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Functional Assessment of Non-culprit Lesions Using Instantaneous Wave-free Ratio and Fractional Flow Reserve in Patients with Acute and Chronic Coronary Syndromes: A Retrospective Cohort Study

Akut ve Kronik Koroner Sendromlu Hastalarda Non-kulprit Lezyonların Anlık Dalgasız Oran ve Fraksiyonel Akım Rezervi Kullanılarak Fonksiyonel Değerlendirilmesi: Retrospektif Kohort Çalışması

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Abstract

Objectives: This study examined the concordance between fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) in patients with angiographically intermediate coronary lesions presenting with either acute coronary syndrome (ACS) or chronic coronary syndrome (CCS).

Material and Methods: This single-center retrospective analysis enrolled 48 patients who underwent coronary angiography with physiological assessment using both FFR and iFR. 16 patients presented with ACS and 32 presented with CCS. In ACS patients, physiological measurements were performed 48 hours after stabilization of the acute phase. Functional significance was defined as FFR ≤0.80 and iFR ≤0.89. Agreement between iFR and FFR was assessed using Cohen's kappa statistic, and diagnostic performance metrics were calculated.

Results: The overall agreement between iFR and FFR was modest but statistically significant (κ=0.292, p=0.039). Numerically higher agreement was observed in patients with ACS (κ=0.429, p=0.037) than in those with CCS (κ=0.238, p=0.178). In the ACS subgroup, iFR demonstrated specificity and a positive predictive value of 100%, indicating strong concordance with FFR when iFR classified a lesion as functionally significant after the acute phase. Concordance between the two indices was lower in patients with CCS.

Conclusion: iFR and FFR showed modest overall agreement in intermediate coronary lesions. Concordance was numerically higher in ACS after clinical stabilization, although this exploratory finding should be interpreted cautiously given the limited sample size.

Keywords: Fractional flow reserve, instantaneous wave-free ratio, acute coronary syndrome, chronic coronary syndrome, coronary artery disease

Öz

Amaç: Bu çalışmada, anjiyografik olarak orta dereceli koroner lezyonları bulunan akut koroner sendrom (AKS) veya kronik koroner sendrom (KKS) hastalarında fraksiyonel akım rezervi (FAR) ile *instantaneous wave-free ratio* (iFR) arasındaki uyum araştırıldı.

Gereç ve Yöntemler: Bu tek merkezli retrospektif analize, hem FAR hem de iFR kullanılarak fizyolojik değerlendirme yapılan 48 hasta dahil edildi. Hastaların 16'sı AKS, 32'si KKS ile başvurmuştu. AKS hastalarında fizyolojik ölçümler akut fazın stabilizasyonundan 48-72 saat sonra

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gerçekleştirildi. Fonksiyonel anlamlılık FAR ≤0,80 ve iFR ≤0,89 olarak tanımlandı. iFR ile FAR arasındaki uyum Cohen kappa istatistiği ile değerlendirildi ve tanısal performans ölçütleri hesaplandı.

Bulgular: iFR ile FAR arasındaki genel uyum orta düzeyde ancak istatistiksel olarak anlamlıydı (κ=0,292; p=0,039). Uyum AKS hastalarında (κ=0,429; p=0,037), KKS hastalarına göre (κ=0,238; p=0,178) daha yüksekti. AKS alt grubunda iFR'nin özgüllüğü ve pozitif öngörü değeri %100 olup, iFR'nin bir lezyonu akut faz sonrasında fonksiyonel olarak anlamlı sınıflandırdığı durumlarda FFR ile güçlü uyum gösterdi. İki indeks arasındaki uyum KKS hastalarında daha düşüktü.

Sonuç: iFR ve FAR, fizyolojik değerlendirme klinik stabilizasyon sonrasında yapıldığında AKS hastalarında kabul edilebilir düzeyde uyum göstermektedir; buna karşılık KKS hastalarında uyum daha düşüktür. Bu bulgular, orta dereceli koroner lezyonlarda invaziv fizyolojik indeksler yorumlanırken klinik bağlam ve zamanlamanın önemini vurgulamaktadır.

Anahtar Kelimeler: Fraksiyonel akım rezervi, *instantaneous wave-free ratio*, akut koroner sendrom, kronik koroner sendrom, koroner arter hastalığı

INTRODUCTION

For decades, invasive coronary angiography has served as the standard method for anatomical evaluation of coronary artery disease (CAD) (1). However, studies have shown that angiographic assessment alone may not be sufficient to determine whether an intermediate (40-70%) coronary lesion results in myocardial ischemia (2). These limitations have led to the development of invasive physiological assessment techniques, among which fractional flow reserve (FFR) has become the most extensively validated and clinically accepted method. Clinical outcome benefits with FFR-guided strategies have been particularly demonstrated in individuals with multivessel disease, by enabling more accurate revascularization decisions (3). Myocardial ischemia is hemodynamically determined by the interaction between coronary pressure and blood flow, and FFR is defined as the pressure-derived index calculated as distal coronary pressure (Pd) divided by aortic pressure (Pa) during pharmacologically achieved maximal hyperemia (4,5). To reduce dependence on hyperemic agents, the instantaneous wave-free ratio (iFR) was introduced as a resting physiological metric derived from a specific diastolic interval during which microvascular resistance is naturally minimized and relatively stable (6). iFR allows functional lesion assessment without the need for pharmacologic vasodilation (7). Evidence from large-scale randomized trials has demonstrated that iFR provides clinical outcomes comparable to those of FFR, confirming its non-inferiority in stable CAD (8,9).

More recently, attention has increasingly shifted toward complete revascularization as a potentially advantageous strategy in patients admitted with acute coronary syndromes (ACS) and multivessel coronary involvement, compared with treatment of the culprit lesion alone (10). In this context, we conducted a retrospective analysis to examine the concordance between iFR and FFR measurements in both ACS and chronic coronary syndromes (CCS) and to explore their diagnostic performance across different clinical scenarios.

MATERIAL AND METHODS

Study Population and Study Protocol

This retrospective study, conducted at a single tertiary referral center, employed an observational design. The study included 48 consecutive patients diagnosed with ACS or CCS who underwent coronary angiography and invasive physiological assessment. All patients had angiographically intermediate coronary lesions (40-70% diameter stenosis by visual estimation) and were evaluated using both FFR and iFR. Of the total study population, 43 patients were male. Sixteen patients were classified into the ACS group and 32 into the CCS group. Patients with a history of coronary artery bypass grafting or presenting with cardiogenic shock were excluded from the study. The functional significance of intermediate coronary lesions was assessed using invasive physiological indices in all included patients.

The study was approved by the Local Ethics Committee of İzmir Bakırçay University (approval no: 2818, date: February 25, 2026) and conducted in accordance with the principles of the Declaration of Helsinki. Due to the retrospective design and anonymized data analysis, the requirement for informed consent was waived.

FFR and iFR Measurement Techniques

Functional significance was defined as an FFR value ≤0.80 and an iFR value ≤0.89, in accordance with current guideline recommendations and large randomized clinical trials (11-13). Physiological assessments using both FFR and iFR were obtained in all patients using the Volcano S5 system (Volcano Corporation, Rancho Cordova, CA, USA). In patients presenting with ACS, physiological assessments were performed 48 hours after primary percutaneous coronary intervention (PCI), once clinical stabilization had occurred. Before the procedure, all patients received intravenous heparin. The pressure transducer was positioned at heart level (approximately 5 cm below the sternal angle), and adequate flushing of the pressure system was confirmed. Guiding catheters with side holes were not used for

FFR measurements. A 0.014-inch pressure-sensitive guidewire featuring a radiopaque distal 3-cm segment was used for all measurements. Following advancement into the target vessel, pressure equalization was achieved at the guiding catheter tip (Pd/Pa=1.0), after which the wire was advanced 1-2 cm distal to the lesion for subsequent physiological assessment.

iFR measurements were obtained at rest during the diastolic wave-free period. For FFR measurements, adenosine was used to induce maximal hyperemia. Intracoronary adenosine was administered at a dose of 150 µg, with an additional 150 µg if adequate hyperemia was not achieved. Intravenous adenosine was administered as a continuous infusion at 140 µg/kg/min for 2-3 minutes. FFR values were recorded after confirmation of stable maximal hyperemia. Following intracoronary adenosine injection, a similar volume of saline was rapidly injected for flushing purposes. During the study period, treatment decisions were primarily guided by FFR measurements in accordance with routine clinical practice. Lesions with FFR ≤0.80 were considered for revascularization, whereas those with FFR >0.80 were managed conservatively with optimal medical therapy and clinical follow-up. iFR was assessed for comparative purposes. In cases of discordance between FFR and iFR, treatment decisions were made based on the overall clinical context, including angiographic lesion characteristics and operator discretion. Because treatment decisions were primarily FFR-driven, a predefined change in treatment decision specifically attributable to FFR-iFR discordance was not prospectively or systematically recorded.

Statistical Analysis

Statistical analyses were conducted using SPSS Statistics version 15 (IBM Corp., Armonk, NY, USA). Categorical variables were compared between groups using the chi-square test and were presented as counts (n) and percentages (%). Continuous variables were evaluated with respect to their distribution characteristics and sample size. When comparing two independent groups, either the independent samples t-test or the Mann-Whitney U test was applied as appropriate. Continuous data are expressed as mean ± standard deviation. A two-sided p-value <0.05 was considered statistically significant.

RESULTS

Forty-eight patients with angiographically defined intermediate coronary stenoses underwent invasive physiological evaluation using both FFR and iFR. Of these, 16 were diagnosed with ACS, whereas 32 were classified as having CCS. The majority of patients were male (n=43, 89.6%). The baseline demographic and clinical features of the study population are presented in Table 1. The mean age was 55.84±9.6 years in the ACS group and 58.9±10.4 years in the CCS group (p=0.330). The proportion of males was similar between groups (87.5% vs. 90.6%, p=0.546). Diabetes mellitus was significantly more prevalent in ACS than in CCS (43.7% vs. 15.6%, p=0.041); a family history of cardiovascular disease was also more prevalent in the ACS group (56.3% vs. 15.6%, p=0.050). Smoking showed a non-significant trend toward higher prevalence in ACS (56.3% vs. 28.1%, p=0.058). The remaining baseline parameters were similar across groups. Procedural characteristics are outlined in Table 2. The left anterior descending artery was the predominant target vessel in both groups (87.5%). In the ACS group, the remaining lesions were located in the right coronary artery (12.5%), whereas in the CCS group, circumflex and right coronary artery lesions each accounted for 6.3%. All ACS patients received intravenous adenosine, while intracoronary adenosine was predominantly used in CCS patients (81.3%).

Hemodynamic parameters are summarized in Table 3. Compared with CCS patients, those with ACS had significantly lower systolic blood pressure (124.6±20.4 mmHg vs. 143.38±26.38 mmHg, p=0.015), diastolic blood pressure (74.1±11.2 mmHg vs. 84.4±13.9 mmHg, p=0.014), and mean arterial pressure (90.96±13.5 mmHg vs. 104.06±10.7 mmHg, p=0.006). Left ventricular ejection fraction showed a non-significant trend toward lower values in ACS (56.4±9.4% vs. 60.8±7.5%, p=0.069).

Table 1. Baseline demographic and clinical characteristics

Variable	ACS (n=16)	CCS (n=32)	p
Age, years	55.84±9.6	58.9±10.4	0.330
Male sex, n (%)	14 (87.5%)	29 (90.6%)	0.546
Diabetes mellitus, n (%)	7 (43.7%)	5 (15.6%)	0.041
Hypertension, n (%)	9 (56.3%)	12 (37.5%)	0.177
Hyperlipidemia, n (%)	3 (18.8%)	4 (12.5%)	0.429
Current smoking, n (%)	9 (56.3%)	9 (28.1%)	0.058
Family history, n (%)	9 (56.3%)	5 (15.6%)	0.050

Values are presented as mean ± standard deviation or n (%), as appropriate
ACS: Acute coronary syndrome, CCS: Chronic coronary syndrome

Table 2. Target vessel and route of adenosine administration

Characteristic	ACS (n=16)	CCS (n=32)
LAD, n (%)	14 (87.5%)	28 (87.5%)
Cx, n (%)	0 (0.0%)	2 (6.3%)
RCA, n (%)	2 (12.5%)	2 (6.3%)
Intracoronary adenosine, n (%)	0 (0.0%)	26 (81.3%)
Intravenous adenosine, n (%)	16 (100.0%)	6 (18.7%)

Distribution of target coronary vessels and route of adenosine administration during physiological assessment in ACS and CCS groups
ACS: Acute coronary syndrome, LAD: Left anterior descending artery, Cx: Circumflex artery, RCA: Right coronary artery, CCS: Chronic coronary syndrome

Using an FFR threshold of ≤0.80 as the reference standard, 24 of 48 patients (50%) had functionally significant lesions. Overall concordance between iFR and FFR was modest but statistically significant (Cohen's κ=0.292, p=0.039), with a discordance rate of 35.4% (Table 4). Discordance between FFR and iFR was observed in 17 patients (35.4%) in the overall cohort. Among these, 11 patients had FFR-positive/iFR-negative results, whereas 6 patients had FFR-negative/iFR-positive results. In the overall cohort, iFR yielded a sensitivity of 54.2% [95% confidence interval (CI): 34.3-74.1] and a specificity of 75.0% (95% CI: 57.7-92.3), with corresponding positive and negative predictive values of 68.4% (95% CI: 47.5-89.3) and 62.1% (95% CI: 44.5-79.7), respectively. In the ACS subgroup, agreement remained statistically significant (κ=0.429, p=0.037) (Table 5). Sensitivity and specificity were 50.0% (95% CI: 18.7-81.3) and 100% (95% CI: 54.1-100), with positive and negative predictive values of 100% (95% CI: 47.8-100) and 54.5% (95% CI: 23.4-83.3), respectively. Conversely, in the CCS subgroup, concordance did not reach statistical significance (κ=0.238, p=0.178) (Table 6). Sensitivity was 57.1% (95% CI: 28.9-82.3), specificity was 66.7% (95% CI: 41.0-86.7), and the positive and negative predictive values were 57.1% and 66.7%, respectively.

Table 3. Hemodynamic parameters and left ventricular function

Parameter	ACS (n=16)	CCS (n=32)	p
Systolic blood pressure, mmHg	124.6±20.4	143.38±26.38	0.015
Diastolic blood pressure, mmHg	74.1±11.2	84.4±13.9	0.014
Mean arterial pressure, mmHg	90.96±13.5	104.06±10.7	0.006
Pulse pressure, mmHg	50.5±13.2	58.92±18.4	0.076
Left ventricular ejection fraction, %	56.4±9.4	60.8±7.5	0.069
LV end-diastolic pressure, mmHg	8.2±8.0	10.7±4.5	0.371

Comparison of blood pressure measurements, left ventricular ejection fraction, and left ventricular end-diastolic pressure between ACS and CCS groups. Values are mean ± standard deviation unless otherwise indicated
ACS: Acute coronary syndrome, LV: Left ventricle, CCS: Chronic coronary syndrome

Table 4. Concordance between iFR and FFR in the overall cohort (n=48)

	iFR positive (critical)	iFR negative (non-critical)
FFR positive critical)	13 (54.2%)	11 (45.8%)
FFR negative (non-critical)	6 (25.0%)	18 (75.0%)

Agreement: Kappa=0.292; p=0.039. Sensitivity 54.2%, specificity 75%, PPV 68.4%, NPV 62.1%
FFR: Fractional flow reserve, iFR: Instantaneous wave-free ratio, PPV: Positive predictive value, NPV: Negative predictive value

DISCUSSION

In this retrospective study evaluating angiographically intermediate coronary lesions, we observed a modest but statistically significant overall agreement between iFR and FFR, with clear differences according to clinical presentation. Numerically higher agreement was observed in the ACS subgroup than in the CCS subgroup; however, given the small subgroup sample sizes, particularly in ACS, these differences should be interpreted cautiously and considered exploratory. These findings indicate that the diagnostic behavior and agreement of pressure-derived physiological indices may vary according to the clinical context and underlying coronary pathophysiology.

Large randomized trials have established that iFR-guided revascularization strategies provide clinical outcomes comparable to those of FFR-guided strategies in patients with CCS (12,13). However, these trials primarily focused on stable populations, and evidence comparing the performance of these indices in ACS remains limited. In the present study, iFR demonstrated high specificity and positive predictive value in the

Table 5. Concordance between iFR and FFR in acute coronary syndrome (ACS) (n=16)

	iFR positive (critical)	iFR negative (non-critical)
FFR positive (critical)	5 (50.0%)	5 (50.0%)
FFR negative (non-critical)	0 (0.0%)	6 (100.0%)

Concordance and discordance between iFR and FFR measurements in the ACS subgroup
Agreement: Kappa=0.429; p=0.037. Sensitivity 50%, specificity 100%, PPV 100%, NPV 54.5%
FFR: Fractional flow reserve, iFR: Instantaneous wave-free ratio, PPV: Positive predictive value, NPV: Negative predictive value

Table 6. Concordance between iFR and FFR in chronic coronary syndrome (CCS) (n=32)

	iFR positive (critical)	iFR negative (non-critical)
FFR positive (critical)	8 (57.1%)	6 (42.9%)
FFR negative (non-critical)	6 (33.3%)	12 (66.7%)

Concordance and discordance between iFR and FFR measurements in the CCS subgroup
Agreement: Kappa=0.238; p=0.178. Sensitivity 57.1%, specificity 66.7%, PPV 57.1%, NPV 66.7%
FFR: Fractional flow reserve, iFR: Instantaneous wave-free ratio, PPV: Positive predictive value, NPV: Negative predictive value

ACS subgroup; however, its relatively low sensitivity and negative predictive value indicate that a negative iFR result should be interpreted cautiously when excluding functionally significant lesions. Given the limited number of patients in this subgroup, these findings should be considered exploratory. Moreover, the relatively wide CIs around these diagnostic performance estimates further emphasize the uncertainty associated with the small ACS subgroup.

Contemporary evidence suggests that deferring the physiological assessment of non-culprit lesions until after resolution of the acute phase improves the reliability of invasive indices (14). Consistent with these observations, our findings suggest that concordance between iFR and FFR may be preserved when physiological evaluation is performed beyond the early acute phase of ACS. A numerically lower agreement was observed in CCS; however, this subgroup finding should be interpreted cautiously given the limited sample size. The difference in the route of adenosine administration between the ACS and CCS groups should also be considered when interpreting these subgroup findings. Intravenous and intracoronary adenosine may differ in the consistency and duration of the hyperemia achieved, potentially contributing to variability in FFR measurements. This finding is consistent with recent data demonstrating that discordance between resting and hyperemia-based indices is more frequently observed in CCS and may reflect diffuse atherosclerotic disease, gradual pressure loss along the vessel, and resting translesional pressure gradients (5,15,16). A substantial proportion of patients in our study demonstrated discordant results between FFR and iFR. Although treatment decisions in our cohort were primarily guided by FFR, these findings suggest that discordance should be interpreted within the broader clinical context. Currently, no clear guideline-based strategy or standardized algorithm exists for the management of such cases. Therefore, clinical decision-making should be individualized, taking into account the overall clinical context, angiographic characteristics, and patient-specific factors. Importantly, our findings suggest that discordance between FFR and iFR is not uncommon and may need to be considered during clinical decision-making rather than being overlooked.

These results should be considered in light of the continuously evolving revascularization strategies applied to ACS. Randomized trials and contemporary analyses have demonstrated that complete revascularization may confer clinical benefit over a culprit-lesion-only approach in patients with multivessel disease (10). Nevertheless, the optimal strategy for identifying non-culprit lesions that truly require intervention remains a matter of ongoing debate. In this regard, a recent network meta-analysis comparing physiology-guided and complete revascularization strategies guided by angiographic findings in patients with ST-segment elevation myocardial infarction and multivessel involvement reported that angiography-guided revascularization was associated with a lower incidence of major adverse cardiovascular events relative to culprit-only PCI, whereas physiology-guided approaches did not consistently result in superior outcomes across all clinical endpoints (17). Similarly, the iMODERN randomized trial demonstrated that immediate iFR-guided PCI of non-culprit lesions did not demonstrate superiority over a deferred ischemia-based strategy using cardiac magnetic resonance imaging in terms of hard clinical outcomes during long-term follow-up (18). These findings suggest that in ACS, invasive physiological indices should be interpreted with caution and within the appropriate clinical and temporal context. These observations suggest that discordance, particularly FFR-positive/iFR-negative patterns, may help to explain why FFR-guided strategies result in higher revascularization rates without a corresponding improvement in clinical outcome (8,9). In the present study, physiological measurements were performed beyond the early acute phase, which may have partially mitigated the influence of transient microvascular dysfunction and contributed to the observed concordance between iFR and FFR in the ACS subgroup.

Study Limitations

This study is subject to important limitations. It was designed as a retrospective single-center analysis with a limited sample size, which may limit the external validity and the broader applicability of the results. Second, differences in the routes of adenosine administration between patients with ACS and CCS may have influenced the degree of hyperemia and, consequently, the FFR measurements. Third, physiological assessment was performed at a single time point; serial measurements were unavailable to evaluate temporal changes in coronary physiology. Finally, long-term clinical outcomes were not assessed, precluding direct conclusions regarding the prognostic implications of the observed physiological findings. In addition, treatment changes specifically attributable to FFR-iFR discordance were not systematically recorded, limiting the ability to assess the direct clinical impact of discordance on decision-making. Despite these limitations, the study reflects routine clinical practice and provides clinically relevant insights into the interpretation of invasive physiological indices across different clinical presentations of CAD.

CONCLUSION

This study demonstrated modest overall agreement between iFR and FFR in patients with angiographically intermediate coronary lesions. In the ACS subgroup, iFR showed high specificity and positive predictive value, but relatively low sensitivity and

negative predictive value. Although agreement was numerically higher in ACS than in CCS, small sample sizes in subgroups preclude definitive comparisons between clinical presentations. These exploratory findings highlight the importance of clinical context and timing when interpreting invasive physiological assessments and warrant confirmation in larger prospective studies.

*Ethics

Ethics Committee Approval: The study was approved by the Local Ethics Committee of İzmir Bakırçay University (approval no: 2818, date: February 25, 2026) and conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Due to the retrospective design and anonymized data analysis, the requirement for informed consent was waived.

Footnotes

Authorship Contributions

Concept: N.Ö., Design: Ç.G., C.D., Z.B., N.Ö., Data Collection or Processing: Ç.Ö., B.G.Ş., Analysis or Interpretation: Ç.Ö., Ç.G., C.D., Z.B., Literature Search: Ç.Ö., B.G.Ş., Writing: Ç.Ö., Ç.G., C.D., Z.B., B.G.Ş., N.Ö.

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