ORIGINAL RESEARCH

Diagnostic Accuracy of Diastolic Fractional Flow Reserve for Functional Evaluation of Coronary Stenosis

DIASTOLE Study

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ABSTRACT

BACKGROUND In the resting conditions, narrowing the window of coronary pressure measurements from the whole cardiac cycle to diastole improves diagnostic performance of coronary pressure–derived physiological index. However, whether this also applies to the hyperemic conditions has not yet been thoroughly evaluated.

OBJECTIVES The purpose of this study was to assess whether diastolic fractional flow reserve (diastolic FFR) has better diagnostic performance in identifying ischemia-causing coronary lesions than conventional FFR in a prospective, multi-center, and independent core laboratory–based environment.

METHODS In this prospective multicenter registry at 29 Japanese centers, we compared the diagnostic performance of FFR, diastolic FFR, resting distal to aortic coronary pressure (Pd/Pa), and diastolic pressure ratio (dPR) using myocardial perfusion scintigraphy (MPS) as the reference standard in 378 patients with single-vessel coronary disease.

RESULTS Inducible myocardial ischemia was found on MPS in the relevant myocardial territory of the target vessel in 85 patients (22%). In the receiver-operating curve analyses, diastolic FFR had comparable area under the curve (AUC) compared with FFR ($AUC_{diastolic\ FFR}$: 0.66; 95% confidence interval [CI]: 0.58-0.73, vs AUC_{FFR}: 0.66; 95% CI: 0.58-0.74, $P = 0.624$). FFR and diastolic FFR showed significantly larger AUCs than resting Pd/Pa (0.62; 95% CI: 0.54-0.70; $P = 0.033$ and $P = 0.046$) but did not show significantly larger AUCs than dPR (0.62; 95% CI: 0.55-0.70; $P = 0.102$ and $P = 0.113$).

CONCLUSIONS Diastolic FFR showed a similar diagnostic performance to FFR as compared with MPS. This result reaffirms the use of FFR as the most accurate invasive physiological lesion assessment. (Diagnostic accuracy of diastolic fractional flow reserve (d-FFR) for functional evaluation of coronary stenosis; UMIN000015906)
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In stable coronary artery disease, an accurate assessment of myocardial ischemia is paramount for decision making related to coronary revascularization (1). To this end, invasive physiological tests play an important role in cardiac cathlabs. Fractional flow reserve (FFR) is a pressure-derived estimate of coronary flow impairment and one of the most established invasive physiological tests (2). Recently, resting coronary pressure indices such as instantaneous wave-free ratio (iFR) have been shown to have comparable diagnostic performance to FFR (3). The resting indices achieve their high diagnostic performance by narrowing the window during which coronary pressures are measured to diastole (4). This prompts the idea that FFR also might improve its diagnostic performance if calculated only by the diastolic pressures instead of the whole cardiac cycle.

In addition, coronary flow estimate by FFR is based on a fundamental principle of coronary physiology called pressure-flow relationship that driving pressure linearly correlates with myocardial blood flow under the conditions of maximal hyperemia (5). The pressure-flow linear relationship, however, holds up only in diastole where the myocardial resistance becomes minimum but not in systole (6). FFR, which is by definition calculated as the ratio between mean distal and proximal coronary pressures during the whole cardiac cycle, might have an inherent limitation in terms of coronary flow estimation because it contains the systolic component.

Diastolic FFR is another hyperemic pressure-derived physiological index calculated exclusively by diastolic pressures (6,7). As described previously, it can be hypothesized that diastolic FFR might outperform FFR with regard to the identification of ischemia-causing coronary lesions. However, this hypothesis has not yet been adequately evaluated. Therefore, we conducted a clinical study entitled DIASTOLE ("DIagnostic Accuracy of diaStolic fracTional flow reserve for functiOnal evaLuation of coronary stEnosis: DIASTOLE Study (UMIN000015906)") to test this hypothesis.

METHODS

STUDY DESIGN. DIASTOLE is a prospective multi-center registry designed to test the superiority of diastolic FFR over FFR in terms of the identification of inducible myocardial ischemia done at 29 study sites in Japan. Wakayama Medical University (Wakayama, Japan) coordinated this study and undertook data management, statistical analysis, and site management.

STUDY POPULATION. Patients who underwent a stress myocardial perfusion scintigraphy (MPS) in a 3-month period either before or after an invasive physiological study for a single epicardial coronary artery disease with at least 1 de novo stenosis (≥50% angiographic stenosis of the diameter on visual assessment) were registered. In patients who underwent revascularization, they were registered only when MPS and invasive physiological study were done before the revascularization. The native epicardial coronary artery showing the stenosis was defined as the target vessel and the stenosis revealing the maximum degree of diameter stenosis in the target vessel was defined as the target lesion. Exclusion criteria were left main disease, chronic total occlusion, in-stent restenosis, acute coronary syndrome, prior myocardial infarction, frequent arrhythmias (atrial fibrillation or ventricular premature contractions), overt heart failure (New York Heart Association functional classification ≥2), significant valvular disease, previous coronary artery bypass graft surgery, inability to give consent, and deemed inappropriate for the enrollment by investigators. Patient demographics, angiography, MPS, and FFR data were collected at each site and sent to the data management center and individual core laboratories. This study was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan. The ethical committee in each participating center approved the study protocol. All patients gave written informed consent.

CORONARY ANGIOGRAPHY. Coronary angiography was performed in a standard manner using a 5- or 6-F catheter in each center. All images were digitally stored for off-line analysis and assessed at an
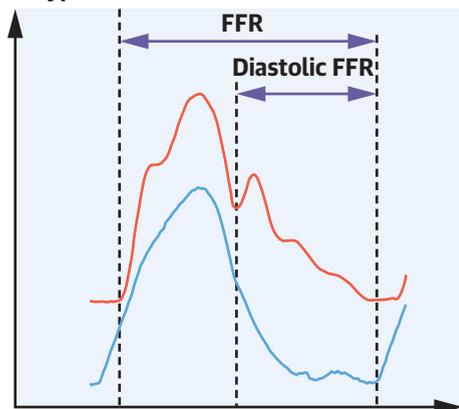
CENTRAL ILLUSTRATION Diagnostic Performance of Fractional Flow Reserve and Diastolic Fractional Flow Reserve as Compared With Myocardial Perfusion Scintigraphy
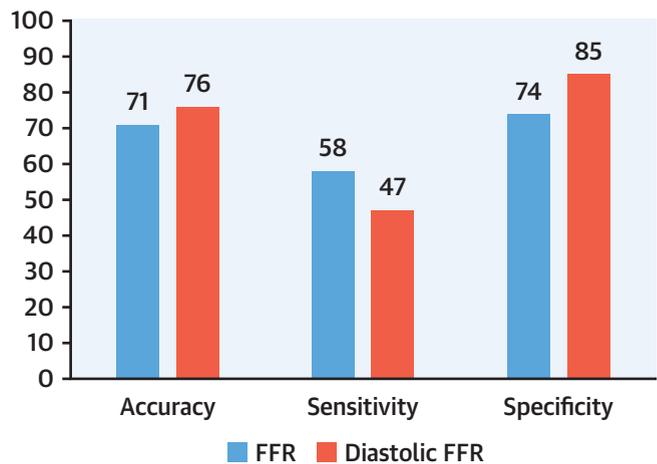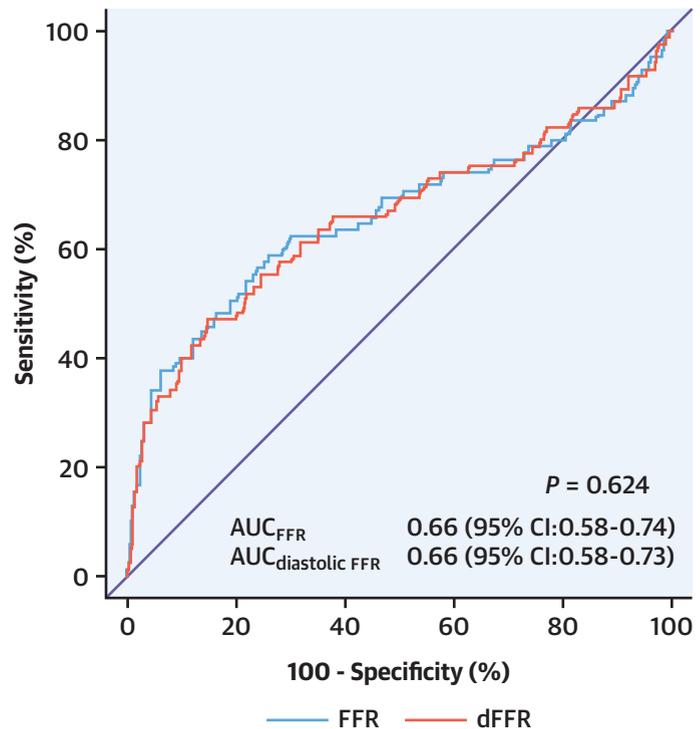
Coronary Angiography

Invasive Pressure Measurements

Hyperemia

FFR

Diastolic FFR

Myocardial Perfusion Scintigraphy

Resting   Stress

$P = 0.624$

AUC$_{FFR}$ 0.66 (95% CI:0.58-0.74)
AUC$_{diastolic\ FFR}$ 0.66 (95% CI:0.58-0.73)

— FFR   — dFFR

	Accuracy	Sensitivity	Specificity
FFR	71	58	74
Diastolic FFR	76	47	85
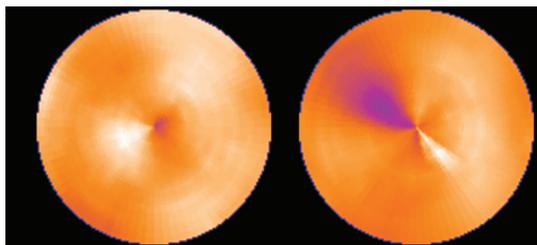
Shiono, Y. et al. JACC: Asia. 2021;1(2):230–241.

In patients presenting with single-vessel disease, the diagnostic performance of FFR and diastolic FFR was compared with the use of MPS as the reference standard. The diagnostic performance of FFR and diastolic FFR were comparable on ROC analysis. Abbreviations as in **Figures 1, 2, and 6**.

angiographic core laboratory (Wakayama Medical University, Wakayama, Japan). Quantitative coronary angiography (QCA) analysis for the target lesion was performed using validated quantitative coronary angiography software (CASS II, Pie Medical). The QCA measurements included reference vessel diameter (RVD), minimal luminal diameter (MLD), percent diameter stenosis ([RVD − MLD] × 100/RVD), and

lesion length. The angiographic lesion patterns were assessed in the target vessel and classified into 3 groups: focal, tandem, and diffus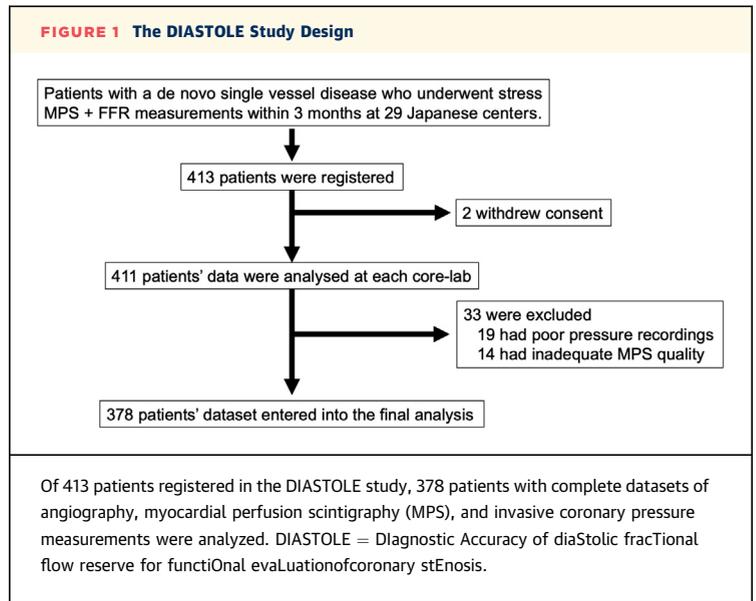e lesions. A focal lesion was defined as a stenosis <20 mm in length, a diffuse lesion as a stenosis ≥20 mm in length, and a tandem lesion as 2 or more stenoses separated by angiographically normal-appearing segment of ≥10 mm in the target vessel (8).

PRESSURE-DERIVED INDICES MEASUREMENTS. A coronary guidewire equipped with sensors of pressure and temperature (Abbott Vascular) was used for intracoronary pressure measurements. After administration of intracoronary nitrate and equalization of the pressure wire, the pressure wire was placed at the distal part of the target vessel. In resting conditions, distal coronary pressure (Pd) and proximal coronary pressure (Pa) were simultaneously recorded for at least 5 seconds. After the resting pressure recording, hyperemia was induced by intravenous adenosine triphosphate (180 μg/kg/min through central or antecubital vein). During stable hyperemia, hyperemic Pd and Pa were recorded simultaneously. At the end of each recording, the pressure sensor was retracted to the catheter tip to assess pressure drift.

Pressure raw data were analyzed off-line at a physiological core laboratory (Kawasaki University of Medical Welfare, Okayama, Japan) using a custom software package designed with Scilab (Scilab Enterprises). Resting and hyperemic periods were carefully chosen from the entire pressure recordings for the analysis. The diastole was identified from the aortic pressure waveforms as the period from the beginning of dicrotic notch to the pressure nadir at the end of diastole (**Central Illustration**). Resting Pd/Pa was calculated as the ratio of averaged resting Pd to Pa during the whole cardiac cycle. Resting diastolic pressure ratio (dPR) was the ratio of resting Pd to Pa during diastole (10). FFR was the ratio of averaged hyperemic Pd to Pa during the whole cardiac cycle. Diastolic FFR was the ratio of hyperemic Pd to Pa during diastole. This calculation method for diastolic FFR was slightly different from that in the original article, which took account of left ventricular pressure; we adopted another method from a subsequent study for the sake of simplicity (7,9).

MYOCARDIAL PERFUSION SCINTIGRAPHY. Stress MPS was performed in accordance with local protocols. When technetium 99m-labeled (Tc-99m) tracer (tetrofosmin or sestamibi) was used, rest/stress or stress/rest images were acquired either by 1- or 2-day protocol. When thallium-201 (Tl-201) was used, stress/redistribution rest images were acquired. When dual-isotope was used, Tl-201 stress/Tc-99m

FIGURE 1 The DIASTOLE Study Design

Patients with a de novo single vessel disease who underwent stress MPS + FFR measurements within 3 months at 29 Japanese centers.

↓

413 patients were registered → 2 withdrew consent

↓

411 patients' data were analysed at each core-lab → 33 were excluded
19 had poor pressure recordings
14 had inadequate MPS quality

↓

378 patients' dataset entered into the final analysis

Of 413 patients registered in the DIASTOLE study, 378 patients with complete datasets of angiography, myocardial perfusion scintigraphy (MPS), and invasive coronary pressure measurements were analyzed. DIASTOLE = DIagnostic Accuracy of diaStolic fracTional flow reserve for functiOnal evaLuationofcoronary stEnosis.

rest images were acquired. All patients underwent pharmacological or exercise stress testing. In the pharmacological test, adenosine was used. In the exercise stress test, graded exercise was given according to a predetermined standardized incremental exercise protocol.

MPS images were analyzed at an MPS core laboratory (Gifu Heart Center, Gifu, Japan). The SPECT images were semiquantitatively scored by 2 experienced physicians who were blind to patients' clinical, angiographic, and invasive physiological information. The left ventricular wall was divided into 17 segments according to the American Heart Association consensus (11), and a semiquantitative scoring system in each of the 17 segments was used and scored in accordance with a 5-point scale (0: normal uptake, 1: mildly reduced uptake, 2: moderately reduced uptake, 3: severely reduced uptake, and 4: almost no uptake) (12). The total scores of the 17 segments in the stress and rest images provided the summed stress score (SSS) and the summed rest score (SRS), respectively. The summed difference score (SDS) was

TABLE 1 Patient Characteristics (N = 378)

Age, y	72.5 (66.0-77.0)
Male	259 (69)
Body mass index (kg/m^2)	24.2 (22.0-26.4)
Hypertension	275 (73)
Diabetes mellitus	137 (36)
Dyslipidemia	265 (70)
Current smoker	58 (15)
Family history coronary artery disease	62 (16)

Values are n (%) or median (interquartile range).

TABLE 2 Angiographic and Physiological Lesion Characteristics (N = 378)

Target vessel location	
RCA	70 (19)
LAD	252 (66)
LCX	56 (15)
Angiographic patterns	
Focal	276 (73)
Diffuse	78 (21)
Tandem	24 (6)
QCA	
Reference vessel diameter, mm	2.8 (2.4-3.2)
Minimum lumen diameter, mm	1.3 (1.0-1.7)
%DS, %	52 (43-65)
Lesion length, mm	12.1(8.8-17.1)
Physiological indices	
Pd/Pa	0.93 (0.89-0.97)
dPR	0.91 (0.84-0.96)
FFR	0.82 (0.73-0.88)
Diastolic FFR	0.72 (0.60-0.83)
FFR ≤0.80	166 (43)

Values are n (%) or median [interquartile range].

dPR = diastolic pressure ratio; FFR = fractional flow reserve; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; %DS = percent diameter stenosis; Pa = proximal aortic pressure; Pd = distal coronary pressure; QCA = quantitative coronary angiography; RCA = right coronary artery.

defined as the difference between the SSS and SRS. In this model, the left anterior descending artery (LAD) distribution territory consists of 7 segments (ie, segments 1, 2, 7, 8, 13, 14, and 17); the left circumflex artery (LCx) consists of 5 segments (ie, segments 5, 6, 11, 12, and 16); and the right coronary artery (RCA) consists of 5 segments (ie, segments 3, 4, 9, 10, and 15). The MPS findings were considered positive for myocardial ischemia when the improvement at rest was 2 or more points in the relevant coronary territory.

SAMPLE SIZE DETERMINATION. Because, in a relevant previous study, an area under the curve (AUC) of receiver-operating characteristic (ROC) analysis was not given, we calculated our sample size assuming an absolute difference of 6.5% in the accuracy between diastolic FFR and FFR in the identification of inducible myocardial ischemia (97.8% for diastolic FFR and 91.3% for FFR) ([7]). To achieve a power of 90% to detect the superiority for diastolic FFR with a 2-sided 5% significant level, we calculated a minimum of 359 participants using the McNemar test. To accommodate a potential dropout of 15% due to various types of protocol violations, withdrawals, and missing or unanalyzable data, the total sample size was calculated as 413 cases.

STATISTICAL ANALYSIS. Categorical variables were expressed as numbers and percentages. Continuous

variables were expressed as median (interquartile range [IQR]). The distributions of physiological indices were shown in density and scatter plots. Correlations between each physiological index was assessed by Pearson correlation coefficient. Sensitivity, specificity, accuracy, AUC, and best cutoff values were analyzed for each physiological index using ROC curves by maximizing the Youden index. Comparisons were performed by Student's *t*-tests or Mann-Whitney test for continuous variables, and by chi-square or Fisher's exact tests for categorical variables as appropriate. The AUCs for each physiological index were compared using DeLong's methods. The *P* values were 2-sided, and *P* values <0.05 were considered statistically significant. Statistical analyses were performed using R version 3.6.0 (R Foundation).

RESULTS

PATIENT RECRUITMENT AND POPULATION. Between January 14, 2015, and May 22, 2019, a total of 413 patients were enrolled. Of these, 2 patients withdrew. Of the remaining 411 patients, 318 (77%) underwent MPS before invasive angiography with FFR, and 93 (23%) underwent invasive angiography with FFR before MPS. At core-lab analyses, 33 patients were excluded because 19 had poor pressure recordings and 14 had inadequate MPS quality. As a result, 378 entered into the final analysis (Figure 1). Clinical characteristics of the study population are summarized in Table 1.

LESION CHARACTERISTICS. Table 2 shows the angiographic and physiological lesion characteristics. The target vessel was most often located in LAD (66%), and followed by RCA (19%), and LCX (15%). Target lesions presented with a focal lesion in most cases (n = 276, 73%). The median value of percent diameter stenosis was 52% (IQR 43%-65%), indicating that most of the target lesions had intermediate stenosis. Median values of resting Pd/Pa, dPR, FFR, and diastolic FFR were 0.93 (IQR 0.89-0.97), 0.91 (IQR 0.84-0.96), 0.82 (IQR 0.73-0.88), and 0.72 (IQR 0.60-0.83), respectively. FFR ≤0.80 was found in 166 (43%) lesions. All the distributions of resting Pd/Pa, dPR, FFR, and diastolic FFR values deviated from normal distribution with negative skewness (Figure 2). Diastolic FFR had the largest dynamic range of values (IQR 0.09-1.05) compared with FFR (IQR 0.33-1.05), resting Pd/Pa (IQR 0.37-1.04), and dPR (IQR 0.14-1.09).

RELATIONSHIP AMONG RESTING PD/PA, dPR, FFR, AND DIASTOLIC FFR. The correlations between

FIGURE 2 The Distribution of Resting Pd/Pa, dPR, FFR, and Diastolic FFR
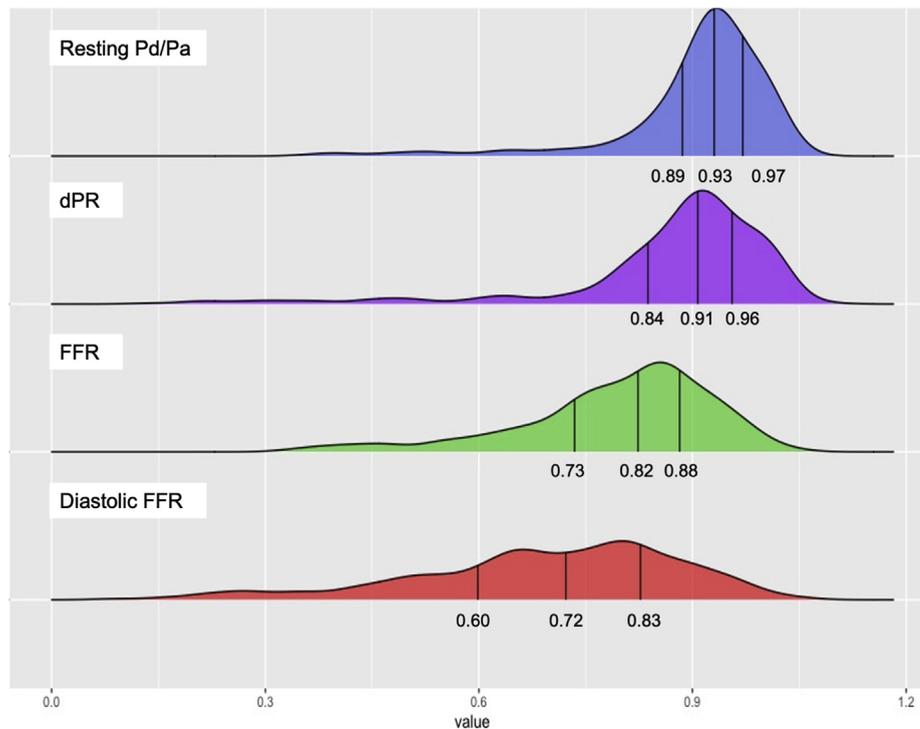
Density plots show the different distribution of resting distal to aortic coronary pressure (Pd/Pa), diastolic pressure ratio (dPR), fractional flow reserve (FFR), and diastolic FFR from the same 378 vessels. Vertical black lines indicate median, and upper and lower interquartile range of each index.

diastolic FFR and FFR ($r = 0.98$, $P < 0.001$), and resting Pd/Pa and dPR ($r = 0.99$, $P < 0.001$) were near perfect. Other combinations of physiological indices also showed very strong correlations with each other (FFR and resting Pd/Pa, $r = 0.83$, $P < 0.001$; FFR and dPR, $r = 0.81$, $P < 0.001$; diastolic FFR and resting Pd/Pa, $r = 0.81$, $P < 0.001$; diastolic FFR and dPR, $r = 0.81$, $P < 0.001$, respectively) (**Figure 3**).

MYOCARDIAL PERFUSION SCINTIGRAPHY. For MPS, 336 (89%) patients underwent pharmacological stress and 42 (11%) did the exercise stress test. Myocardial ischemia was found in 85 (22%) patients in the relevant territory of the target lesions (**Table 3**). Unexpectedly, 67 (18%) patients showed myocardial ischemia in the territories outside the target lesions; it was most often found in inferior walls (34 of 67). According to SDS, 226 (60%) patients showed no ischemia, whereas mild ischemia was found in 103 (27%), moderate in 29 (8%), and severe in 20 (5%).

DIAGNOSTIC PERFORMANCE OF FFR AND DIASTOLIC FFR. FFR and diastolic FFR showed comparable

diagnostic performance (AUC$_{FFR}$: 0.66, 95% CI: 0.58-0.74 vs AUC$_{diastolic\ FFR}$: 0.66, 95% CI: 0.58-0.73, $P = 0.624$) (**Central Illustration**). The cutoff values to identify MPS-derived ischemia were 0.77 for FFR and 0.56 for diastolic FFR. With these cutoff values, sensitivity, specificity, and accuracy were 58%, 74%, and 71% for FFR, and 47%, 85%, and 76% for diastolic FFR, respectively.

In the subgroup analysis of each coronary artery, the diagnostic performance of FFR and diastolic FFR did not differ in LAD (AUC$_{FFR}$: 0.73, 95% CI: 0.64-0.84 vs AUC$_{diastolic\ FFR}$: 0.73, 95% CI: 0.63-0.83, $P = 0.543$), in RCA (AUC$_{FFR}$: 0.63, 95% CI: 0.47-0.77 vs AUC$_{diastolic\ FFR}$: 0.65, 95% CI: 0.50-0.80, $P = 0.101$), and in LCX (AUC$_{FFR}$: 0.80, 95% CI: 0.67-0.93 vs AUC$_{diastolic\ FFR}$: 0.81, 95% CI: 0.68-0.93, $P = 0.442$) (**Figure 4**).

ROC curve for diastolic FFR to predict an established FFR cutoff of ≤0.80 showed that the AUC was 0.99 (95% CI: 0.99-1.00) and the optimal cutoff value of diastolic FFR was 0.69 (**Figure 5**). The sensitivity, specificity, and accuracy were 98%, 96%, and 97%, respectively.

FIGURE 3   Relationship Between Physiological Indices
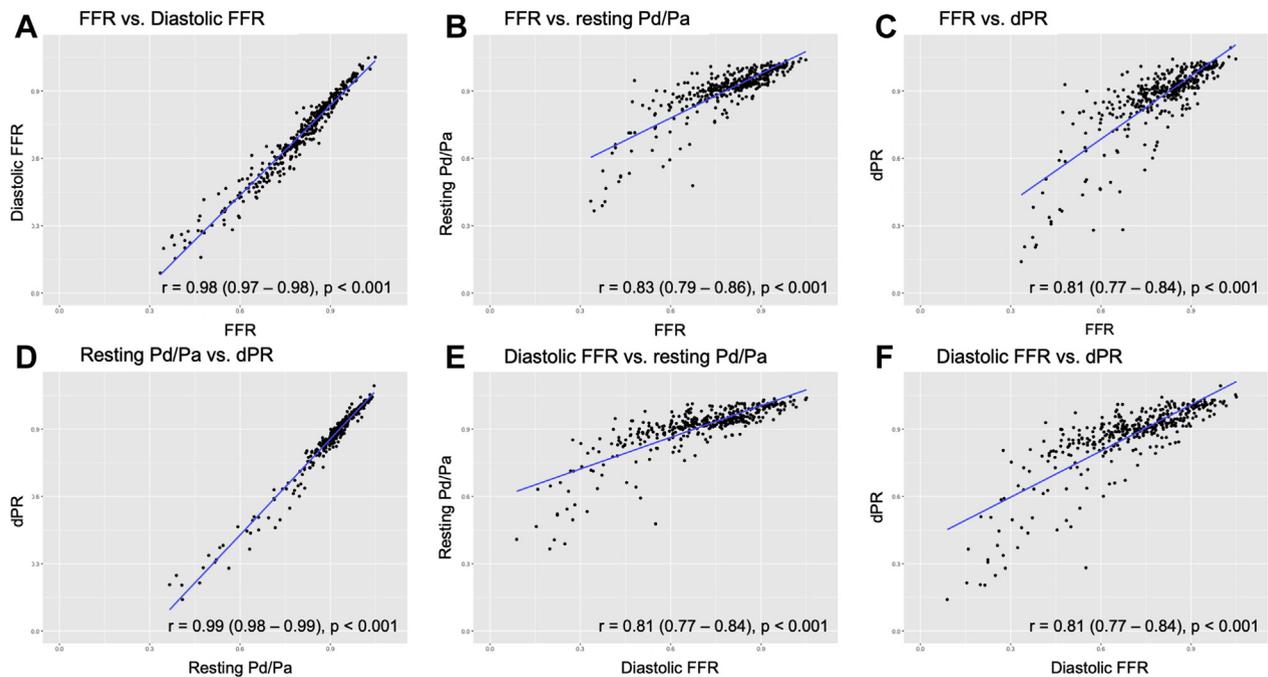
Scatter plots of each 2 physiological indices with their corresponding correlation coefficients and 95% confidence interval.

DIAGNOSTIC PERFORMANCE OF RESTING VERSUS HYPEREMIC INDICES AGAINST MPS.

In Figure 6, resting Pd/Pa, dPR, FFR, and diastolic FFR are compared against MPS as the reference standard. FFR and diastolic FFR showed significantly larger AUC than resting Pd/Pa (AUC_{FFR}: 0.66, 95% CI: 0.58-0.74, vs $AUC_{Pd/Pa}$: 0.62, 95% CI: 0.54-0.70, $P = 0.033$; $AUC_{diastolic\ FFR}$: 0.66, 95% CI: 0.58-0.73 vs $AUC_{Pd/Pa}$: 0.62, 95% CI: 0.54-0.70, $P = 0.046$, respectively). On

the other hand, the AUC for FFR and diastolic FFR were numerically larger but statistically insignificant as compared with dPR (AUC_{FFR}: 0.66, 95% CI: 0.58-0.74, vs AUC_{dPR}: 0.62, 95% CI: 0.55-0.70, $P = 0.102$; $AUC_{diastolic\ FFR}$: 0.66, 95% CI: 0.58-0.73 vs AUC_{dPR}: 0.62, 95% CI: 0.55-0.70, $P = 0.113$, respectively). The cutoff value for resting Pd/Pa to predict MPS-derived ischemia was 0.82, and sensitivity, specificity, and accuracy were 34%, 95%, and 81%, and those for dPR were 0.85, and 51%, 77%, and 71%, respectively.

DISCUSSION

In this study, we compared 4 physiological indices, FFR, diastolic FFR, Pd/Pa, and dPR, with the use of MPS as the reference standard and found that: 1) diastolic FFR was not superior to FFR; and 2) both FFR and diastolic FFR had significantly higher diagnostic performance than resting Pd/Pa, but the significance was not seen when compared with dPR.

COMPARABLE DIAGNOSTIC PERFORMANCES BETWEEN FFR AND DIASTOLIC FFR.

We conducted this study in the hope that we could demonstrate the superiority of diastolic FFR over the conventional FFR in identifying ischemia-causing coronary lesions; however, this study failed to show the superiority.

TABLE 3 MPS Results (N = 378)	
Stress methods	
Adenosine	336 (89)
Exercise	42 (11)
Grade of ischemia (SDS*)	
no ischemia (SDS ≤1)	226 (60)
Mild (SDS: 2-4)	103 (27)
Moderate (SDS: 5-6)	29 (8)
Severe (SDS ≥7)	20 (5)
Ischemia in the target lesion	
Positive for ischemia	85 (22)
Negative for ischemia	293 (78)

Values are n (%).
MPS = myocardial perfusion scintigraphy; SDS = summed difference score.

FIGURE 4   Diagnostic Agreement of FFR and Diastolic FFR With MPS in Each Coronary Artery

(A to C) Area under the curve (AUC) calculated for FFR and diastolic FFR to correspond with MPS-derived myocardial ischemia in left anterior descending artery (LAD), right coronary artery (RCA), and left circumflex artery (LCX). (D to F) Corresponding diagnostic properties of FFR and diastolic FFR in each coronary artery. Abbreviations as in **Figures 1 and 2**.
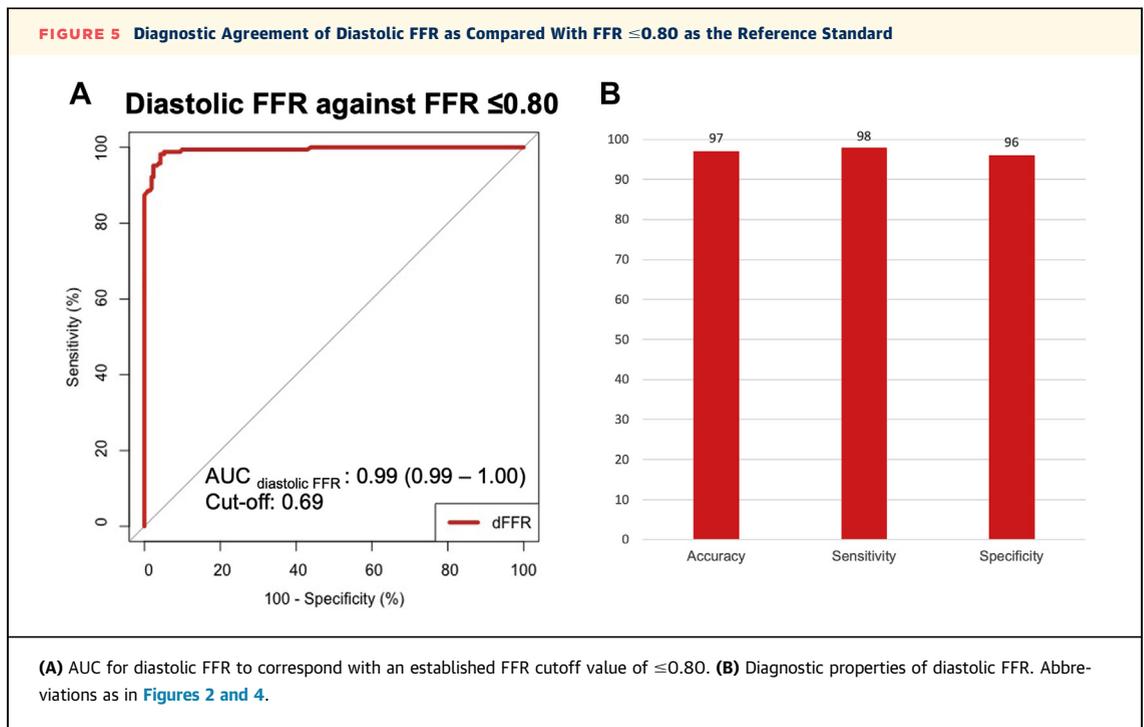
There are some possible explanations for this result. First, systole only constitutes one-fourth or less of the whole cardiac cycle and including systolic pressures in FFR calculation might barely affect its capability of coronary flow estimation despite the fact that the relationship curve between coronary pressure and coronary flow distorts in systole (13,14). Second, although coronary blood flow occurs predominantly in diastole, there is also a forward flow in systole that diastolic FFR does not take into account at all. The negligence of systole in diastolic FFR might influence its accuracy of coronary flow estimation to some extent. Last, in contrast to the original study, a simplified calculation algorithm was used for diastolic FFR in this study. This might have affected the sample size calculation (7,9).

Although there have been previous studies showing that the diagnostic accuracy of hyperemic diastolic pressure indices akin to diastolic FFR was not superior to the conventional FFR, none of them were conclusive because they were not performed as rigorously as in the DIASTOLE study with prospective, multicenter, and independent core laboratory settings (15,16). With the results of the DIASTOLE study, however, we can draw a certain conclusion that FFR does not improve its diagnostic performance by narrowing the window of pressure measurements from whole cardiac cycle to diastole.
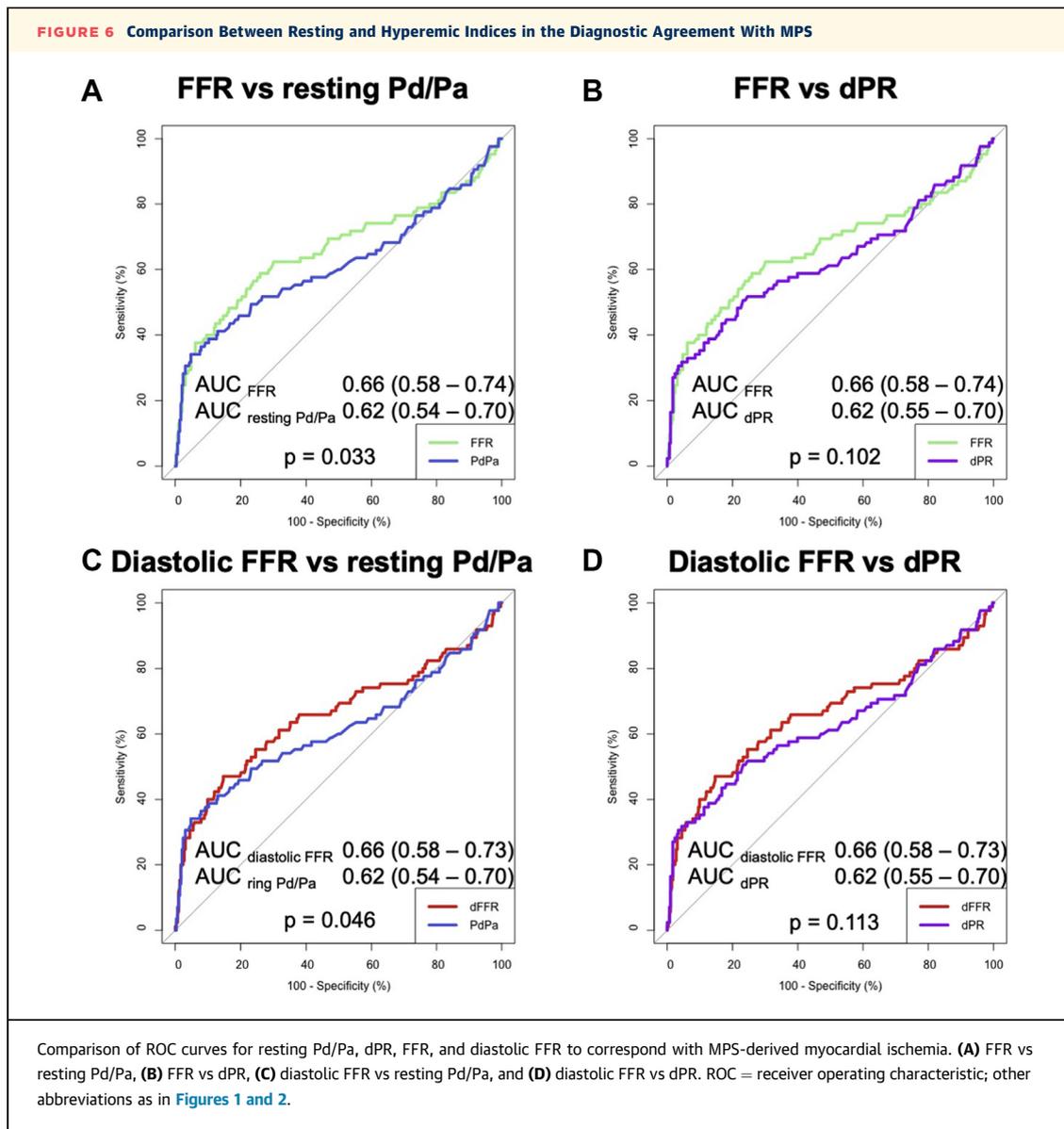
RESTING VS HYPEREMIC INDICES. In the comparison between hyperemic and resting indices, both FFR and diastolic FFR showed significantly larger AUC than resting Pd/Pa, but their significance was not found as compared with that of dPR. These findings mirror previous studies, one of which compared FFR, resting Pd/Pa, and iFR against MPS, and the other of which compared them against H_2O positron emission tomography (PET) (15,17). These suggest that the hyperemic index, whether it is whole-cycle or diastolic index, is more closely associated with myocardial perfusion images than resting Pd/Pa, and the agreement of resting indices with myocardial perfusion images become better by narrowing the period of

FIGURE 5 Diagnostic Agreement of Diastolic FFR as Compared With FFR ≤0.80 as the Reference Standard

(A) AUC for diastolic FFR to correspond with an established FFR cutoff value of ≤0.80. **(B)** Diagnostic properties of diastolic FFR. Abbreviations as in Figures 2 and 4.

pressure measurements from whole cardiac cycle to diastole. Other studies also have reported better diagnostic performance of diastolic resting indices than the whole cardiac-cycle Pd/Pa (18,19). It should be noted, however, that the RESOLVE (Multicenter core laboratory comparison of the instantaneous wave-free ratio and resting Pd/Pa with fractional flow reserve) study, which is the largest multicenter core laboratory comparison between iFR and the whole cardiac cycle Pd/Pa with FFR, has reported that the diagnostic performances of iFR and the whole cardiac cycle Pd/Pa are not different (20). Also, another study has reported that the measurement window for the resting index does not necessarily need to be in the diastole (21). The optimal measurement period for the resting index is still debatable.

AGREEMENT BETWEEN MPS AND PRESSURE INDICES. Another notable finding in this study is that diagnostic agreements between MPS and pressure indices were not as high as those in previous literature and MPS-derived ischemia was found in nontarget vessel territories in many cases, even though we excluded patients with multiple vessel or left main diseases that are known to diminish the diagnostic performance of MPS (5,22). One reason for this is that MPS detects myocardial ischemia caused

by epicardial coronary lesions, microvascular diseases, or a combination of them, whereas pressure-derived indices identify ischemia caused by epicardial coronary lesions. In case of microvascular diseases, pressure-derived indices cannot detect myocardial ischemia, which MPS can. Patel et al. (23) reported that only 41% of patients with a positive result on a noninvasive test revealed an obstructive coronary artery disease on an invasive coronary angiography (23). Because MPS and pressure-derived indices evaluate the different domains of coronary circulatory system, discordance between MPS and pressure-derived indices is a natural phenomenon. Another reason might lie in the fact that target lesions in our study predominantly consisted of focal stenosis. In focal stenosis, pressure losses are likely to happen due to flow separation and lead to significantly lower values in pressure indices even in lesions with well-preserved coronary flow (24). With regard to the ischemic findings of MPS in nontarget vessel territories, they were perhaps due to microvascular disease, flow-limitation (despite only mild stenosis) in nontarget vessels, or artifacts in inferior walls. Finally, by design, the interpreters for MPS were blinded to all the relevant information other than MPS images. This helped to increase the

FIGURE 6 Comparison Between Resting and Hyperemic Indices in the Diagnostic Agreement With MPS

Comparison of ROC curves for resting Pd/Pa, dPR, FFR, and diastolic FFR to correspond with MPS-derived myocardial ischemia. **(A)** FFR vs resting Pd/Pa, **(B)** FFR vs dPR, **(C)** diastolic FFR vs resting Pd/Pa, and **(D)** diastolic FFR vs dPR. ROC = receiver operating characteristic; other abbreviations as in **Figures 1 and 2**.

integrity of this study but could lead to poorer agreement than other reports from single-center studies even after careful assessments by experts (15,17,22).

STUDY LIMITATIONS. First, we used MPS as the reference standard, noting that it has a modest diagnostic performance to identify a flow-limiting coronary stenosis. To improve the diagnostic performance of MPS, repeated MPS pre and post successful revascularization in cases with positive FFR could have been used, as was done in the original FFR validation study (25). The original validation study also used a combination method of other noninvasive tests, such

as an exercise electrocardiogram and a dobutamine-stress echocardiography alongside MPS; this also could have been used to improve diagnostic effectiveness in our study. Alternatively, other ischemic tests such as cardiac magnetic resonance imaging (MRI) or PET that have higher diagnostic performance than MPS would have been better as the reference standard. However, multiple tests for a patient would have been laborious and costly, and MPS is more commonly used than MRI or PET. MPS as the reference standard was a more feasible way to conduct a multicenter prospective study of this kind. In addition, although we performed direct comparisons

between pressure-derived indices and MPS, it must be borne in mind that they are conceptually different ischemic tests. Second, the methods of MPS were not standardized. Standardization of MPS was not feasible to conduct this study in the multicenter setting. Third, the low percentage of ischemia on MPS might have reduced the chance to detect differences between physiologic indices. Fourth, this study only included single-vessel disease and excluded left main disease and prior myocardial infarction to maximize the diagnostic accuracy of MPS. Our study results cannot be applied to patients with these conditions. Fifth, all the analyses for angiography, MPS scans, and pressure data were performed in a blinded fashion at each core laboratory, but patients and physicians were not blinded to these findings. This might have led to a selection bias. Last, cardiac conditions that have peculiar systolic flow patterns, such as aortic stenosis, hypertrophic cardiomyopathy, or myocardial bridge, were not included in this study. Diastolic FFR could show better diagnostic performance than FFR in these conditions (9).

CONCLUSIONS

The diagnostic performance of the diastolic FFR is comparable to the conventional FFR in terms of identification of inducible myocardial ischemia as compared with MPS as the reference standard.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: This study confirmed the medical knowledge that currently used physiological indices such as FFR and nonhyperemic resting index are accurate enough for identification of ischemia-causing coronary lesions.

TRANSLATIONAL OUTLOOK: Physiology-guided revascularization with the use of FFR or nonhyperemic index needs to be more integrated into clinical practice.

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KEY WORDS fractional flow reserve, myocardial ischemia, myocardial perfusion scintigraphy, stable coronary artery disease

APPENDIX For a list of the participating centers and collaborators, please see the online version of this paper.