CLINICAL STUDY

Patients with Moderate Non-Culprit Coronary Lesions of Recent Acute Coronary Syndrome
A Comparison of Fractional Flow Reserve and Dobutamine Stress Echocardiography

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Summary

Fractional flow reserve (FFR) measurement was compared to dobutamine stress echocardiography (DSE) in patients with acute coronary syndrome (ACS) with moderate (< 30%) or non-culprit lesion(s) (NCL(s)) with recent acute coronary syndrome (RACS) in a few trials; however, similar comparisons in patients with moderate NCLs and stable coronary lesion(s) (SCLs) are lacking. Our objectives were to prospectively evaluate the diagnostic performance of FFR with two different cutoff values (< 0.80 and < 0.75) relative to DSE in moderate (30%-70% diameter stenosis) NCLs (ACS group) and to compare these observations with those measured in SCLs (SA group). One hundred seventy-five consecutive patients with SA (n = 89) and ACS (n = 86) with 225 coronary lesions (109 SCLs and 116 NCLs) were enrolled. In contrast to the ACS cohort in SA patients, normal DSE was associated with higher FFR values compared to those with abnormal DSE (P = 0.051 versus P = 0.006). In addition, in the SA group, a significant correlation was observed between DSE (regional wall motion score index at peak stress) and FFR (r = −0.290; P = 0.002), whereas a similar association was absent (r = −0.029; P = 0.760) among ACS patients. In the SA group, decreasing the FFR cutoff value (< 0.80 versus < 0.75) improved the concordance of FFR with DSE (70.6% versus 81.7%) without altering its discriminatory power (area under the curve; 0.68 versus 0.63; P = 0.369), whereas in the ACS group, concordance remained similar (69.0% versus 71.6%) and discriminatory power decreased (0.62 versus 0.51; P = 0.049), respectively. In conclusion, lesion-specific FFR assessment may have different relevance in patients with moderate NCLs than in patients with SCLs.

Key words: Lesion-specific ischemia assessment, Multivessel disease, Stable angina

Moderate non-culprit lesions (NCLs) are present in more than 50% of patients with acute coronary syndrome (ACS), and the 30-day mortality is higher in this population than in single-vessel ACS; nonetheless, the treatment strategy of these coronary stenoses poses challenges. Despite the fact that fractional flow reserve (FFR) provides important diagnostic information and is considered the gold-standard invasive diagnostic method for lesion-specific ischemia assessment in patients with stable angina (SA) with stable coronary lesion(s) (SCL(s)), it is not clearly validated in patients with ACS and, especially, those with NCLs. Moreover, its impact on hard cardiovascular endpoints, such as cardiac death or myocardial infarction is limited in both clinical scenarios. By contrast, dobutamine stress echocardiography (DSE) has an excellent prognostic value both in SA and ACS patients with NCL(s) and DSE-guided revascularization also improves outcomes. Importantly, there are few data regarding the prospective comparison between DSE and FFR in patients with SCL(s); however, similar data on the issue of ACS accompanied by intermediate NCL(s) are lacking. In our prospective clinical study, we sought to assess the diagnostic performance of FFR relative to DSE and to determine the impact of different FFR cutoff values (< 0.80 and < 0.75) on its diagnostic ability to identify coronary lesions with ischemia in ACS patients with moderate NCL(s) (ACS group) and compare these results with the same observations measured in patients with moderate SCLs (SA group). We also aimed to investigate correlations between FFR, quantitative DSE and quantitative coronary angiography (QCA) in both groups.

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Methods

Population and study design: From December 2014 to December 2017, 175 consecutive patients (89 in the ACS group and 86 in the SA group) were prospectively enrolled (Figure 1) with moderate (30%-70% diameter) coronary artery stenosis. In the ACS group, moderate NCLs were detected during acute coronary angiography. ACS was determined as Type 1 myocardial infarction according to the (at that time actual) third universal definition of myocardial infarction.15) In the SA group, the angiogram was indicated due to a positive/equivocal non-invasive ischemia test, positive/equivocal coronary CT angiography, or high pre-test probability for significant coronary lesions.16) In the ACS group, staged FFR was planned to be performed more than a month after the index episode (62 days median; interquartile range (IQR): 49-79.5 days), whereas in the SA group, FFR was measured during the initial invasive coronary angiography. DSE and FFR measurements were performed within 3 months in all cases (ACS group: 12 days median, IQR: 5-21.5 days; SA group: 29 days median, IQR: 10.5-44.25 days). In the ACS group, culprit lesions were treated with percutaneous coronary intervention with stent implantation (n = 82; 92.2 %) or managed medically (n = 7; 7.8 %) because of small vessel size; however, every other severe lesions (> 70% diameter stenosis) on ≥ 2.5 mm vessels were treated with percutaneous coronary intervention before DSE and FFR measurements in both groups. The imaging cardiologists were blinded to the quantitative angiography and FFR data, and the interventional cardiologists were blinded to the DSE results. The results of the two methods were matched during the data analysis period (considering the coronary dominancy). Exclusion criteria were left main coronary artery stenosis, age > 80 years, pregnancy, known non-cardiovascular disease with poor prognosis, < 2 years of life expectancy, FFR or DSE contraindicated per institutional standard of care, inadequate image quality for DSE, co-dominant coronary circulation, coronary anomalies, severe valvular disease, or inability to provide informed consent.

Coronary angiography and FFR: Coronary angiography (Innova 2100 IQ, General Electric Healthcare Europe, UK, and Axiom Artis dTA, Siemens Healthineers, Germany) and QCA was performed according to international standards.17,18) On this basis, diameter stenosis was expressed in a percentage calculated by an automated software.18) During the FFR procedure (after equalization), the pressure wire (Aeris or Certus, St. Jude Medical, USA) sensor was positioned beyond the coronary lesion (Pd) through a guiding catheter (Pa), and the FFR value was calculated as a continuously measured mean Pd/Pa ratio after systemic adenosine infusion (140-180 μg/kg/minute).17) Since we performed a diagnostic accuracy study of FFR relative to DSE (as a non-invasive comparator), we used two different FFR cutoff values (< 0.75 and < 0.80) on the basis of a meta-analysis of diagnostic accuracy studies of FFR compared to non-invasive methods.19) In our institution, intracoronary nitroglycerine is not routinely used during primary percutaneous coronary interventions; therefore, diameter stenosis was calculated before nitroglycerine administration to FFR measurements in both groups to make the results accurately comparable between ACS and SA groups and between the two invasive procedures in the ACS group.

Dobutamine stress echocardiography: All DSE proce-
dures were performed according to the European Society of Cardiology expert consensus statement. Owing to the imperceptible nature of the endocardial excursion and the thickening of the tip of the apex, the 16-segment left ventricle model was used on a Vivid 7 Pro system (General Electric Healthcare Europe, UK). The patients were encouraged to stop taking beta-blockers at least 24 hours before the procedure; other medication was continued. Dobutamine infusion was titrated in 3-minute intervals from 5 to 10, 20, 30, 40 μg/kg/minute, and if the submaximal frequency was not achieved, the dose was further increased up to 50 μg/kg/minute, and iv. atropine was administered (up to 2 mg). In patients with insufficient image quality for native wall motion evaluation, an intravenous ultrasound contrast agent (Sonovue, Bracco, Italy) was administered. Endpoints were determined as the maximum dose of pharmacological agents, achievement of at least age-predicted submaximal (85%) target heart rate, echocardiographic positivity for ischemia [new or worsening wall motion abnormality (WMA) or biphasic response echocardiographic positivity for ischemia [new or worsening]. At rest and at peak dose of dobutamine; thus, the expert echocardiographer (PA). A final DSE decision was made after the interpretation of the expert echocardiographer (PA).

**Statistical analysis:** Continuous values were presented as means ± standard deviations, whereas categorical values were described as numbers and percentages. Normality of distribution of continuous parameters was determined using the Kolmogorov-Smirnov test. Continuous parameters were compared using an independent or paired t-test, Mann-Whitney U or Wilcoxon’s test, and correlation analysis was done using the Spearman’s or Pearson’s correlation coefficient as appropriate. Chi-squared test or Fisher’s exact test was used to compare groups with categorical values. Diagnostic performance was evaluated by determining the number of true and false positives and true and false negatives. Sensitivity, specificity, positive and negative predictive value (PPV and NPV), and concordance (the sum of true positives and true negatives divided by the total number of investigated lesions) were calculated from the 2 × 2 contingency tables. A chi-squared test of independence was performed to examine the relation between categorical FFR and categorical DSE results, whose association was investigated further using Cramér’s V coefficient (V). As an overall descriptor of discriminatory power, we calculated receiver operating characteristic (ROC) area under the curve (AUC) values for the pre-specified FFR cutoff values in predicting DSE positivity. AUC values were compared using the DeLong method. In comparison, DSE was used as the reference. Optimal FFR cutoff values were determined in both groups using Youden’s index. P values < 0.05 were considered to indicate statistical significance. Statistical analysis was completed using SPSS Statistics 22 (IBM, USA). ROC analysis was conducted using R v.3.5.1 (R Foundation for Statistical Computing, Austria).

**Results**

**Demography and clinical presentation:** A total of 175 patients were consecutively enrolled: 86 in the SA group and 89 in the ACS group [58 ST-segment elevation myocardial infarction and 31 non-ST-segment elevation ACS; 20 (22.5%) anterior and 69 (77.5%) non-anterior localization; prevalence of acute heart failure, cardiogenic shock, and survived ventricular tachycardia or ventricular fibrillation before admission or during hospital stay at 7 (7.9%), 0 (0%), 2 (2.2%), and 2 (2.2%), respectively]. Although the majority of SA patients were investigated invasively due to angina (86%), non-invasive ischemia test was performed only in 43% of the patients prior to the angiogram (Table I). The rest of SA patients (57%) had high pre-test probability or positive/equivocal CT angiography for significant coronary stenosis (Table I). Patients in the SA group had more severe symptoms at the time of enrollment than those in ACS patients at the time of the repeated coronary angiography evaluated based on the Canadian Cardiovascular Society angina classification (Table II). Demography data and medications are listed in Table II.

**Lesion characteristics and FFR:** Of the 225 vessels, 109 SCLs (67 LAD, 18 LCx, and 24 RCA) and 116 NCLs (72 LAD, 20 LCx, and 24 RCA) were analyzed. The anatomical distribution of investigated lesions was not different between the two groups (P = 0.967). Coronary circulation dominancy distribution was also similar between the two groups [SA group right dominant versus ACS group right dominant: 75 (78.6%) versus 85 (81.4%); P = 0.061]. In the SA group, 24 patients have more than one moderate SCL; however, 25 patients have two moderate NCLs in the ACS group. At the time of enrollment, stenosis severity in the SA group revealed by QCA was less than that of the NCLs in the ACS group (52.0% ± 8.5% versus 54.6% ± 7.3%; P = 0.017). Notably, the diameter stenosis of NCLs decreased significantly during the time of the staged FFR procedure (from 54.6% ± 7.3% to 47.9% ± 8.0%; P < 0.001), which was lower than SCLs’ diameter stenosis (47.9% ± 8.0% versus 52.0% ± 8.5%; P < 0.001). The FFR values did not differ between the SA and the ACS groups (0.82 ± 0.07 versus 0.82 ± 0.08; P = 0.940), and the ratio of lesions with FFR < 0.80 was also similar (34.9% versus 31.9%; P = 0.637), respectively.
FFR < 0.80 was not associated with more severe diameter stenosis in either group (FFR < 0.80 versus FFR ≥ 0.80 in the SA group: 53.6% ± 9.4% versus 51.2% ± 7.9%; \( P = 0.165 \); FFR < 0.80 versus FFR ≥ 0.80 in the ACS group: 0.79 ± 0.07 versus 0.83 ± 0.08, \( P = 0.460 \)).

**Rest and dobutamine stress echocardiography:** Ejection fraction and WMSI at rest were better, and the frequency of resting WMA occurrence was lower in the SA group than in the ACS group (55.6% ± 12.0% versus 47.4% ± 7.2%, \( P < 0.001 \); 1.11 ± 0.22 versus 1.21 ± 0.21, \( P < 0.001 \), and 33.7% versus 74.2%, \( P < 0.001 \), respectively). Most of the patients achieved the target heart rate during DSE: 83 (96.5%) in the SA group and 83 (93.3%) in the ACS group. Global DSE parameters, such as AWMSI and the WMSI rest/peak ratio, were higher in the SA group than those in the ACS group (0.09 ± 0.19 versus 0.02 ± 0.19, \( P = 0.012 \) and 1.08 ± 0.18 versus 1.02 ± 0.16, \( P = 0.011 \), respectively); however, WMSI at peak stress did not differ between the groups (1.20 ± 0.27 versus 1.23 ± 0.24; \( P = 0.123 \)), and the ratios of lesions confirmed as positive by DSE were also similar (20.2% versus 16.4%; \( P = 0.460 \)), respectively. We identified no difference in regional (vessel based) DSE parameters between the groups (Table III). Abnormal DSE was associated with lower FFR values (0.79 ± 0.09 versus 0.83 ± 0.07, \( P = 0.030 \); Figure 2A) and more severe diameter stenosis (55.5% ± 6.8% versus 54.2% ± 7.5%; \( P = 0.438 \)).

**Correlation analysis:** In the SA group, FFR had a modest inverse correlation with diameter stenosis (\( r = -0.231 \); \( P = 0.016 \)) and with regional WMSI at peak dose of dobutamine (\( r = -0.290 \); \( P = 0.002 \)). The extensive sub-

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**Table I.** Clinical Indications, Preoperative Ischemia Tests, and Imaging-based Referrals for Invasive Coronary Angiography in the SA Group

| Variable                                      | SA group (n = 86) | ACS group (n = 89) | \( P \) value |
|-----------------------------------------------|------------------|-------------------|-------------|
| Clinical indications (n = 86)                 |                  |                   |             |
| Angina pectoris, n (%)                        | 74 (86.0)        |                   |             |
| Symptoms of heart failure, n (%)              | 12 (14.0)        |                   |             |
| Preoperative ischemia tests and imaging-based referrals (n = 49) | 33 (66.35) |                   |             |
| Exercise ECG, n (%)                           | 3 (6.1)          |                   |             |
| SPECT, n (%)                                  | 12 (24.5)        |                   |             |
| Coronary CT angiography, n (%)                |                  |                   |             |
| Stress MRI, n (%)                             | 1 (2.05)         |                   |             |

CT indicates computed tomography; ECG, electrocardiography; MRI, magnetic resonance imaging; SA, stable angina; and SPECT, single photon emission computer tomography.

**Table II.** Baseline Demographic Data in the SA and ACS Groups

| Baseline demography data and medical history | SA group (n = 86) | ACS group (n = 89) | \( P \) value |
|---------------------------------------------|------------------|-------------------|-------------|
| Age (years)                                 | 62.2 ± 8         | 59.4 ± 9.3        | 0.034       |
| Female gender, n (%)                        | 34 (39.5)        | 19 (21.3)         | 0.009       |
| Hypertension, n (%)                         | 77 (89.5)        | 64 (71.9)         | 0.003       |
| Diabetes mellitus, n (%)                    | 35 (40.7)        | 27 (30.3)         | 0.152       |
| Hyperlipidemia, n (%)                       | 62 (72.1)        | 54 (60.7)         | 0.110       |
| Current smoker, n (%)                       | 34 (39.5)        | 48 (53.9)         | 0.056       |
| Family history of coronary artery disease, n (%) | 40 (46.5) | 39 (43.8)        | 0.721       |
| Angina stage (CCS Classification), n (%)     |                  |                   | < 0.001     |
| I                                           | 25 (29.1)        | 80 (89.9)         |             |
| II                                          | 31 (36.0)        | 5 (5.6)           |             |
| III                                         | 8 (9.3)          | 2 (2.25)          |             |
| IV                                          | 22 (25.6)        | 2 (2.25)          |             |
| Medication                                  |                  |                   |             |
| Aspirin, n (%)                               | 67 (77.9)        | 88 (98.9)         | < 0.001     |
| Clopidogrel/prasugrel, n (%)                 | 32 (37.2)        | 87 (97.8)         | < 0.001     |
| ACE-i/ARB, n (%)                             | 74 (86.0)        | 89 (100)          | < 0.001     |
| Calcium-channel blocker, n (%)               | 44 (51.2)        | 21 (23.6)         | < 0.001     |
| Beta-blocker, n (%)                          | 80 (93.0)        | 87 (97.8)         | 0.128       |
| Statin, n (%)                                | 70 (81.4)        | 88 (98.9)         | < 0.001     |

ACE-i indicates angiotensin converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; CCS, Canadian Cardiovascular Society; and SA, stable angina.
Table III. Regional DSE Parameters in the SA and ACS Groups

| Regional DSE parameters | SA group (n = 109) | ACS group (n = 116) | P value |
|-------------------------|-------------------|---------------------|---------|
| Regional WMS at rest    | 7.7 ± 3.2         | 7.4 ± 2.9           | 0.826   |
| Regional WMS at peak stress | 8.7 ± 4.2       | 8.1 ± 3.6           | 0.710   |
| Regional WMSI at rest   | 1.08 ± 0.23       | 1.08 ± 0.23         | 0.596   |
| Regional WMSI at peak stress | 1.23 ± 0.46     | 1.17 ± 0.34         | 0.685   |

ACS indicates acute coronary syndrome; DSE, dobutamine stress echocardiography; SA, stable angina; WMS, wall motion score; and WMSI, wall motion score index.

![Figure 2](image)

Figure 2. Association of FFR and diameter stenosis with abnormal and normal DSE. Abnormal DSE is associated with lower FFR values (A) and more severe diameter stenosis (B) in the SA group (blue bars). In the ACS group (orange bars), neither FFR value (C) nor diameter stenosis (D) is different in cases of abnormal vs. normal DSE. Error bars indicate mean ± standard deviation on every panel. ACS indicates acute coronary syndrome; DSE, dobutamine stress echocardiography; and FFR, fractional flow reserve.

Diagnostic performance and discriminatory power of FFR: Using the FFR < 0.80 cutoff value, the association between FFR and DSE was moderate in the SA group (V = 0.304; P = 0.002) and low in the ACS group (V = 0.197; P = 0.034); however, the discriminatory ability of FFR was modest in SA and ACS groups (AUC<sub>SA</sub> < 0.80 vs. AUC<sub>ACS</sub> < 0.80: 0.680 and 0.624, respectively). Decreasing the FFR cutoff value to < 0.75 had the following impact on the diagnostic performance of FFR: In the SA group, the concordance of FFR with DSE improved (from 70.6% to 81.7%) without a significant change in the association level (V = 0.334; P < 0.001) and its discriminatory power (AUC<sub>SA</sub> < 0.80: 0.680 versus AUC<sub>SA</sub> < 0.75: 0.630, P = 0.369; Figure 3A); however, in the ACS group, a similar concordance (69.0% versus 71.6%) without any associa-
tion between FFR and DSE (V = 0.024; P = 0.800) and a significant decrease in AUC value (AUC\_ACS < 0.80: 0.624 versus AUC\_ACS < 0.75: 0.513, P < 0.049; Figure 3B) were detected. Extended diagnostic performance analysis data are presented in Table V. In the SA group, the optimal FFR cutoff value was 0.80; by contrast, it was 0.85 in the ACS group.

**Discussion**

**Major findings of our study:** This is the first prospective clinical study that established that the functional relevance of lesion-specific FFR assessment may be different in intermediate NCLs of recent ACS than those in SCLs. There was no correlation between FFR values and global and regional DSE parameters in NCLs of ACS patients, whereas it was verified in SCLs of SA patients. Our results demonstrated that abnormal DSE is associated with a lower FFR value and more severe diameter stenosis in patients with SCL, whereas these associations were not observed in NCLs of ACS patients. In the SA cohort, the diagnostic accuracy of FFR was similar to the results of previously published studies with smaller sample sizes.\(^{13,22,28}\) Decreasing the FFR cutoff value from < 0.80 to < 0.75 improved the concordance of FFR with DSE in the SA group without significant changes in its discriminatory power (according to AUC values). In the ACS group, the lower cutoff value further deteriorated the diagnostic performance of FFR. Additionally, we found a significant decrease of NCLs’ diameter stenosis during the time of the staged FFR procedure, compared to the initial angiogram.

**Comparison with other studies:**

**Stable angina population** There are only small-scale prospective trials comparing FFR and DSE in SA population.\(^{12,14,28}\) Although the inclusion criteria (e.g., lesion severity), the DSE method (e.g., in our study contrast agent was used only in selected patients with a poor acoustic window), and the FFR cutoff values (< 0.80 versus < 0.75) were slightly different, our results are in line with the prospective trials that we have cited above and other previously published retrospective studies.\(^{23}\) In most of these previous studies, the AUC value was not calculated, and the diagnostic accuracy was not assessed using two different cutoff values. The ratios of discordant DSE-FFR results in our SA group are 29.4% and 18.3% depending on the FFR cutoff value (< 0.80 versus < 0.75) were slightly different, our results are in line with the prospective trials that we have cited above and other previously published retrospective studies.\(^{23}\) In most of these previous studies, the AUC value was not calculated, and the diagnostic accuracy was not assessed using two different cutoff values. The ratios of discordant DSE-FFR results in our SA group are 29.4% and 18.3% depending on the FFR cutoff value (< 0.80 versus < 0.75, respectively). In some trials, more remarkable discordance is observed in the comparison of FFR and coronary flow reserve (CFR) measurement,\(^{29}\) which could be explained by their different physiological background. FFR represents a pressure drop through a mainly focal epicardial stenosis during hyperemia, whereas CFR shows the vasodilation ability of the coronary arteriolar bed, hence the myocardial blood flow in the response of metabolic demands. CFR impairment is more directly related to subendocardial myocardial ischemia than FFR. The regional WMA is a surrogate of CFR.\(^{21}\) In FFR positive-DSE, a negative mismatch, probably the contribution of focal coronary stenosis, is more significant with a normal microvascularity, whereas in the FFR negative-DSE, positive cases diffuse coronary disease, with microvascular impairment be-

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### Table IV. Correlation Analysis of FFR Values with Stenosis Severity and DSE Parameters in the SA and ACS Groups

|                      | SA group | ACS group |
|----------------------|----------|-----------|
|                      | All lesions (n = 109) | LAD (n = 67) | LCx (n = 18) | RCA (n = 24) | All lesions (n = 116) | LAD (n = 72) | LCx (n = 20) | RCA (n = 24) |
| Diameter stenosis (%) | r        | P         | r        | P         | r        | P         | r        | P         |
|                      | -0.231   | 0.016     | -0.155   | 0.209     | -0.487   | 0.040     | -0.513   | 0.010     |
| Ejection fraction (%) | r        | P         | r        | P         | r        | P         | r        | P         |
|                      | 0.034    | 0.718     | 0.134    | 0.296     | 0.147    | 0.574     | -0.365   | 0.114     |
| Global WMSI at peak stress | r        | P         | r        | P         | r        | P         | r        | P         |
|                      | -0.276   | 0.004     | -0.262   | 0.032     | -0.327   | 0.185     | -0.331   | 0.114     |
| Global peak/rest WMSI | r        | P         | r        | P         | r        | P         | r        | P         |
|                      | -0.209   | 0.029     | -0.133   | 0.282     | -0.256   | 0.306     | -0.363   | 0.081     |
| Global delta-WMSI    | r        | P         | r        | P         | r        | P         | r        | P         |
|                      | -0.221   | 0.021     | -0.140   | 0.260     | -0.334   | 0.176     | -0.342   | 0.102     |

ACS indicates acute coronary syndrome; DSE, dobutamine stress echocardiography; FFR, fractional flow reserve; LAD, left anterior descending artery; LCx, left circumflex artery; r, correlation coefficient; RCA, right coronary artery; SA, stable angina; and WMSI, wall motion score index.
ACS population There are only few studies evaluating moderate NCLs’ functional significance in ACS. Multivessel disease is commonly present in patients with ACS, and these patients are at higher risk of further adverse cardiac events. ACS patients presented with multivessel disease may benefit from additional assessment of residual ischemia. The best validated and widely available non-invasive tests for the detection of residual ischemia are stress echocardiography and single photon emission computed tomography. After uncomplicated myocardial infarction, DSE has a strong prognostic power to predict cardiac events, such as cardiac death and myocardial reinfarction. In DSE studies, new regional WMA on the non-culprit area (ischemia at a distance) is one of the prognostic factors on hard cardiac events. By contrast, patients with ST-elevation myocardial infarction and multivessel disease without significant residual ischemia, determined using non-invasive methods, on the non-culprit related area have a prognosis similar to patients with ST-elevation myocardial infarction and single-vessel disease. In our prospective study, we found a poor correlation between FFR and the prognostically important DSE parameters. This finding may explain why the few randomized trials on the invasive assessment of moderate NCLs did not prove the benefit of the FFR-guided revascularization strategy on hard cardiovascular endpoints. As far as we know, there is no other study available that compares invasive FFR to the non-invasive DSE in cases of moderate NCLs. The FFR validation process is not completely reassuring in the setting of ACS, especially in the evaluation of NCLs.

Differences between SA and ACS groups: The concordance between FFR and DSE was higher in the SA group, and a significant correlation was observed between the two investigated methods in the SA group. This significant correlation was also detected on a vessel-based sub-analysis on LAD and RCA territories; however, the sample size of LCx was probably too small (n = 18) to show a significant correlation. SA patients had more severe symptoms and slightly more severe lesions by QCA, compared to patients with NCLs after ACS; however, there was no difference between the two groups in the FFR values. Although in the SA group, a symptom- and non-invasive test-guided approach indicated the angiogram, the moderate NCLs were found “accidentally” during the acute angiography in the ACS group. Therefore, the functional pathophysiologies of two anatomically similar lesions on the angiogram are not necessarily identical. The correlation between FFR and CFR (as a surrogate of DSE) is better in the more symptomatic (“disease-enriched”) population than in the patients without symptoms or with mild symptoms only, such as in our ACS group.

Potential factors affecting FFR measurement of non-culprit lesions: Achievement maximal hyperemia is the cornerstone of FFR measurement; however, it can be affected by various factors. It has been investigated by other researchers that the presence of microvascular obstruction (assessed using cardiac magnetic resonance imaging) in the supplying territory of the culprit vessel in patients with ST-segment elevation myocardial infarction increases the FFR value at the acute phase but decreases it in the course of long-term observations. Reduced coronary blood flow is demonstrable not only in culprit coronary...
arteries immediately after thrombolysis or percutaneous coronary intervention\(^{37}\) in patients with acute myocardial infarction but also in the non-culprit vessels.\(^{38}\) Many other factors, such as microvascular dysfunction, impaired endothelium-dependent vasodilatation response and enhanced response of resistance vessels not only to systemic but also local neurohormonal factors,\(^{39}\) and α-adrenergic blockade\(^ {31}\) can affect coronary blood flow, pressure gradients, and, thus, FFR values in non-culprit coronary arteries. These observations might explain our findings of a high discordant ratio between FFR and DSE as the surrogate marker of CFR.

**Clinical implications:** In patients with moderate SCL, FFR-guided revascularization is a simple, easily accessible, and, therefore, frequently used strategy because of the large number of patients having angiogram without a prior non-invasive functional test, even though this approach does not improve the prognosis in terms of the hard endpoints of myocardial infarction and mortality. Our study demonstrates that the FFR cutoff value of < 0.80 has a poor PPV of 36.8%. Decreasing the cutoff to < 0.75 can moderately improve the PPV of FFR to 58.3% and its diagnostic concordance with DSE from 70.6% to 81.7% without significant worsening of NPV from 88.7% to 84.5%. In addition, our data demonstrated that the discriminatory ability of FFR does not change with the lower cutoff value. These observations might suggest that an additional DSE in planning the treatment strategy may improve the prognosis in SA patients with a positive FFR as a first functional test on a moderate coronary stenosis. By contrast, a negative FFR test in the same clinical setting might be sufficient to avoid unnecessary revascularization without further ischemia evaluation even with the < 0.75 cutoff value. These observations are in line with the results of the DEFER trial.\(^ {40}\) The deferral of revascularization by negative FFR (> 0.80) of NCLs is accompanied by a higher rate of MACE than that in the SA population with a similar deferral strategy, as it described previously by other authors,\(^ {41,42}\) whereas in the FFR positive (< 0.80) cases, the revascularization of NCLs did not improve the prognosis.\(^ {43}\) The lack of any correlation between FFR and regional DSE parameters at the non-culprit area in our study might explain the results of these previously cited studies.\(^ {36,37}\) In the ACS group in our study, the lowering of the FFR cutoff value did not improve its diagnostic concordance; moreover, the discriminatory ability decreased close to random. Based on these data, FFR may not be used for the evaluation of moderate NCLs after ACS as a single functional test to plan revascularization. This finding is in line with a recent meta-analysis that demonstrated that using an additional FFR measurement in tailoring the revascularization strategy of NCLs does not improve the prognosis after ACS.\(^ {43}\) By contrast, our results proposed that because of the diameter stenosis improvement of NCLs in patients with an unsellected type of ACS during the time of the staged invasive procedure, careful adjudication is considered to indicate a further revascularization strategy, relying only on the acute angiogram. By contrast, it is well known that accurate determination of diameter stenosis using QCA has limited evidence.

**Study limitations:** Our study is a single-center, non-randomized, observational clinical study for diagnostic performance analysis with a relatively small sample size. Although 14% of our patients in the SA group were referred to our department for coronary angiography predominantly because of symptoms of heart failure (and at least Canadian Cardiovascular Society angina class I), this clinical setting was not further investigated during the study. We decided to refrain from power calculations; as for diagnostic accuracy studies, it is not well defined. Power calculations are typically done for clinical trials or interventional studies. Probably because of these reasons the, STARD checklist\(^ {44}\) does not require unequivocally power calculations prior to studies. Accordingly, previously published similar studies neither completed the power calculation before the study\(^ {45,46}\) nor did it post-hoc;\(^ {46}\) nevertheless, these cited studies had smaller sample sizes. The absence of significant association between abnormal DSE and lower FFR value in the ACS group might be due to sample size issues; however, we demonstrated the correlations between FFR and DSE in the SA patients with a positive FFR as a first functional test on a moderate coronary stenosis. By contrast, a negative FFR test in the same clinical setting might be sufficient to avoid unnecessary revascularization without further ischemia evaluation even with the < 0.75 cutoff value. These observations are in line with the results of the DEFER trial.\(^ {40}\) The deferral of revascularization by negative FFR (> 0.80) of NCLs is accompanied by a higher rate of MACE than that in the SA population with a similar deferral strategy, as it described previously by other authors,\(^ {41,42}\) whereas in the FFR positive (< 0.80) cases, the revascularization of NCLs did not improve the prognosis.\(^ {43}\) The lack of any correlation between FFR and regional DSE parameters at the non-culprit area in our study might explain the results of these previously cited studies.\(^ {36,37}\) In the ACS group in our study, the lowering of the FFR cutoff value did not improve its diagnostic concordance; moreover, the discriminatory ability decreased close to random. Based on these data, FFR may not be used for the evaluation of moderate NCLs after ACS as a single functional test to plan revascularization. This finding is in line with a recent meta-analysis that demonstrated that using an additional FFR measurement in tailoring the revascularization strategy of NCLs does not improve the prognosis after ACS.\(^ {43}\) By contrast, our results proposed that because of the diameter stenosis improvement of NCLs in patients with an unsellected type of ACS during the time of the staged invasive procedure, careful adjudication is considered to indicate a further revascularization strategy, relying only on the acute angiogram. By contrast, it is well known that accurate determination of diameter stenosis using QCA has limited evidence.

**Table V.** Diagnostic Performance Analysis of FFR with 2 × 2 Contingency Tables with Different Pre-Specified Cutoff Values Compared with DSE in SA and ACS Groups

|              | TP  | FP  | FN  | TN  | Sensitivity % (95% CI) | Specificity % (95% CI) | PPV % (95% CI) | NPV % (95% CI) | Concordance % (95% CI) |
|--------------|-----|-----|-----|-----|------------------------|------------------------|--------------|--------------|------------------------|
| **SA group (n = 109)** |     |     |     |     |                        |                        |              |              |                        |
| FFR < 0.80   | 14  | 24  | 8   | 63  | 70.6 (61.2–79.0)        | 63.6 (26.2–44.7)       | 88.7 (78.5–94.7) | 63.6 (40.7–82.8) | 70.6 (61.8–81.5)       |
| FFR < 0.75   | 7   | 5   | 15  | 82  | 81.7 (73.1–88.4)        | 84.5 (32.9–80.0)       | 93.8 (80.4–88.0) | 31.8 (13.9–54.9) | 84.5 (87.1–98.1)       |
| **ACS group (n = 116)** |     |     |     |     |                        |                        |              |              |                        |
| FFR < 0.85*  | 16  | 52  | 3   | 45  | 52.6 (43.1–61.9)        | 93.8 (19.0–28.7)       | 84.6 (83.9–97.7) | 46.4 (60.4–96.6) | 84.6 (36.2–56.8)       |
| FFR < 0.80   | 10  | 27  | 9   | 70  | 69.0 (59.7–77.2)        | 88.6 (17.9–38.7)       | 93.8 (82.7–92.7) | 52.6 (28.9–75.6) | 93.8 (62.1–80.8)       |
| FFR < 0.75   | 4   | 18  | 15  | 79  | 71.6 (62.4–79.5)        | 84.0 (7.8–36.9)        | 93.8 (80.4–87.1) | 21.1 (6.1–45.6) | 93.8 (72.3–88.6)       |

ACS indicates acute coronary syndrome; CI, confidence interval; DSE, dobutamine stress echocardiography; FFR, fractional flow reserve; FN, false negative; FP, false positive; NPV, negative predictive value; PPV, positive predictive value; SA, stable angina; TN, true negative; and TP, true positive. *Calculated as the optimal cutoff value.
group as a reproduction of earlier studies,\textsuperscript{11} whose results have also validated our methodology for the ACS group. Resting 1D/1Pa ratios and CFR results are not available. We do not have exact information about how many patients actually stopped their beta-blocker medication before DSE procedures; however, the majority of our patients achieved the target heart rate as we described it above. A contrast agent was used only in cases with inadequate image quality during DSE. The territories delineated on DSE do not consistently correlate with coronary artery distributions; however, some studies have demonstrated that DSE had an additive prognostic value on hard cardiovascular endpoints, even when anterior/non-anterior territory distributions were investigated.\textsuperscript{20}

Conclusions

In SA patients with borderline SCL(s), an FFR with a cutoff value of ≥ 0.75 could be useful as a single functional test to defer revascularization; however, in cases of abnormal FFR, an additional DSE might be required to tailor a further treatment plan. In ACS patients, an FFR test may have a different role in the evaluation of concomitant moderate NCL(s), and it is probably not accurate enough in ischemia assessment to plan the revascularization, as a single functional test. Further studies with a clinical follow-up are required in both clinical scenarios to find the optimal treatment strategy to improve prognosis.

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Disclosure

Conflicts of interest: None.

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