All Resting Physiological Indices May Not Be Equivalent
— Comparison Between the Diastolic Pressure Ratio and Resting Full-Cycle Ratio —

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Background: Differences between resting full-cycle ratio (RFR) and diastolic pressure ratio (dPR) have not been sufficiently discussed. This study aimed to investigate if there is a difference in diagnostic performance between RFR and dPR for the functional lesion assessment and to assess if there are specific characteristics for discordant revascularization decision-makings between RFR and dPR.

Methods and Results: A total of 936 intermediate lesions in 776 patients who underwent measurements of fractional flow reserve (FFR), coronary flow reserve (CFR), and the index of microcirculatory resistance (IMR) were retrospectively studied. Physiological indices were measured from anonymized pressure recordings at an independent core laboratory. Both RFR and dPR measures were highly correlated (r=0.997, P<0.001), with equivalent diagnostic performance relative to FFR-based decision-makings measured by using a dichotomous threshold of 0.80 (accuracy, 79.7% vs. 80.1%, respectively, P=0.960). The rate of diagnostic discordance was 4.7% (44/936), with no RFR−/dPR+ lesions observed. An overall significant difference in FFR and CFR values were detected among RFR/dPR-based classifications. The prevalence of positive studies was significantly higher for RFR than dPR (54.3% vs. 49.6%, respectively, P=0.047) when using the cut-off value of 0.89.

Conclusions: Both RFR and dPR were highly correlated, but the prevalence of positive studies was significantly different. The revascularization rate may differ significantly according to the resting index used.

Key Words: Coronary artery disease; Diastolic pressure ratio; Fractional flow reserve; Resting full-cycle ratio
agreement and disagreement between dPR and RFR and determinants of disagreement have not been sufficiently discussed. Therefore, the aim of this study was to evaluate the frequency of diagnostic discordance between dPR and RFR, and to investigate if there are specific characteristics in cases of discordant diagnosis in patients with intermediate (angiographically 30–80% stenosis by visual estimation) coronary stenoses.

Methods

From September 2015 to January 2018, a total of 3,159 patients with known or suspected coronary artery disease underwent catheterizations at Tsuchiura Kyodo General Hospital. Among them, patients who underwent coronary physiological assessments using a pressure-temperature sensor-tipped wire (Abbott Vascular, St. Paul, MN, USA), were retrospectively identified from our institutional database of FFR measurements. A total of 1,102 measurements of FFR, coronary flow reserve (CFR), and the index of microcirculatory resistance (IMR), were performed in 908 patients. For the present study, lesions with angiographically intermediate stenosis (30–80% diameter stenosis by visual estimation) were included. Patients with left main disease, contraindication for adenosine, shock status, congestive heart failure, atrial fibrillation, in-stent lesions, and a history of coronary artery bypass grafting and a lack of hemodynamic data during the examination, were excluded from the analysis. Thus, a total of 978 lesions in 810 patients were studied in the present study. All patients underwent FFR assessment, and anonymized Digital Imaging and Communications in Medicine (DICOM) files of pressure signal recordings were analysed by using a fully automated off-line software algorithm at an independent core laboratory (CoroLab; Coroventis Research AB, Uppsala, Sweden) for RFR and dPR. Waveform tracings with insufficient quality or unstable pressure periods (n=42) were excluded from the analysis by the core laboratory. Before catheterization, all patients provided written informed consent for enrollment of their details into the institutional database for potential future analysis. All patient data and procedural details were obtained from medical records. Prompt optimal medical therapy was initiated in all patients after coronary angiography and FFR measurements.

Ethical Approval

This study was conducted in accordance with the Declaration of Helsinki, and our institutional ethics committee approved the study protocol (Tsuchiura Kyodo General Hospital; Reference number is 859).

Coronary Physiological Assessment

The FFR, mean transit time (Tmn), CFR, and IMR were determined using a RadiAnalyzer Xpress instrument with a pressure-temperature sensor-chipped wire (Abbott Vascular), as per previously described methods. First, we recorded DICOM pressure tracings at resting state. Afterwards, hyperemia was induced by an intravenous infusion of adenosine 5’-triphosphate (160 μg/kg/min). The FFR was calculated by dividing the mean distal pressure by the mean aortic pressure during stable hyperemia. For IMR measurements, hyperemic thermodilution curves (measured 3 times each, using a 3-mL saline bolus injection) and the hyperemic Tmn were obtained. The IMR was calculated as the product of the mean distal coronary pressure during stable hyperemia and mean hyperemic Tmn. The CFR was measured simultaneously with FFR and IMR, using the thermodilution method, and expressed as the ratio of the Tmn at rest divided by the hyperemic Tmn. After physiological measurements, the pressure wire was retracted into the guiding catheter to evaluate the pressure drift. As per our institutional standard protocol, FFR assessment was repeated when a pressure drift 3 mmHg was identified.

All waveform tracing and pressure data was performed at the core laboratory, in a blinded fashion for FFR, CFR, and IMR.

The RFR was defined as the point at which the ratio of Pd to Pa was lowest over the entire cardiac cycle. The dPR was also calculated from each individual waveform as the average Pd/Pa over the entire period of diastole, as previously described. The calculation of RFR and dPR from pressure tracing data was performed at the core laboratory, in a blinded fashion (CoroLab; Coroventis Research AB, Uppsala, Sweden).
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and the Bayesian Information Criterion was used for avoiding overfitting. Receiver-operating characteristic (ROC) curves were constructed to determine the diagnostic value (area under the curve [AUC] and accuracy) for each index measurement, with respect to \( \text{FFR} \leq 0.80 \), using an identical cut-off value of 0.89 for dPR and RFR. A P-value <0.05 was considered statistically significant.

Results

**Baseline Patient and Lesion Characteristics**

The final dataset included a total of 936 vessels from 776 patients. Baseline patient and lesion characteristics are shown in **Table 1**. Of the 776 patients that made up the study population, 604 (77.8%) were men, 313 (40.3%) had diabetes, and 251 (32.4%) had a prior history of myocardial infarction. Coronary pressure measurements were analysed in 936 coronary arteries, of which 585 (62.3%) were in the left anterior descending artery (LAD). The median percent diameter of stenosis was 53.0%. The most frequent indication for angiography was stable angina (n=860, 91.9%). The median FFR value was 0.79 (IQR, 0.71–0.86), with a median dPR of 0.90 (IQR, 0.83–0.95) and RFR of 0.89 (IQR, 0.82–0.94). The distribution of FFR, dPR, RFR, and resting Pd/Pa is shown in **Figure 1**. Of a total cohort, 769 lesions (82.2%) showed FFR values between 0.60 and 0.90 in the present study.
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Diagnostic Performance of RFR and dPR Relative to FFR as the Reference Standard

The diagnostic accuracy to predict FFR-based decision-making with a binary cut-off value of 0.80 was 79.7% for dPR and 80.1% for RFR, indicating equivalent performance (P = 0.960). Any small difference in sensitivity, specificity, and positive and negative predictive value between dPR and RFR indices may be negligible, whereas resting Pd/Pa had similar diagnostic accuracy, higher sensitivity, lower specificity, lower positive predictive value, higher negative predictive value compared with 2 other resting indices. Abbreviations as per Figure 1.

Differences and Correlation Between dPR and RFR

The dPR and RFR values were highly correlated (r = 0.997, P < 0.001; Supplementary Figure 1A). In addition, both measures similarly correlated with the FFR (dPR: r = 0.797, P < 0.001; RFR: r = 0.796, P < 0.001; Supplementary Figure 2). The diagnostic performance of dPR vs. RFR, when the cut-off of 0.89 was used, was as follows: accuracy, 95.3%; sensitivity, 99.2%; specificity, 95.8%; positive predictive value, 96.6%; and negative predictive value, 99.0% (Supplementary Figure 1B), indicating that no cases of RFR−/dPR+ was observed.

For a reference standard of FFR ≤ 0.80, RFR and dPR demonstrated equivalent diagnostic performance (accuracy, 80.1% vs. 79.7%, respectively, P = 0.960; and AUC, 0.874 vs. 0.878, P = 0.528; Supplementary Figure 2).

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**Figure 2.** Comparison of 2 resting indexes with FFR. The diagnostic accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of RFR vs. FFR, and dPR vs. FFR are nearly identical, whereas resting Pd/Pa had similar diagnostic accuracy, higher sensitivity, lower specificity, lower positive predictive value, higher negative predictive value compared with 2 other resting indices. Abbreviations as per Figure 1.

**Figure 3.** Frequencies of concordance and discordance between RFR and dPR. When all lesions were divided into groups according to the concordance and discordance between dPR and RFR, no lesion showed RFR−/dPR+. Abbreviations as per Figure 1.
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The prevalence of positive tests using resting indices ≤0.89

![Figure 4](image)

**Figure 4.** Prevalence of positive tests using a resting index of ≤0.89 as a reference standard. The prevalence of positive results was significantly higher when evaluated by RFR (54.3% vs. 49.6%, P=0.047), and when using the cut-off value of 0.89. Abbreviations as per Figure 1.

Pd/Pa had similar diagnostic accuracy, but with higher sensitivity and negative predictive value and lower specificity and positive predictive value (Figure 2).

**Discordance Between dPR and RFR**

The frequency of diagnostic discordance between the RFR and dPR was 4.7% (44/936 of cases). As mentioned earlier, no RFR−/dPR+ cases were identified (Figure 3). The RFR+/dPR− lesions had a lower FFR compared to the RFR−/dPR− cases. We observed all RFR+/dPR− lesions with a dPR between 0.90 and 0.93, whereas for RFR, the distribution range was between 0.86 and 0.89. Discordance between RFR and dPR may occur at various locations; in the present cohort, 6/202 (3.0%) lesions were located in the proximal part of the right coronary artery (RCA), 2/202 (1.0%) lesions in the mid part of the RCA, 17/590 (2.9%) lesions in the proximal part of the left anterior descending artery (LAD), 14/590 (2.4%) lesions in the mid part of the LAD, 1/140 (0.7%) lesions in the proximal part of the left circumflex artery (LCX), and 4/140 (2.9%) lesions in the mid part of the LCX. Multivariate logistic regression analysis demonstrated that higher FFR and the lesion of the RCA were independent predictors of discordance between RFR+/dPR− lesions compared to the RFR−/dPR− lesions (Supplementary Table A). When compared to the RFR+/dPR+ lesions, multivariate logistic regression analysis showed that higher FFR and the lesion of non-RCA were independent predictors of discordance with RFR+/dPR− (Supplementary Table B). The prevalence of ischemia was significantly higher by using RFR than dPR (54.3% vs. 49.6%, respectively, P=0.047), when using the cut-off value of 0.89 (Figure 4). Both FFR and CFR values were significantly different among the RFR+/dPR+, RFR−/dPR− and RFR+/dPR− groups; so was the prevalence of lesions with a FFR ≤0.80 and CFR ≤2.0 (Table 2).

When limiting the analysis in lesions of either RFR or dPR showing the values between 0.86 and 0.93 (408/936), FFR values distributed in the wide range and were not restricted in the so-called FFR grey zone (96/408, 23.5%), but were also scattered outside of the 0.75–0.80 range (312/408, 76.5%). Of note, FFR values in RFR+/dPR− lesions were also distributed in a wide range, and more than 75% of these lesions were scattered outside of the range from 0.75 to 0.80 (Figure 5).

**Discussion**

This is the first study to demonstrate a significant difference in revascularization decision-making between dPR and RFR in a cohort of angiographically intermediate lesions. We also identified a significant difference in the prevalence of positive results, defined by a FFR ≤0.80, between dPR and RFR, with a higher rate of ischemia decisions with RFR than dPR. The important findings of our study were as follows: (1) the prevalence of diagnostic discordance between dPR and RFR was 4.7%, using a reference FFR standard ≤0.8 and 0.89 for both dPR and RFR cut-offs; (2) RFR−/dPR+ cases were not identified in the present cohort. Among the remaining 3 groups (RFR+/dPR+, RFR−/dPR−, and RFR+/dPR−), the prevalence of not only FFR ≤0.80 but CFR ≤2.0, as well as FFR and CFR values, were significantly different, whereas IMR was not different; (3) the prevalence of revascularization decision was significantly higher when using dPR compared to RFR (P=0.047), and when using the cut-off value of 0.89; (4) FFR values of RFR/dPR discordant lesions distributed in the wide range and were not restricted in the so-called grey zone (0.75–0.80), but more than 75% of discordant lesions were scattered outside of the FFR grey zone.

Given the fundamentals of the RFR algorithm, RFR may present a lower value than other diastolic resting indices because the measurement is not limited during diastole, although further studies are needed to elucidate the physiological and baseline factors of discordance between resting indices. As RFR is calculated from the lowest value of Pd/Pa over the entire cardiac cycle, this difference in basic algorithms can cause discordance between RFR and other resting diastolic indices. Although a previous report showed that peak flow in the RCA may occur during systole or very early in diastole, and the frequency of a RFR
The frequency of discordance between the RFR and dPR was 5.1% (30/583 of cases), which was similar to the result obtained in the total cohort. Although our study demonstrated that RFR and dPR showed an excellent correlation and agreement with FFR-based decision-making, which is similar to the results of previous studies, the presence of ischemia, using the cut-off value of 0.89, was significantly greater when using RFR compared with dPR. Lee et al recently reported that the diagnostic performance of iFR, RFR, and dPR was not different in predicting myocardial ischemia, where ischemia was defined by both low hyperemic myocardial blood flow and low CFR on 13N-ammonia positron emission tomography (PET). Nevertheless, they also noted the presence of RFR+/iFR− lesions in 71 vessels (6.9%), with these lesions being associated with higher stenosis severity, lower FFR, and higher PET-derived stenosis resistance, compared to diagnostically discordant normal lesions. However, they did not report a significant difference in flow characteristics between lesions of the discordantly abnormal group and the discordant group. Partially different results obtained between the present study and the study by Lee et al may be attributable, at least in part, to the difference in study populations. Compared to our study population (median measurement timing outside of diastole was higher in the RCA, the RFR values were determined outside diastole in only 2.4% (112/4,680) in the study. As RCA lesion location was not an independent predictor of discordance between RFR and dPR (Supplementary Table B), lesion location may not an important factor for predicting discordance at least in this cohort. Multiple factors might be involved in the mechanisms of discordance between RFR and dPR, and further studies are needed to clarify the exact mechanisms of discordance between resting indices.

Our results indicated that, in ∼5% of the present cohort, discordance of revascularization decision-making occurred between RFR and dPR, whereas no RFR−/dPR+ discordance was identified. As previous studies have shown that FFR and resting indices were affected by pressure drift, we performed a subgroup analysis of 583 lesions without pressure drift. The frequency of diagnostic discordance between the RFR and dPR was 6.3% (37/583 of cases), which was similar to the result obtained in the total cohort. These results suggest that the difference between resting indices is not simply due to pressure drift, but due to the nature of these indices. Furthermore, we performed a subgroup analysis, which was limited to patients with stable angina, because the present cohort included 77/936 (8.2%) non-culprit lesions of acute coronary syndrome. The frequency of discordance between the RFR and dPR was 4.9% (42/859 of cases), and the prevalence of positive studies was significantly higher for RFR than dPR (52.2% vs. 47.3%, respectively, P=0.048). Subgroup analyses, limited to patients with stable angina, are similar to the results obtained using the total cohort. Although our study demonstrated that RFR and dPR showed an excellent correlation and agreement with FFR-based decision-makings, which is similar to the results of previous studies, the presence of ischemia, using the cut-off value of 0.89, was significantly greater when using RFR compared with dPR. Lee et al recently reported that the diagnostic performance of iFR, RFR, and dPR was not different in predicting myocardial ischemia, where ischemia was defined by both low hyperemic myocardial blood flow and low CFR on 13N-ammonia positron emission tomography (PET). Nevertheless, they also noted the presence of RFR+/iFR− lesions in 71 vessels (6.9%), with these lesions being associated with higher stenosis severity, lower FFR, and higher PET-derived stenosis resistance, compared to diagnostically discordant normal lesions. However, they did not report a significant difference in flow characteristics between lesions of the discordantly abnormal group and the discordant group. Partially different results obtained between the present study and the study by Lee et al may be attributable, at least in part, to the difference in study populations. Compared to our study population (median
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regarding revascularization may not have a significant effect on the mortality rate in these patients, sound clinical judgment should inform the final decision. Our results indicated that, as was suggested by the ADVISE II study for iFR, lesions within the resting index-defined grey-zone (0.86–0.93) showed scattered FFR distributions mostly outside of the FFR grey zone, suggesting the need of individually tailored decisions for these lesions (Supplementary Figure 3).

Although our findings do not extend to patient outcomes, the prevalence of positive results was significantly greater based on RFR than on dPR, which might lead to a higher rate of revascularization in patients diagnosed using RFR compared to those diagnosed using dPR. These findings and suggestions are hypothesis-generating, and clinical significance of the difference in resting index-based decision-makings and the effect on outcomes remain to be further elucidated.

Study Limitations
The limitations of our study should be acknowledged in the interpretation of our results. First, the relatively low number of patients from a single center may not allow extensive subgroup analysis. Second, resting physiological indices were calculated offline in the independent physiology core laboratory, with the cut-off values of 0.89 both for RFR or dPR. Third, the use of Tmn had a potential limitation, which might have resulted in the wider distribution of CFR values compared with Doppler flow velocity-derived CFR. Although obtaining high-quality Doppler

![Figure 5. FFR values in cases of discordance between RFR and dPR.](image-url)

FFR 0.79 (0.71–0.86), the median FFR found in the study by Lee et al was 0.85 (0.81–0.95), with the prevalence of diagnostically concordant normal lesions being much higher in their study than in the present study. Our study identified an overall significant difference in the prevalence of a FFR ≤0.80 and CFR ≤2.0, as well as lower FFR and CFR values, among the RFR+/dPR+, RFR−/dPR−, and RFR+/dPR− groups. Considering the results of the previous studies linking lower CFR and FFR with poor prognosis, clinical outcomes may be favourable for lesions with discordant dPR and FFR than for those with concordantly positive results, although IMR was not different. Physiological indices have been reported to be affected by the microvascular function. With increasing IMR values, FFR values might become higher and CFR values would be lower. Given that no difference in IMR was observed in these 3 subgroups divided by RFR and dPR, our results suggest that IMR, which is a hyperemic index, may not identify the characteristic difference in functional classifications by using 2 different resting indices. Further studies are needed to clarify the significance of microvascular function in relation to concordance or discordance between resting indices.

Of note, discordant cases between RFR and dPR distributed within the range of 0.86 and 0.89 of RFR and 0.90 and 0.93 of dPR, whereas they showed a broad range of the corresponding FFR values beyond the so-called FFR grey zone (Figure 5). Given that these invasive physiological indices are primarily indicated for the evaluation of patients with stable angina pectoris, and the decision regarding revascularization may not have a significant effect on the mortality rate in these patients, sound clinical judgment should inform the final decision. Our results indicated that, as was suggested by the ADVISE II study for iFR, lesions within the resting index-defined grey-zone (0.86–0.93) showed scattered FFR distributions mostly outside of the FFR grey zone, suggesting the need of individually tailored decisions for these lesions (Supplementary Figure 3).

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flow velocity data remains challenging. Doppler flow velocity CFR has been reported to have a superior agreement with CFR by [15 O]H 2O PET compared with thermodilution-derived CFR. Finally, the present retrospective analysis is limited by non-uniform patient and lesion characteristics, showing wide FFR variation and causing potential selection bias.

Conclusions

Both RFR and dPR were highly correlated, as previously reported, whereas their discordance of revascularization decision-making occurred in ∼5%, with no RFR−/dPR+ discordance identified. As FFR values of RFR/dPR discordant lesions were scattered in a wide range beyond the FFR grey zone, sound clinical judgment should inform the final decision, and clinical significance of the difference in resting index-based decision-making should be further elucidated.

Disclosures

The authors have no conflicts of interest to declare.

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