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Similarity and Difference of Resting Distal to Aortic Coronary Pressure and Instantaneous Wave-Free Ratio

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ABSTRACT

BACKGROUND Instantaneous wave-free ratio (iFR) has been used in clinical practice to identify functionally significant stenosis and to guide treatment strategy. However, there are limited clinical data regarding another resting pressure-derived index, resting distal to aortic coronary pressure (Pd/Pa), and similarities and differences between resting Pd/Pa and iFR.

OBJECTIVES The authors investigated the changes in resting Pd/Pa and iFR according to anatomic and hemodynamic stenosis severity and their prognostic implications.

METHODS From the 3V FFR-FRIENDS (Clinical Implication of 3-vessel Fractional Flow Reserve) and the IRIS-FFR (Study of the Natural History of FFR Guided Percutaneous Coronary Intervention) studies, 1,024 vessels (n = 435) with available pre-intervention resting Pd/Pa and iFR were used to explore the changes in resting physiological indices according to percent diameter stenosis. Among 115 patients who underwent ^{13}N-ammonia positron emission tomography, the changes in those indices according to basal and hyperemic stenosis resistance and absolute hyperemic myocardial blood flow were compared. The association between physiological indices and the risk of 2-year major adverse cardiac events (MACE) (a composite of cardiac death, myocardial infarction, and ischemia-driven revascularization) were analyzed among 375 deferred patients.

RESULTS There was a significant linear correlation between resting Pd/Pa and iFR ($R = 0.970$; $p < 0.001$, iFR $= 1.370 \times$ resting Pd/Pa $- 0.370$). Both resting Pd/Pa and iFR changed significantly according to percent diameter stenosis, basal and hyperemic stenosis resistance, and hyperemic absolute myocardial blood flow (all p values <0.001). Percent difference of iFR according to the increase in anatomic and hemodynamic severity was higher than that of resting Pd/Pa. Both resting Pd/Pa and iFR showed a significant association with the risk of 2-year MACE (resting Pd/Pa hazard ratio [per 0.10 increase]: 0.480; 95% confidence interval: 0.250 to 0.923; $p = 0.027$; iFR hazard ratio [per 0.1 increase]: 0.586; 95% confidence interval: 0.373 to 0.919; $p = 0.020$) in deferred patients. However, the difference between the upper- and lower-bound estimated MACE rates according to the approximate measurement variability of each index was significantly higher with resting Pd/Pa compared with iFR (resting Pd/Pa 3.85 $\pm$ 4.00% and iFR 3.27 $\pm$ 3.39%; $p < 0.001$).

CONCLUSIONS Both resting Pd/Pa and iFR showed similar associations with anatomic and hemodynamic stenosis severity and the risk of MACE. However, iFR was more sensitive to the difference in stenosis severity and showed a lower maximum difference in estimated MACE risk influenced by the measurement variability compared with resting Pd/Pa. (Clinical Implication of 3-Vessel Fractional Flow Reserve [3V FFR-FRIENDS]; NCT01621438; and Study of the Natural History of FFR Guided Percutaneous Coronary Intervention [IRIS-FFR]; NCT01366404) (J Am Coll Cardiol 2017;70:2114–23) © 2017 by the American College of Cardiology Foundation.

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Identification of functionally significant coronary stenosis and ischemia-directed percutaneous coronary intervention (PCI) has been standard practice for patients with coronary artery disease. Fractional flow reserve (FFR) has been regarded as a reference invasive method to evaluate the functional significance of epicardial coronary artery stenosis (1,2). Recently, a physiological index that does not require hyperemia, instantaneous wave-free ratio (iFR), was introduced, and 2 randomized controlled trials showed noninferiority of iFR-guided strategy compared with FFR-guided strategy in terms of 1-year clinical outcomes (3,4). Although iFR is measured during rest, it is different from the whole-cycle resting distal to aortic coronary pressure (resting Pd/Pa) and relies on the identification of a wave-free period during diastole in which microvascular resistance is stable (5,6). Despite this methodological difference between resting Pd/Pa and iFR, previous studies reported an equivalent diagnostic performance of resting Pd/Pa and iFR using FFR (7–13) or the parameters from positron emission tomography (PET) as the reference standard (14). However, there was no study that comprehensively evaluated the similarity and difference between these 2 resting pressure-derived indices beyond the comparison of diagnostic performance.

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We sought to explore the similarity and difference between resting Pd/Pa and iFR in response to anatomic and hemodynamic stenosis severity and their association with clinical outcomes.

METHODS

STUDY DESIGN AND PATIENT POPULATION. The study population was derived from the 3V FFR-FRIENDS study (Clinical Implication of 3-Vessel Fractional Flow Reserve; NCT01621438) (15) and IRIS-FFR registry (Study of the Natural History of FFR Guided Percutaneous Coronary Intervention; NCT01366404) (16). In both studies, patients with depressed left ventricular systolic function (ejection fraction <35%), acute ST-segment elevation myocardial infarction (MI) within 72 h, previous coronary artery bypass graft surgery, chronic renal disease, abnormal epicardial coronary flow (Thrombolysis In Myocardial Infarction flow grade <3) or planned coronary artery bypass graft surgery after diagnostic angiography were excluded. When PCI was indicated, coronary interventions were performed using current standard techniques. For lesions with significant per-vessel FFR (≤0.80), PCI was recommended as per the current guideline. However, the decision for PCI was at the discretion of the operators.

Among the total population, 1,024 vessels (435 patients) with available iFR and resting Pd/Pa were included in the current study. Among these patients, 115 patients who underwent ^{13}N-ammonia PET within 3 months of invasive physiological study for single lesion in the left anterior descending coronary artery (17) were analyzed as a PET subcohort. The study protocol was approved by the institutional review board or ethics committee at each participating center and all patients provided written informed consent.

ABBREVIATIONS AND ACRONYMS

%DS = percent diameter stenosis
BSR = basal stenosis resistance
CI = confidence interval
FFR = fractional flow reserve
HR = hazard ratio
HSR = hyperemic stenosis resistance
iFR = instantaneous wave-free ratio
IQR = interquartile range
MACE = major adverse cardiac events
MBF = myocardial blood flow
MI = myocardial infarction
PCI = percutaneous coronary intervention
Pd/Pa = distal to aortic coronary pressure
PET = positron emission tomography

^{13}N-AMMONIA PET PROTOCOL AND QUANTIFICATION OF ABSOLUTE MYOCARDIAL BLOOD FLOW. The ^{13}N-ammonia PET protocol and quantification of absolute myocardial blood flow (MBF) were presented previously (17). Briefly, all ^{13}N-ammonia PET images were acquired at baseline and in hyperemic states by continuous intravenous infusion of adenosine (140 μg/kg/min), started 3 min before the stress scan, employing low-dose computed tomography to correct for scatter and attenuation. A bolus of ^{13}N-ammonium (370 MBq) was injected via peripheral vein in both resting and hyperemic states, and list mode dynamic imaging was performed using a Siemens Biograph-40 PET/CT scanner (Siemens Medical Solutions, Erlangen, Germany). A 2-compartment model was applied to quantify absolute MBF (ml/min/g). In PET images, the 6 basal segments were not quantified due to low counts in membranous interventricular septum and artifacts. Parametric stress MBF polar maps were used to delineate defect areas in target myocardial territories and to obtain MBF values of target segments. For image analysis and quantification of resting and stress absolute MBF in milliliters per minute per

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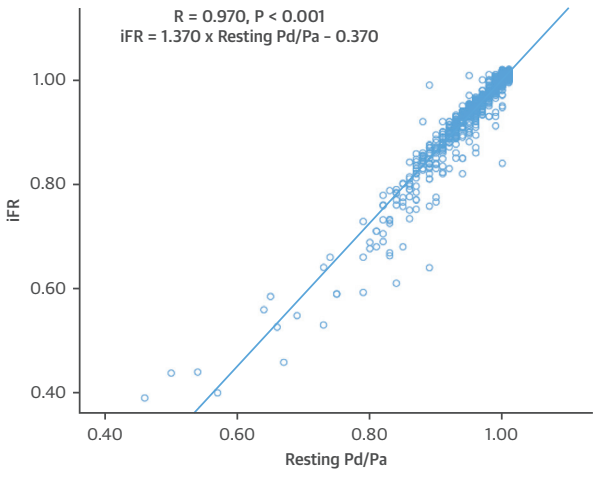
TABLE 1 General Characteristics of Patients and Lesions

	Total Cohort	PET Subcohort
Patients		
General characteristics	435	115
Age, yrs	63.8 ± 9.7	63.6 ± 9.0
Male	341 (78.4)	103 (89.6)
Ejection fraction, %	61.6 ± 6.6	60.1 ± 6.0
Cardiovascular risk factors		
Hypertension	274 (63.1)	79 (68.7)
Diabetes mellitus	156 (35.9)	38 (33.0)
Hypercholesterolemia	309 (71.2)	105 (91.3)
Current smoker	96 (22.1)	19 (16.5)
Clinical presentation		
Stable angina	379 (87.1)	115 (100.0)
Unstable angina	37 (8.5)	0 (0.0)
Myocardial infarction	19 (4.4)	0 (0.0)
SYNTAX score	11.0 (7.0–18.0)	11.0 (5.3–19.0)
Lesions	1,024	115
Measured vessel location		
Left anterior descending artery	387 (37.8)	115 (100.0)
Left circumflex artery	339 (33.1)	0 (0.0)
Right coronary artery	298 (29.1)	0 (0.0)
Quantitative coronary angiography		
Reference diameter, mm	2.97 ± 0.59	3.02 ± 0.40
Minimum lumen diameter, mm	1.67 ± 0.69	1.41 ± 0.49
Diameter stenosis, %	44.3 ± 17.5	46.7 ± 16.0
Lesion length, mm	10.8 ± 8.2	16.0 ± 9.7
Coronary physiological parameters		
iFR	0.94 ± 0.10 0.97 (0.92–1.00)	0.87 ± 0.13 0.92 (0.87–0.94)
Resting Pd/Pa	0.96 ± 0.07 0.97 (0.94–1.00)	0.91 ± 0.09 0.93 (0.90–0.95)

Values are N, mean ± SD, n (%), or median (interquartile range).

iFR = instantaneous wave-free ratio; resting Pd/Pa = resting distal to aortic coronary pressure; PET = positron emission tomography; SYNTAX = Synergy between PCI with Taxus and Cardiac Surgery.

FIGURE 1 Correlation Between Resting Pd/Pa and iFR



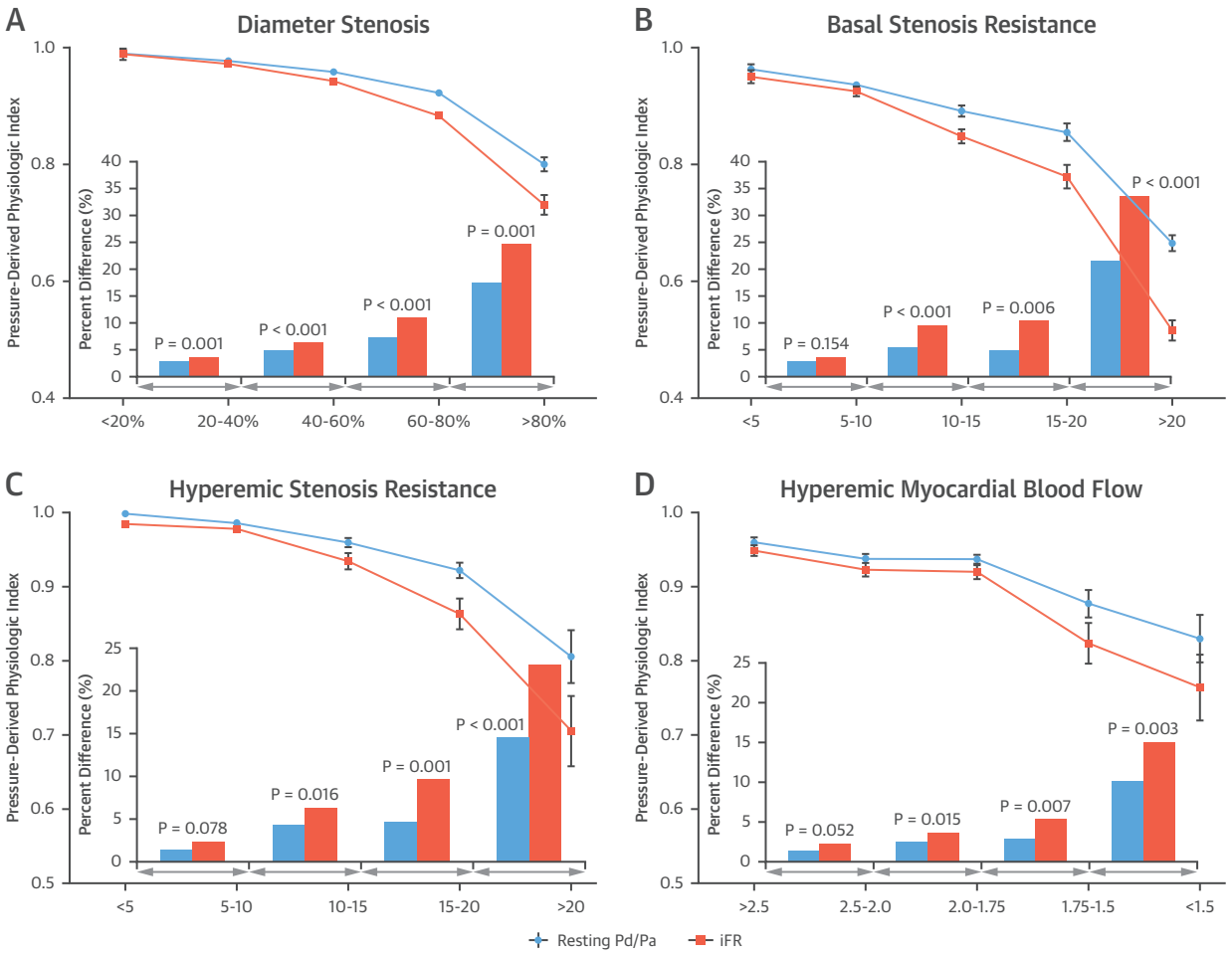
In the total 1,024 vessels, there was a significant linear correlation between resting Pd/Pa and iFR. iFR = instantaneous wave-free ratio; Pd/Pa = distal to aortic coronary pressure.

gram of tissue image acquisition, Carimas software version 2.9 (Turku PET Centre, Turku, Finland) was used.

ANGIOGRAPHIC ANALYSIS AND QUANTITATIVE CORONARY ANGIOGRAPHY. Coronary angiography was performed using standard techniques. Angiographic views were obtained following the administration of intracoronary nitrate (100 or 200 μg). All angiograms were analyzed at a core laboratory (Seoul National University Hospital) blinded to other data. Quantitative coronary angiography was performed in optimal projections with validated software (CAAS II, Pie Medical System, Maastricht, the Netherlands). Minimal lumen diameter, reference vessel size, and lesion length were measured, and percent diameter stenosis (%DS) was calculated.

CORONARY PHYSIOLOGICAL MEASUREMENTS AND CUTOFF VALUES. All coronary physiological measurements were obtained after diagnostic angiography as previously described (17). Briefly, a 5- to 7-F guide catheter was used to engage the coronary artery. The pressure-temperature sensor guidewire (Abbott Vascular, Santa Clara, California) was zeroed and equalized to aortic pressure, and then positioned at the distal segment of a target vessel. Intracoronary nitrate (100 or 200 μg) was administered before each set of physiological measurements. Resting Pd/Pa was calculated as the ratio of mean distal coronary artery pressure to mean aortic pressure in the resting state. The tracing was recorded after full recovery from the influence of intracoronary nitrate administration. All pressure readings were collected and validated at the core laboratory in a blinded fashion. iFR was calculated as the mean pressure distal to the stenosis divided by the mean aortic pressure during the diastolic wave-free period. The baseline tracing data of more than 5 heartbeats were extracted and then anonymized and coded as an ASCII text file. Those data were sent to the iFR core laboratory (Imperial College, London, United Kingdom), where iFR was calculated using fully automated algorithms acting over the wave-free period of a minimum of 5 beats (5). In order to derive stenosis resistance (mm Hg · min · g/ml) at rest and hyperemia (basal stenosis resistance [BSR] and hyperemic stenosis resistance [HSR], respectively), trans-stenotic pressure gradients (mm Hg) were calculated both at rest and hyperemia, and divided by absolute MBF (ml/min/g) in resting and hyperemic conditions, respectively. In comparison of clinical outcomes in high and low resting Pd/Pa or iFR groups, the cutoff values of ≤0.91 (8,9) and ≤0.89 (3,4,9) were used for resting Pd/Pa and iFR, respectively.

FIGURE 2 Comparison of Resting Physiological Indices According to Different Anatomic or Hemodynamic Stenosis Severity



This figure shows the values of resting Pd/Pa and iFR according to **(A)** angiographic stenosis severity, **(B)** basal stenosis resistance, **(C)** hyperemic stenosis resistance, and **(D)** hyperemic myocardial blood flow. The **bar graph** represents the percent differences of resting Pd/Pa **(blue)** and iFR **(orange)** between the 2 successive subgroups **(arrow)**. The p values represent the significance in comparison of percent differences between resting Pd/Pa and iFR. Abbreviations as in Figure 1.

FOLLOW-UP OF THE PATIENTS, OUTCOME MEASUREMENTS, AND ADJUDICATION OF CLINICAL EVENTS. Clinical data were obtained at outpatient clinic visits or by telephone contact when needed. An independent clinical events committee, whose members were unaware of clinical, angiographic, and physiological data, adjudicated all events. The primary outcome was major adverse cardiac events (MACE) at 2 years, including cardiac death, target vessel-related MI and target vessel-related ischemia-driven revascularization. All clinical outcomes were defined according to the Academic Research Consortium, including the addendum to the definition of MI. All deaths were considered cardiac unless an undisputable noncardiac cause was present. Ischemia-driven revascularization was defined as a revascularization procedure with at least 1 of the following: 1) recurrence of angina; 2) positive noninvasive test; and 3) positive invasive physiological test.

STATISTICAL ANALYSIS. Categorical variables were presented as numbers and relative frequencies (percentages), and continuous variables were presented as mean ± SD or median with interquartile range (IQR) according to their distribution, which was checked by the Kolmogorov-Smirnov test. Data were analyzed on a per-patient basis for clinical characteristics and outcomes, and on a per-vessel basis for all other analyses. Linear regression analysis

TABLE 2 Comparison of Resting Indices According to Different Angiographic and Hemodynamic Stenosis Severity

	Angiographic Diameter Stenosis (N = 1,024)								
	<20%	20%–30%	30%–40%	40%–50%	50%–60%	60%–70%	70%–80%	>80%	p_{trend}
No. of observations	77	162	184	217	187	109	63	25	
Resting Pd/Pa	0.99 ± 0.01	0.98 ± 0.01	0.97 ± 0.01	0.97 ± 0.01	**0.95 ± 0.01**	0.93 ± 0.01	0.90 ± 0.01	0.80 ± 0.01	<0.001
iFR	0.99 ± 0.01	0.98 ± 0.01	0.96 ± 0.01	0.95 ± 0.01	**0.93 ± 0.01**	0.90 ± 0.01	0.86 ± 0.01	0.73 ± 0.02	<0.001
	Fractional Flow Reserve (N = 1,024)								
	<0.70	**0.71–0.75**	**0.76–0.80**	**0.81–0.85**	**0.86–1.00**				p_{trend}
No. of observations	97	53	99	156	619				
Resting Pd/Pa	0.82 ± 0.01	**0.90 ± 0.01**	0.93 ± 0.01	0.95 ± 0.01	0.99 ± 0.01				<0.001
iFR	0.75 ± 0.01	**0.85 ± 0.01**	0.91 ± 0.01	0.94 ± 0.01	0.98 ± 0.01				<0.001
	Basal Stenosis Resistance, mm Hg · min · g/ml (n = 115)								
	<5	**5–10**	**10–15**	**15–20**	**>20**				p_{trend}
No. of observations	25	53	**21**	7	9				
Resting Pd/Pa	0.96 ± 0.01	0.94 ± 0.01	**0.89 ± 0.01**	0.85 ± 0.02	0.66 ± 0.01				<0.001
iFR	0.95 ± 0.01	0.92 ± 0.01	**0.85 ± 0.01**	0.78 ± 0.02	0.52 ± 0.02				<0.001
	Hyperemic Stenosis Resistance, mm Hg · min · g/ml (n = 115)								
	<5	**5–10**	**10–15**	**15–20**	**>20**				p_{trend}
No. of observations	13	49	18	18	17				
Resting Pd/Pa	0.96 ± 0.02	0.95 ± 0.01	0.92 ± 0.01	0.88 ± 0.01	**0.77 ± 0.01**				<0.001
iFR	0.94 ± 0.02	0.94 ± 0.01	0.89 ± 0.02	**0.82 ± 0.02**	0.67 ± 0.02				<0.001
	Hyperemic Myocardial Blood Flow, ml/min/g (n = 115)								
	>2.5	**2.5–2.0**	**2.0–1.75**	**1.75–1.5**	**<1.5**				p_{trend}
No. of observations	11	38	20	27	19				
Resting Pd/Pa	0.96 ± 0.02	0.94 ± 0.01	0.94 ± 0.02	**0.88 ± 0.01**	0.83 ± 0.02				<0.001
iFR	0.95 ± 0.03	0.92 ± 0.02	0.92 ± 0.02	**0.82 ± 0.02**	0.76 ± 0.02				<0.001

Values are mean ± 95% SE unless otherwise indicated. The p for trend is in comparison among classifications. **Bold** indicates the point of first significant change compared with previous classification of stenosis severity, namely the significant transition point.

Abbreviations as in Table 1.

was used to estimate the correlation coefficient (Pearson or Spearman according to the normality of the variables) between quantitative variables. The comparison of resting Pd/Pa and iFR according to different classification of %DS, BSR, HSR, and hyperemic absolute MBF were performed, using generalized estimating equations without post hoc adjustment for the clustered data (patients with multivessel interrogation).

In comparison of clinical outcomes according to resting Pd/Pa or iFR cutoff values, event rates were calculated on the basis of Kaplan-Meier censoring estimates, and the log-rank test was used to compare survival curves between groups. Those clinical event

TABLE 3 Comparison of Clinical Outcomes According to Resting Pressure-Derived Physiological Indices

	High Resting Pd/Pa (>0.91)	Low Resting Pd/Pa (≤0.91)	p Value*	High iFR (>0.89)	Low iFR (≤0.89)	p Value†
Per-patient analysis (n = 375)	329/375 (87.7)	46/375 (12.3)		322/375 (85.9)	53/375 (14.1)	
Cardiac death	0.6 (2)	2.2 (1)	0.267	0.6 (2)	1.9 (1)	0.334
Myocardial infarction	0.6 (2)	2.2 (1)	0.291	0.6 (2)	1.9 (1)	0.332
Ischemia driven revascularization	0.9 (3)	6.5 (3)	0.004	0.9 (3)	5.7 (3)	0.008
MACE‡	1.5 (5)	8.7 (4)	0.003	1.6 (5)	7.5 (4)	0.006

Values are n/N (%) or % (n). The cumulative incidences of clinical outcomes were presented as Kaplan-Meier estimates during the median follow-up of 729.0 (699.0 to 747.0) days. p Values were log-rank or Breslow p value in survival analysis. *Log rank p values for the comparison of cumulative incidence of events between high and low resting Pd/Pa groups. †Log-rank p values for the comparison of cumulative incidence of events between high and low iFR groups. ‡Major adverse cardiac events included cardiac death, myocardial infarction, and ischemia-driven revascularization.

MACE = major adverse cardiovascular events; other abbreviations as in Table 1.

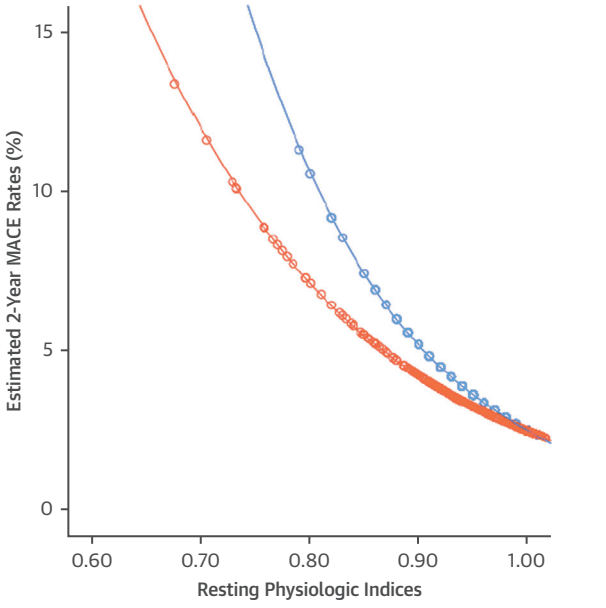
data were compared, using a Cox proportional hazards regression model, to calculate hazard ratio (HR) and 95% confidence interval (CI). Among patients who underwent multivessel measurements, the vessel with the lowest iFR value was selected as a representative vessel for the patient. In order to explore the prognostic implications of resting Pd/Pa and iFR as continuous values, estimated MACE rates derived from the Cox proportional hazards regression model were plotted according to resting Pd/Pa or iFR values. The discriminant function of a model with resting Pd/Pa or iFR was compared with %DS using Harrell's c-statistics.

In order to compare the variability in the estimated event rates according to the approximate measurement variability of resting Pd/Pa and iFR, we used the procedure of upper-lower bound methods of uncertainty propagation, which is a well known method to explore resultant uncertainty caused by measurement variability (18). Briefly, we calculated the upper- and lower-bound values of cumulative 2-year MACE rates according to upper and lower values of resting Pd/Pa and iFR for each patient using 1 SD of resting Pd/Pa and iFR, respectively. For this, SD of repeated measurement of resting Pd/Pa and iFR presented in the CONTRAST (Can contrast injection better approximate FFR compared to pure resting physiology?) study were used (8). In the CONTRAST study, all physiologic metrics (resting Pd/Pa, iFR, contrast-based FFR, and FFR) were measured twice. Using the measurement variability of resting Pd/Pa (SD: ±0.023) and iFR (SD: ±0.033) from the CONTRAST study (8), the upper-bound cumulative 2-year MACE rate was estimated from the value of 1 SD above the resting Pd/Pa or iFR and the lower-bound cumulative 2-year MACE rate from the value of 1 SD below the resting Pd/Pa or iFR. Then, the difference between upper- and lower-bound estimated event rates was calculated and the averaged difference was compared between resting Pd/Pa and iFR using the paired sample *t* test.

RESULTS

PATIENT AND LESION CHARACTERISTICS. Table 1 shows the characteristics of the study population and the target lesions. Most patients (87.1%) presented with stable angina. Mean angiographic %DS, resting Pd/Pa, and iFR were 44.3 ± 17.5% (median 42.8% [IQR: 30.7% to 56.5%]), 0.94 ± 0.10 (median 0.97 [IQR: 0.92 to 1.00]), and 0.96 ± 0.07 (median 0.97 [IQR: 0.94 to 1.00]), respectively. Online Figure 1 presents the distribution of resting Pd/Pa and iFR.

FIGURE 3 Associations Between Estimated MACE Rates and Resting Physiological Indices

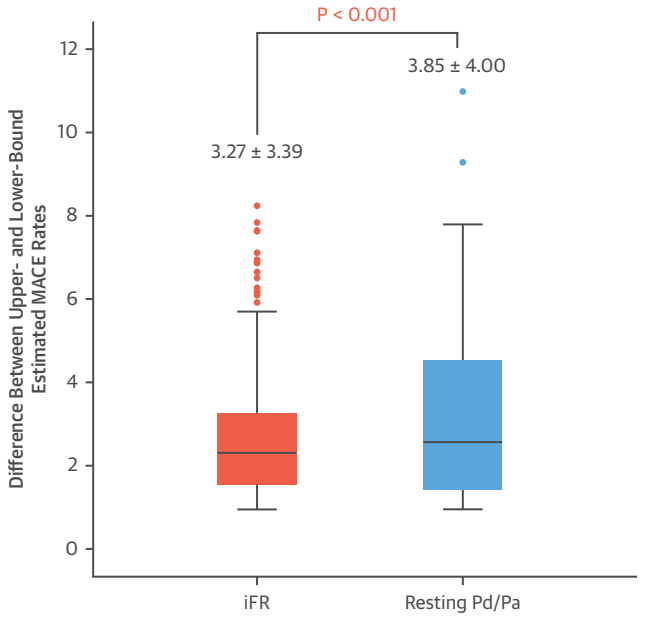


The association between 2-year major adverse cardiac events (MACE) and resting Pd/Pa or iFR was evaluated. Both indices showed significant association with 2-year MACE risk as continuous values. **Orange and blue lines** represent regression lines for iFR and resting Pd/Pa as continuous values, respectively. **Orange and blue circles** represent each patient's iFR and resting Pd/Pa values and estimated MACE rates according to the iFR or resting Pd/Pa values, respectively. CI = confidence interval; HR = hazard ratio; other abbreviations as in Figure 1.

Among the 1,024 vessels (n = 435), 160 vessels were revascularized. Most patients had mild-to-moderate stenosis, and the median SYNTAX score was 11.0 (IQR: 7.0 to 18.0).

RELATIONSHIP BETWEEN INVASIVE PHYSIOLOGICAL INDICES AND STENOSIS SEVERITY. In total of 1,024 vessels, there was a significant linear correlation between resting Pd/Pa and iFR ($R = 0.970$; $p < 0.001$, iFR = 1.370 × resting Pd/Pa − 0.370) (Figure 1). In addition, both resting Pd/Pa and iFR showed significant correlation with %DS (resting Pd/Pa $R = -0.440$; $p < 0.001$; iFR $R = -0.464$; $p < 0.001$) (Online Figure 2). Figure 2 shows the comparison of resting Pd/Pa and iFR according to angiographic stenosis severity, FFR, BSR, HSR, and hyperemic MBF. Both iFR and FFR decreased with increasing angiographic stenosis severity, BSR, and HSR, and with decreasing FFR and hyperemic MBF (Figure 2, Table 2). However, percent difference of iFR according

FIGURE 4 Difference Between Upper- and Lower-Bound Estimated MACE Rates According to Measurement Variability of Resting Physiological Indices



The difference between upper- and lower-bound estimated 2-year MACE rates according to approximate measurement variability of physiological indices was compared between resting Pd/Pa and iFR. Using the measurement variability of resting Pd/Pa (SD: ±0.023) and iFR (SD ±0.033) from the CONTRAST study (8), the upper-bound cumulative 2-year MACE rates were estimated from the value of 1 SD above the resting Pd/Pa or iFR and the lower-bound cumulative 2-year MACE rates from the value of 1 SD below the resting Pd/Pa or iFR. The values of "3.27 ± 3.39" and "3.85 ± 4.00" represent the means and SDs of the differences between upper- and lower-bound estimated event rates of iFR and resting Pd/Pa, respectively. iFR showed significantly lower difference between upper- and lower-bound estimated risk than resting Pd/Pa. Abbreviations as in Figures 1 and 3.

to the increase in anatomic and hemodynamic severity was higher than that of resting Pd/Pa (Figure 2).

ASSOCIATION BETWEEN INVASIVE PHYSIOLOGICAL INDICES AND CLINICAL OUTCOME IN DEFERRED PATIENTS AND INFLUENCE OF MEASUREMENT VARIABILITY. Deferred patients with low resting Pd/Pa (≤0.91) or low iFR (≤0.89) showed significantly higher rates of 2-year MACE than those with high resting Pd/Pa (>0.91) or high iFR (>0.89), respectively (8.7% in low resting Pd/Pa vs. 1.5% in high resting Pd/Pa; p = 0.003; 7.5% in low iFR vs. 1.6% in high iFR; p = 0.006). The difference was mainly driven by higher risk of ischemia-driven revascularization (Table 3). Both resting Pd/Pa and iFR as continuous values showed significant association with clinical outcomes in deferred patients (HR of resting Pd/Pa [per 0.1 increase] 0.480; 95% CI: 0.250 to 0.923; p = 0.027; HR of iFR [per 0.10 increase] 0.586; 95% CI: 0.373 to 0.919; p = 0.020) (Figure 3). Both resting Pd/Pa and iFR showed a nonlinear relationship with the estimated risk of MACE, and lower values showed an exponentially increased risk of MACE (Figure 3). Both resting Pd/Pa and iFR values showed significantly higher c-index to predict 2-year MACE risk than %DS (%DS 0.652, resting Pd/Pa 0.741, and iFR 0.739; p = 0.019) and the c-index was comparable between resting Pd/Pa and iFR (p = 0.365).

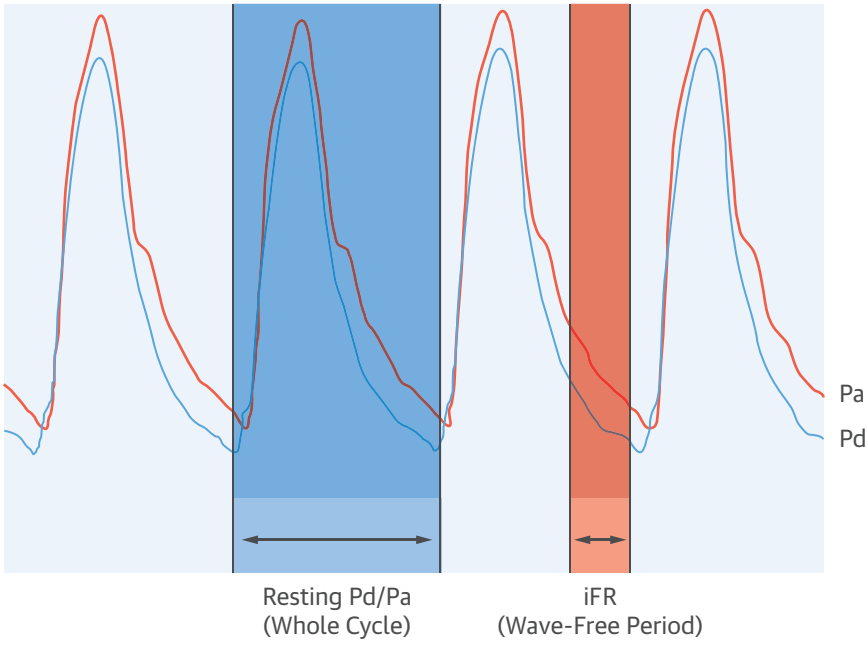
When the difference between the upper- and lower-bound estimated MACE rates according to approximate measurement variability was compared, the lower- and upper-bound estimated event rates of resting Pd/Pa were 2.96 ± 3.98% and 6.81 ± 7.94%, respectively, and those of iFR were 2.96 ± 3.85% and 6.24 ± 7.22%, respectively. For the difference between the lower- and upper-bound estimated event rates according to measurement variability, iFR showed significantly lower variability in estimated event rates than resting Pd/Pa (3.27 ± 3.39% vs. 3.85 ± 4.00%; p < 0.001) (Figure 4).

DISCUSSION

The current study focused on 2 different invasive pressure-derived indices measured at resting status and evaluated the changes of resting Pd/Pa and iFR according to different anatomic and hemodynamic stenosis severity and their association with clinical outcomes (Central Illustration). The main findings were as follows. First, resting Pd/Pa and iFR were well correlated, and both indices changed significantly according to anatomic and hemodynamic stenosis severity. Second, iFR showed more sensitive changes to different level of stenosis severity than resting Pd/Pa. Third, both indices showed significant prognostic implication as binary and continuous values. Fourth, despite the similar discrimination ability for 2-year MACE, iFR showed significantly lower variability in the estimated event rates than resting Pd/Pa according to measurement variability.

SIMILARITY OF PRESSURE-DERIVED RESTING PHYSIOLOGICAL INDICES. In determining functional significance of coronary stenosis, pressure-derived physiological indices have been used in clinical practice. Flow-based indices such as coronary flow reserve or absolute myocardial blood flow can be influenced by the presence of microvascular dysfunction and have limitations in the assessment of epicardial coronary stenosis (19). To date, FFR has been regarded as a reference method on the basis of large clinical data (20–23). A recently adopted resting index, iFR, has proved its noninferiority to FFR for 1-year clinical outcomes (3,4). Unlike resting Pd/Pa, which is measured during the entire cardiac cycle,

CENTRAL ILLUSTRATION **Similarity and Difference of Resting Pressure-Derived Physiological Indices**



Response to anatomical or hemodynamic stenosis severity	Resting Pd/Pa	<	iFR
Association with MACE in deferred lesion during follow-up	Resting Pd/Pa	=	iFR
Variability in estimated MACE risk	Resting Pd/Pa	>	iFR

Lee, J.M. et al. J Am Coll Cardiol. 2017;70(17):2114–23.

The current study focused on 2 different invasive pressure-derived indices measured at resting status. Although both resting Pd/Pa and iFR changed significantly according to different anatomic and hemodynamic stenosis severity, iFR showed more sensitive changes to different levels of stenosis severity than resting Pd/Pa. In addition, both indices showed significant prognostic implication as binary and continuous values. Nevertheless, iFR showed significantly lower difference between upper- and lower-bound estimated risk than resting Pd/Pa. iFR = instantaneous wave-free ratio; MACE = major adverse cardiac events; Pd/Pa = distal to aortic coronary pressure.

iFR is an index based on the average value during a selected period of diastole. The theoretical background of this wave-free period has been derived from the wave intensity analysis, and the microvascular resistance is constant during this period (5). Despite this difference in background, previous diagnostic accuracy studies (7–9,11) showed a close linear correlation between the 2 indices and similar diagnostic accuracy between resting Pd/Pa and iFR, using FFR as a reference standard. In the current study, resting Pd/Pa and iFR showed a strong linear relationship ($R = 0.970$; $p < 0.001$, iFR = 1.370 × resting Pd/Pa − 0.370) as shown in the previous studies. In addition, both indices showed significant correlation with anatomic and hemodynamic stenosis severity and also showed similar association with 2-year MACE risk. It was interesting to note that both resting Pd/Pa and iFR values showed higher c-index than angiographic stenosis severity in the prediction of 2-year MACE risk.

DIFFERENCE OF PRESSURE-DERIVED RESTING PHYSIOLOGICAL INDICES IN ASSESSMENT OF STENOSIS SEVERITY. When the difference of resting Pd/Pa and iFR were explored according to different stenosis severity, iFR showed significantly higher percent difference with increasing anatomic stenosis severity than resting Pd/Pa. iFR also showed more sensitive changes according to the level of hemodynamic stenosis severity assessed by BSR, HSR, and

hyperemic MBF than resting Pd/Pa. These results suggest that iFR is a more sensitive marker of anatomic and hemodynamic stenosis severity than resting Pd/Pa. In addition, considering the intrinsic measurement variability of both resting Pd/Pa and iFR, the higher percent difference of iFR with worsening stenosis severity would provide a more reliable assessment of stenosis severity in patients with intermediate stenosis.

DIFFERENCE OF PRESSURE-DERIVED RESTING PHYSIOLOGICAL INDICES IN ASSESSING RISK OF ADVERSE EVENTS IN DEFERRED LESIONS. As for the role of prognostic indicator, both resting Pd/Pa and iFR showed significant association with 2-year MACE in deferred lesions. Regardless of resting Pd/Pa and iFR, deferred patients with high resting indices showed similar cumulative risk of 2-year MACE (high resting Pd/Pa 1.5% and high iFR 1.6%), and it was also similar in deferred patients with low resting indices (low resting Pd/Pa 8.7% and low iFR 7.5%). In addition, the discrimination ability for 2-year MACE was comparable (resting Pd/Pa 0.741 and iFR 0.739; $p = 0.365$). However, the influence of intrinsic measurement variability on estimated event rates was different between the 2 indices. Despite the larger imprecision for iFR (SD: ±0.033) than Pd/Pa (SD: ±0.023) in the CONTRAST study (8), iFR showed significantly lower difference between the upper- and lower-bound estimated risk for MACE according to measurement variability than resting Pd/Pa in our study. This result implies that iFR would provide more stable estimation of potential risk of future events than resting Pd/Pa, despite the similar measurement variability of both resting indices.

STUDY LIMITATIONS. First, iFR was calculated off-line in the independent physiology core laboratory. Second, the current study used approximate measurement variability of resting Pd/Pa and iFR from the CONTRAST study. The variability of each index might be different in the present population compared to that of the CONTRAST study. Third, for the ^{13}N-ammonia PET cohort, ^{13}N-ammonia PET and invasive physiological measurements were not performed simultaneously. However, there were no clinical events in the time interval between these 2 assessments, and both tests used the same protocol of hyperemia induction.

CONCLUSIONS

Both resting Pd/Pa and iFR showed similar association with anatomic and hemodynamic stenosis severity and the risk of MACE. However, iFR was more sensitive to the difference of stenosis severity and showed lower variability in estimated MACE risk influenced by the measurement variability compared with resting Pd/Pa.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The iFR can identify functionally significant coronary artery stenosis and guide treatment. Despite fundamental differences in methods of measuring iFR and resting Pd/Pa, there is a linear correlation between the 2 and their diagnostic performance is similar. The iFR is more sensitive to changes in the severity of stenosis than resting Pd/Pa and provides a more reliable assessment in patients with stenosis of intermediate severity.

TRANSLATIONAL OUTLOOK: Further studies are needed to determine which of these indices better predicts long-term clinical outcomes in patients with coronary disease managed without revascularization.

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APPENDIX For supplemental figures, please see the online version of this article.