	0.77
Hemodialysis	36 (22.8%)	33 (22.8%)	3 (23.1%)	1.0
AVA* (cm^2)			0.73 ± 0.28	
Mean AVG* (mmHg)			44.0 ± 14.6	

AS aortic valve stenosis, *BMI* body mass index, *CAD* coronary artery disease, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting, *LVEF* left ventricular ejection fraction, *CKD* chronic kidney disease, *AVA* aortic valve area, *AVG* aortic valve gradient

*Data are expressed as mean ± SD or as number (percentage)

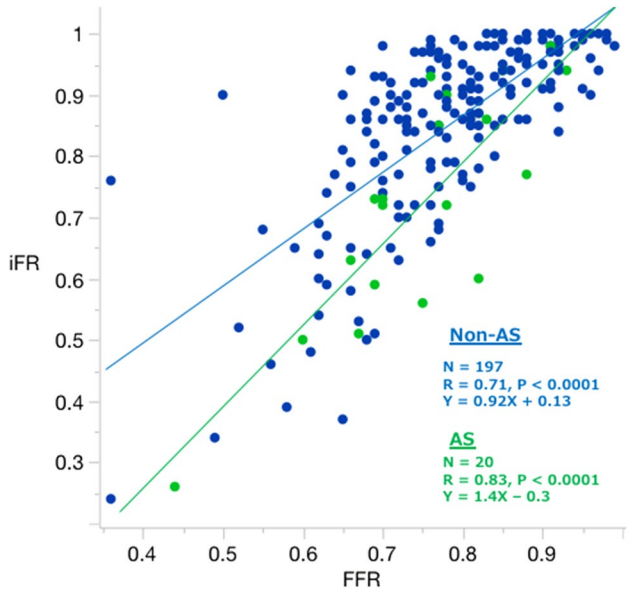

Fig. 2 Correlation between FFR and iFR among lesions in patients without aortic valve stenosis (blue) and with aortic valve stenosis (green). The iFR showed an excellent correlation with FFR regardless of the prevalence of AS. *FFR* fractional flow reserve, *iFR* instantaneous wave-free ratio, *AS* aortic valve stenosis

Table 2 Lesion characteristics in patients with AS and without AS

	Non-AS ($n=197$)	AS ($n=20$)	p value
Site of stenosis			
LAD	106 (53.8%)	9 (45.0%)	0.49
LCX	41 (20.8%)	7 (35.0%)	0.16
RCA	50 (25.4%)	4 (20.0%)	0.79
% DS* (%)	64.2 ± 16.2	68.7 ± 18.1	0.25
FFR*	0.78 ± 0.11	0.75 ± 0.11	0.26
iFR*	0.85 ± 0.14	0.73 ± 0.19	0.0004

AS aortic valve stenosis, *LAD* left anterior descending coronary artery, *LCx* left circumflex coronary artery, *RCA* right coronary artery, *DS* diameter stenosis, *FFR* fractional flow reserve, *iFR* instantaneous wave-free ration

*Data are expressed as mean ± SD or as number (percentage)

non-AS patients. Although there were no significant differences in the percentage of DS and the FFR value for 20 lesions among AS patients and 197 lesions among non-AS patients, the iFR value for AS patients was significantly lower compared to that for non-AS patients. Figure 3 shows the cut-off value for iFR in the ROC analysis to predict FFR of 0.8 for lesions among AS patients and non-AS patients. The cut-off value of iFR to predict FFR of 0.8 was 0.9 for non-AS patients [area under the curve (AUC), 0.82; sensitivity, 0.76; specificity, 0.72; $p < 0.0001$]; however, it was 0.73 for AS patients (AUC 0.84; sensitivity 0.77; specificity 0.86; $p = 0.015$).

Discussion

The primary findings of the present study are as follows: regardless of prevalence of AS, there was a good correlation between iFR and FFR; the mean iFR values for lesions among AS patients were significantly lower than those for lesions among non-AS patients, despite no significant differences were observed in the mean FFR values and percentage of DS; and ROC curves confirmed that the cut-off for iFR to predict FFR of 0.8 differed between lesions with and without AS.

No previous report has examined the impact of the prevalence of AS on iFR. In our examination, the iFR value was significantly lower for lesions among AS patients compared to that for lesions among non-AS patients. In contrast, there was no significant difference in mean FFR value among them. There might be two mechanisms responsible for influencing these two evaluations. One depends on the unique coronary flow pattern in AS patients and the specific cardiac cycle during the iFR evaluation. Another depends on resting coronary conditions for AS patients.

Physiological characteristics of aortic stenosis

For normal patients, coronary flow depicts a biphasic pattern and the systolic coronary flow represents approximately 25% of total coronary flow [14, 17, 18]. In the presence of AS, the systolic coronary flow decreases with increasing stenosis severity, and almost all coronary blood flow is dependent on the diastolic phase in severe AS patient [14, 15]. The trans-lesional pressure gradient has been associated with coronary flow. As a result, the trans-lesional pressure gradient was mainly seen during the diastolic phase in AS patients. The iFR, which is calculated using the trans-lesional pressure gradient during the diastolic phase, could be easily influenced by aortic valve stenosis severity.

iFR was evaluated during resting flow

Some studies have reported that coronary flow reserve is markedly reduced in patients with severe AS [19, 20]. In these studies, one of the mechanisms of coronary flow reserve reduction can be explained by the greater resting coronary flow as a result of increased myocardial metabolic demand with increasing left ventricular workload. The iFR is calculated during resting flow, and pressure wire evaluation using resting flow might be sensitive to hemodynamic changes. Conversely, evaluation during

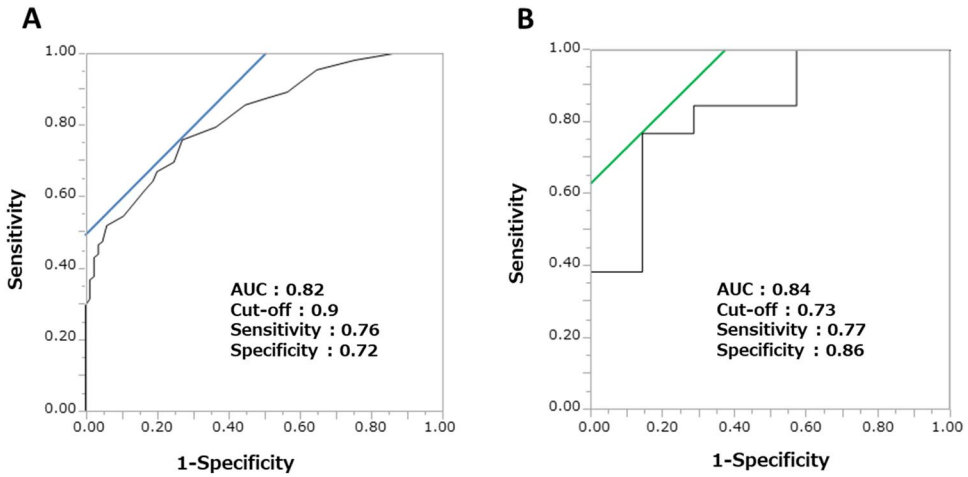

Fig. 3 Receiver-operating characteristic curves of iFR values for 0.8 for FFR among lesions in patients without aortic valve stenosis (**a**) and with aortic valve stenosis (**b**). *iFR* instantaneous wave-free ratio, *FFR* fractional flow reserve

hyperemia is almost independent of these factors. Higher baseline coronary flow induces a greater loss of translesional pressure and could affect iFR values.

The implication and impact of these characteristics on iFR and FFR

During this trial, when using an FFR value of 0.8 as the standard, the optimal cut-off value for iFR to identify lesions with an FFR of 0.8 was 0.9 for non-AS patients, which was an acceptable value compared to previous reports [7]. In contrast, the iFR value of 0.73 was thought to be a predictor of functional significance for AS patients and was lower than the standard predictive value range for iFR. Though vasodilator-free index of iFR is the useful, the cut-off of 0.89 could not apply in patients with severe AS. Further large clinical trials are required to confirm this result for this specific subset.

Study limitations

This study had several important limitations. First, this was a retrospective, single-center, observational cohort study. The number of AS patients was relatively small and we did not have serial echocardiographic data in all patients. We could not exclude the possibility of selection bias. Second, FFR is not a true gold standard evaluation of functional ischemia of coronary artery stenosis in AS patients. In addition, we did not perform comparisons with other stress-inducing coronary functional tests in this study. Third, we speculated the unique flow pattern in AS patients might be one of the reason for decreasing the iFR cut-off value. Theoretically, coronary flow pattern is affected by not only severe AS, but also measured vessels, myocardial viability, stenosis severity, left ventricular hypertrophy and many things. However, we could not compare these factors because of small sample size in this study. Fourth, this study included patients for whom FFR was performed using either intracoronary papaverine (98.6%) or intravenous adenosine (1.4%). Fifth, the subjects in our cohort were mostly men. Moreover, a higher proportion of participants were of advanced age and had hypertension and diabetes mellitus compared with participants in previous studies.

Conclusion

The present study demonstrated good correlation between iFR and FFR for AS patients. Vasodilator-free assessment using iFR may provide potential benefits when evaluating coronary stenosis in patients with AS. In AS patients, the best cut-off of iFR value predicting FFR value of 0.8 was lower than 0.9 that is the standard predictive value of iFR. Further large clinical trials are required to confirm this result for this specific subset.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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