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Fractional flow reserve and frequency of PCI in patients with coronary artery disease

Percutaneous coronary intervention (PCI) is currently the standard of care for flow-limiting coronary lesions associated with myocardial ischemia [1–3]. However, estimation of the hemodynamic relevance in intermediate coronary lesions (50–70% diameter stenosis) is a daily clinical challenge. Fractional flow reserve (FFR) was established as a diagnostic tool to assess the functional relevance of intermediate coronary stenosis, and FFR-guided PCI is associated with a lower events rate and incidence of urgent revascularization [2, 4–8]. However, recent studies have shown that there is an anatomic–functional mismatch in up to two thirds of cases of "intermediate" coronary stenosis estimated by angiography that may lead to incorrect treatment decisions [5]. In addition, FFR-guided PCI has only been validated in patients with stable coronary artery disease and has not yet been verified for specific conditions such as heart failure or microvascular dysfunction [5–8]. Thus, an increased left ventricular end-diastolic pressure that influences coronary flow may have an impact on the FFR assessment, which uses a guidewire to measure blood pressure within a coronary artery [9]. Moreover, diabetes mellitus, which is associated with microvascular dysfunction and impaired vasodilatory capacity, results in increased microvascular resistance that also may influence the FFR assessment. These aspects have not been considered in the assessment and validation of FFR in previous trials [10].

Therefore, the aim of the present study was to examine the influence of specific patient comorbidities on FFR values and the frequency of PCI in patients with intermediate coronary artery stenosis.

Methods

Patients and treatment

A total of 652 patients with coronary artery disease for whom FFR was conducted between January 2014 and December 2017 and who had intermediate coronary diameter stenosis (50–70%) assessed by angiography were included in this retrospective study. All patients who were included in the present study underwent FFR assessment. Clinical history, physical examination, and laboratory test results were assessed for all patients. Physical examination and echocardiography were performed within the routine clinical work-up. In the present study, specific cardiovascular comorbidities were treated according to the current guidelines of the European Society of Cardiology (ESC) at a maximal tolerated dose with consideration of contraindications [11–16].

Assessment of FFR was carried out using the FFR-System OPTIS Integrated System, Abbott Inc. (San Francisco, CA, USA) and was performed according to standard clinical practice at maximal hyperemia induced by intravenous adenosine following a standardized, body weight-adapted protocol (140–160 µg/kg/min). Fractional flow reserve-guided PCI was performed in lesions only if the FFR was considered pathological under maximal hyperemia (FFR < 0.80). Influencing factors were defined as acute coronary syndrome

Abbreviations

ACS	Acute coronary syndrome
AF	Atrial fibrillation
ESC	European Society of Cardiology
FFR	Fractional flow reserve
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
LAD	Left anterior descending coronary artery
LCX	Left circumflex coronary artery
LV	Left ventricle
LVH	Left ventricular hypertrophy
NSTE-ACS	Non-ST-elevated acute coronary syndrome
PCI	Percutaneous coronary intervention
RCA	Right coronary artery

Table 1 Patients characteristics

Patients, *n*	652
Lesions, measured FFR, *n*	808
Age, (year), mean (±SD)	67 (±10)
Gender (male), *n* (%)	493 (75.6%)
Previous MI, *n* (%)	216 (33.1%)
Previous PCI, *n* (%)	356 (54.6%)
Arterial hypertension, *n* (%)	563 (86.3%)
Diabetes, *n* (%)	220 (33.7%)
Hyperlipoproteinemia, *n* (%)	531 (65.9%)
Smoking, *n* (%)	270 (41.4)
Family disposition, *n* (%)	137 (21.0%)
CKD (GFR ≤45 ml/min/1.73m^2), *n* (%)	149 (18.5%)
Electrical device, *n* (%)	117 (17.9%)
Atrial fibrillation, *n* (%)	134 (20.5%)

CKD chronic kidney disease, *FFR* fractional flow reserve, *GFR* glomerular filtration rate, *MI* myocardial infarction, PCI percutaneous coronary intervention, *SD* standard deviation

Table 2 Procedural characteristics

Complications (dissection), *n* (%)	1 (0.12%)
Radial access, *n* (%)	463 (71%)
Target vessel, *n* (%)	808 (100%)
LAD, *n* (%)	418 (51.7%)
LCX, *n* (%)	212 (26.2%)
RCA, *n* (%)	178 (22.1%)

LAD left anterior descending artery, *LCX* left circumflex artery, *RCA* right coronary artery

Table 3 Procedural characteristics

Stenosis grade, *n* (%)	
50%	254 (31.4%)
60%	288 (35.6%)
70%	266 (32.9%)

LAD left anterior descending artery, *LCX* left circumflex artery, *RCA* right coronary artery

Table 4 Patients comorbidities

CCS, *n* (%)	I	64 (9.8%)
	II	327 (50.1%)
	III	226 (34.6%)
	IV	35 (5.4%)
Specific patients comorbidities		
HFrEF [LVEF <30%], *n* (%)		77 (11.8%)
HFpEF, *n* (%)		397 (60.9%)
LVH [septum thickness >12 mm]		311 (47.7%)
ACS, *n (%)*		267 (40.9%)
NSTE-ACS, *n* (%)		263 (40.3%)
STEMI[a], *n* (%)		4 (0.6%)

[a]Nonculprit lesion

ACS acute coronary syndrome, *CCS* Canadian Cardiovascular Society, *HFpEF* heart failure with preserved ejection fraction, *HFrEF* heart failure with reduced ejection fraction *LVH* left ventricular hypertrophy, *NSTE-ACS* non-ST-elevated acute coronary syndrome, *STEMI* ST-elevation myocardial infarction

(ACS), heart failure with reduced ejection fraction (HFrEF: LVEF ≤ 30%), heart failure with preserved ejection fraction, diabetes mellitus, chronic kidney disease defined as a glomerular filtration rate (GFR) <45 ml/min^{-1}, atrial fibrillation (AF), and left ventricular hypertrophy (LVH). Acute coronary syndrome was diagnosed and treated according to the current guidelines of the ESC [13]. Accordingly, patients with ST-elevation infarction were referred directly to the catheter laboratory for invasive diagnostics and treatment [11]. In addition, patients with non-ST-elevated acute coronary syndrome (NSTE-ACS) were diagnosed on the basis of clinical conditions, echocardiographic criteria, and laboratory results considering cardiac biomarkers (troponin-I, creatine kinase, creatine kinase-MB; [14]). Patients at high risk were referred for invasive coronary angiography within 24 h. Patients at intermediate risk were referred for invasive diagnostics within 72 h [14]. Patients with cardiogenic shock, life-threatening ventricular arrhythmias, or hemodynamic instability were not included in the present study. Heart failure with preserved ejection fraction (HFpEF) was defined by the presence of elevated BNP plasma values and echocardiographic criteria related to diastolic dysfunction (E/e′ > 13) [13]. Left ventricular hypertrophy was defined by echocardiography on the basis of a thickness of the posterior wall and septum >12 mm in diastole [16].

Exclusion criteria were defined as left main stenosis (diameter stenosis >50%), serial stenosis within the target vessel, and bypass graft on the target vessel. All clinical parameters and FFR values were assessed retrospectively for all patients with intermediate coronary stenosis between January 2014 and December 2017. Approval for the study was obtained from the institutional review board of the University of Giessen (99/13). The investigation conforms to the principles outlined in the Declaration of Helsinki.

Statistical analysis

All data for continuous variables are expressed as mean ± SD or as median and interquartile range, as appropriate. Categorical variables are reported as number and percentage. After testing for normal distribution, values were compared using the unpaired Student's *t* test or Mann–Whitney test, as appropriate. Fisher's exact test or a chi-squared test was used for categorical variables with nominal scales. Intergroup comparisons were made using the Mann–Whitney test. Multivariate stepwise logistic regression analysis was applied to identify indepen-

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Fractional flow reserve and frequency of PCI in patients with coronary artery disease

Abstract

Background. Fractional flow reserve (FFR) guided percutaneous coronary intervention (PCI) has been validated in patients with stable coronary artery disease (CAD) but has not yet been verified under specific conditions such as heart failure or microvascular dysfunction. The aim of the present study was to examine the influence of specific patient comorbidities on FFR values and thus the frequency of PCI in patients with intermediate coronary stenosis.
Methods. A total of 652 patients with CAD and intermediate coronary stenosis who were assessed for FFR were included in this retrospective study. In a subgroup analysis, specific comorbidities such as heart failure with non-ST-segment-elevated acute coronary syndrome (NSTE-ACS), heart failure, diabetes mellitus, atrial fibrillation (AF), and left ventricular hypertrophy (LVH) were considered.
Results. In all lesions with an FFR ≤ 0.80 (n = 227/808, 28.1%), PCI was performed using drug-eluting stents. Pathological FFR values (FFR ≤ 0.80) before PCI were most frequently observed in the left anterior descending artery (LAD; n = 168/418, 39.9%) followed by the right coronary artery (RCA; n = 37/178, 20.7%) and the left circumflex artery (LCX; 22/223, 9.8%). The comorbidities NSTE-ACS (p = 0.28), heart failure with reduced ejection fraction (HFrEF; p = 0.63), heart failure with preserved ejection fraction (HFpEF; p = 0.3719), diabetes mellitus (p = 0.177), or LVH (p = 0.407) had no major impact on the occurrence of pathological FFR values; there was also no association between FFR and the occurrence of lesions in the different target vessels.
Conclusion. The occurrence of pathological FFR values, most frequently documented in the LAD, was the same in patients with or without HFrEF, HFpEF, diabetes mellitus, AF, and LVH, demonstrating that these comorbidities did not influence FFR values and, thus, the indication for PCI.

Keywords

Coronary artery stenosis · Left ventricular hypertrophy · Microvascular disease · Percutaneous coronary intervention · Heart failure

Fraktionelle Flussreserve und PCI-Häufigkeit bei Patienten mit koronarer Herzkrankheit

Zusammenfassung

Hintergrund. Die mittels der fraktionellen Flussreserve (FFR) gesteuerte perkutane Koronarintervention (PCI) ist für Patienten mit stabiler koronarer Herzkrankheit (KHK) validiert, jedoch nicht unter speziellen Bedingungen wie Herzinsuffizienz oder mikrovaskuläre Dysfunktion bestätigt worden. Ziel der vorliegenden Studie war es, den Einfluss spezifischer Komorbiditäten auf die FFR-Werte und somit die PCI-Häufigkeit bei Patienten mit mittelgradiger Koronarstenose zu untersuchen.
Methoden. Insgesamt wurden 652 Patienten mit KHK und mittelgradiger Koronarstenose, bei denen die FFR ermittelt wurde, in diese retrospektive Studie aufgenommen. In einer Subgruppenanalyse wurden spezifische Komorbiditäten wie Herzinsuffizienz mit akutem Koronarsyndrom ohne ST-Strecken-Hebung (NSTE-ACS), Herzinsuffizienz, Diabetes mellitus, Vorhofflimmern (VF) und linksventrikuläre Hypertrophie (LVH) berücksichtigt.
Ergebnisse. Bei sämtlichen Läsionen mit einer FFR ≤ 0,80 (n = 227/808; 28,1 %) wurde die PCI unter Verwendung von medikamentenfreisetzenden Stents durchgeführt. Pathologische FFR-Werte (FFR ≤ 0,80) vor PCI wurden am häufigsten im Ramus interventricularis anterior (RIVA) beobachtet (n = 168/418; 39,9 %), an zweiter Stelle kam die rechte Koronararterie (RCA; n = 37/178; 20,7 %) und dann der Ramus circumflexus der linken Koronararterie (LCX; 22/223, 9,8 %). Die Komorbiditäten NSTE-ACS (p = 0,28), Herzinsuffizienz mit reduzierter Ejektionsfraktion (HFrEF; p = 0,63), Herzinsuffizienz mit erhaltener Ejektionsfraktion (HFpEF; p = 0,3719), Diabetes mellitus (p = 0,177) oder LVH (p = 0,407) hatten keinen wesentlichen Einfluss auf das Auftreten pathologischer FFR-Werte; auch bestand kein Zusammenhang zwischen FFR und dem Auftreten von Läsionen in den verschiedenen Zielgefäßen.
Schlussfolgerung. Pathologische FFR-Werte, die am häufigsten im RIVA dokumentiert wurden, kamen gleichermaßen bei Patienten mit oder ohne HFrEF, HFpEF, Diabetes mellitus, VF und LVH vor, was zeigt, dass diese Komorbiditäten keinen Einfluss auf die FFR-Werte und somit die Indikation zur PCI hatten.

Schlüsselwörter

Koronararterienstenose · Linksventrikuläre Hypertrophie · Mikrovaskuläre Erkrankung · Perkutane Koronarintervention · Herzinsuffizienz

dent factors at a level of $p < 0.05$. Adjusted odds ratios with 95% confidence intervals were used to quantify the independent factors. For all statistical analyses, the statistical software SPSS 24.0 (Statistical Package for the Social Sciences, Chicago, IL, USA) for Windows was used.

Results

A total of 652 patients (493 men [75.6%], mean age 67 ± 10 years) were included in the present study. Patient baseline characteristics are shown in **Table 1**. Invasive diagnostics and PCI were performed using the radial access in 463 patients (71%). In this study, a total of 808 lesions (left anterior descending artery [LAD]: 418 [51.7%], left circumflex artery [LCX]: 212 [26.2%], and right coronary artery [RCA]: 178 [22.1%]) with coronary diameter stenosis of 50–70% were assessed by FFR (**Table 2 and 3**). In one patient, a coronary dissection occurred that was caused by the FFR wire.

A subset of patients was classified as having HFrEF (n = 77 [11.8%]) or HFpEF (n = 397 [60.9%]) according to the left ventricular ejection fraction and diastolic function assessed by echocardio-

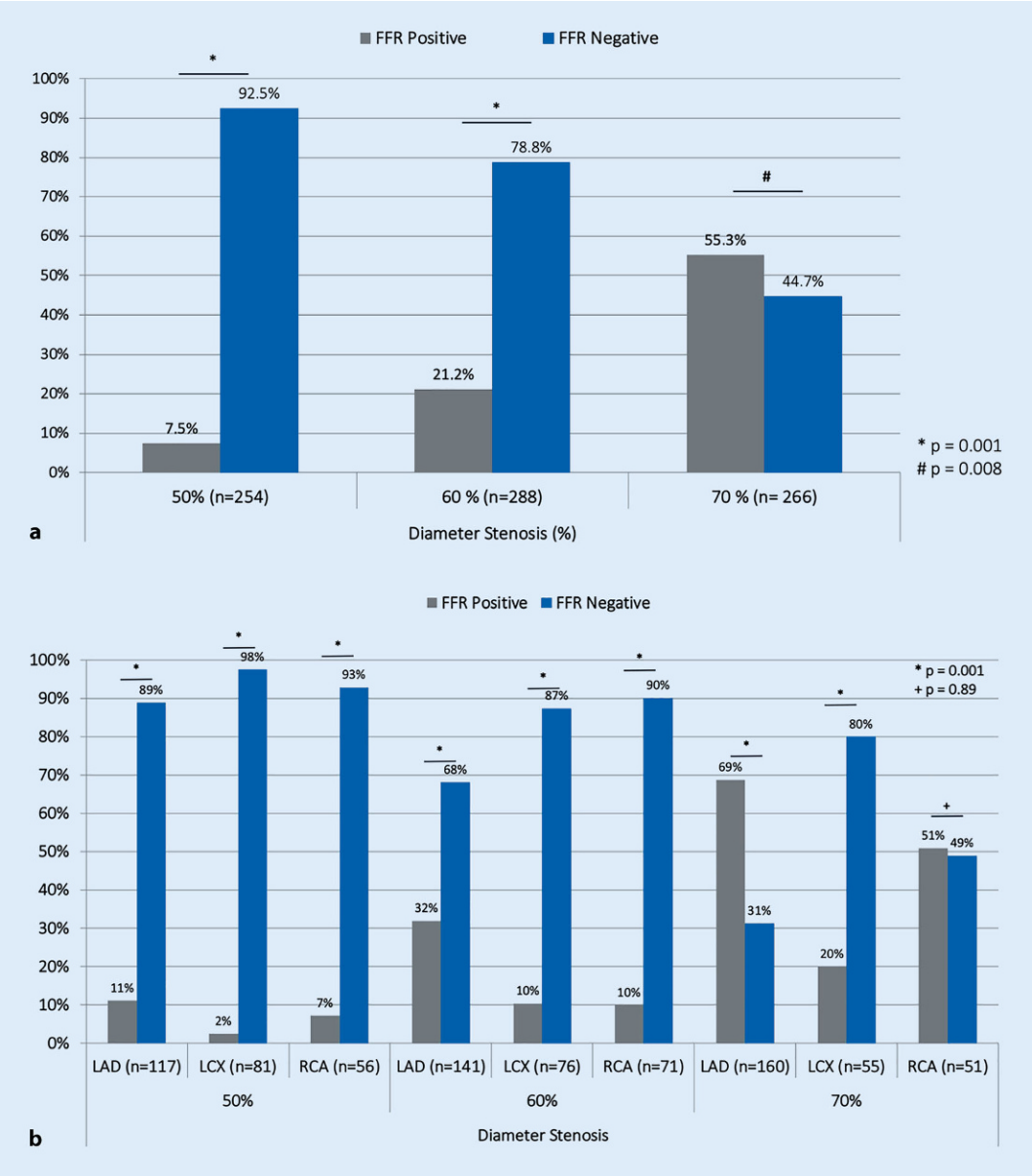

Fig. 1 ◀ Pathological fractional flow reserve (*FFR*) results in 50%, 60%, and 70% diameter stenosis. Pathological values for FFR (≤0.80) were most frequent in the left anterior descending artery (*LAD*; $n = 93/235$; 39.6%) followed by the right coronary artery (*RCA*; $n = 27/90$; 30%), and the left circumflex artery (*LCX*; $n = 12/103$; 11.7%)

graphy (**Table 4**). Left ventricular hypertrophy was diagnosed in 311 (47.7%) patients, and ACS was determined in 267 (40.9%; NSTE-ACS: 263 [30.3%], STEMI: 4 [0.6%]) (**Table 4**).

Pathological values for FFR (≤0.80) obtained immediately before PCI were most frequently observed in the LAD ($n = 168/418$; 40.2%) followed by the RCA ($n = 37/178$; 20.8%) and the LCX ($n = 22/212$; 10.4%). In lesions with 50% diameter stenosis the FFR was pathological in 7.5% of cases (19/254); for 60% diameter stenosis, the FFR was pathological in 21.2% of cases (61/288); and for 70% diameter stenosis, the FFR was pathological in 55.3% of cases (147/266; **Fig. 1**).

The results from the subgroup analysis showed that the presence of comorbidities including NSTE-ACS (26.1% vs. 29.5% in the entire cohort; $p = 0.29$), HFrEF (26.0% vs. 28.4%, $p = 0.90$), HFpEF (27.2% vs. 30.3%; $p = 0.75$), diabetes mellitus (24.8% vs. 29.9%; $p = 0.18$), chronic kidney disease (26.8% vs. 28.5%; $p = 0.14$), AF (25% vs. 29%; $p = 0.19$), and LVH (33.4% vs. 25.4%; $p = 0.35$) was not associated with the occurrence of pathological FFR values (**Fig. 2a–c**).

Discussion

In the present study the measurement of FFR was confirmed to be a safe and feasible method of evaluating coronary artery stenosis in routine clinical practice. Pathological values for FFR were most often observed in the LAD, followed by the RCA and LCX. Furthermore, the FFR values obtained before PCI were not influenced by the presence of comorbidities such as heart failure, diabetes mellitus, and LVH, which confirms the validity of the method in a broad spectrum of patients with cardiovascular disease.

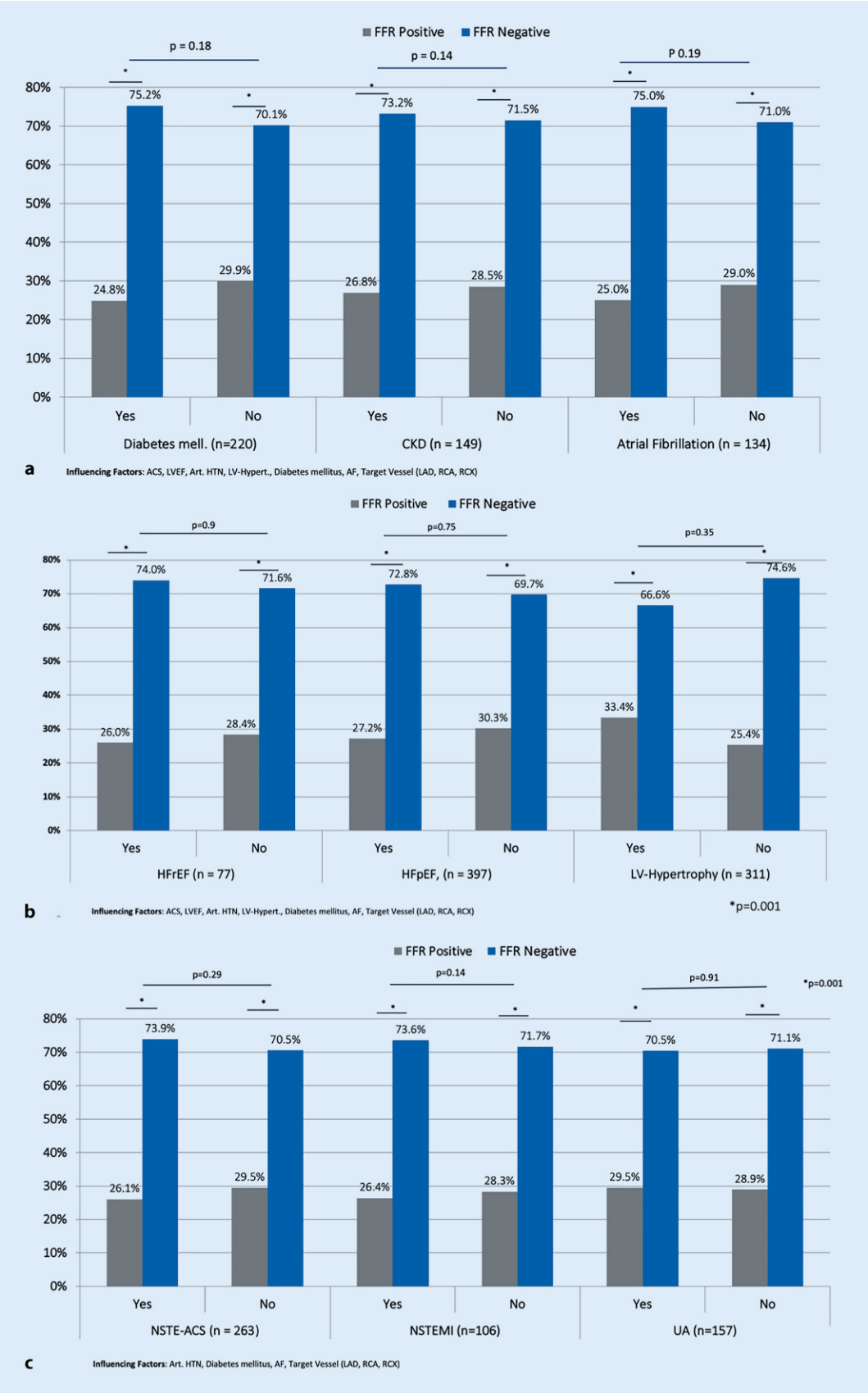

Fig. 2 ◄ Results from the subgroup analysis showed that the presence of comorbidities, including **a** diabetes mellitus, chronic kidney disease (*CKD*), and atrial fibrillation, **b** systolic and diastolic heart failure and left ventricular (*LV*) hypertrophy, and **c** acute coronary syndrome (*ACS*), was not associated with the occurrence of pathological fractional flow reserve (*FFR*) values. *HFpEF* heart failure with preserved ejection fraction, *HFrEF* heart failure with reduced ejection fraction, *NSTEMI* non-ST-elevation myocardial infarction, *UA* unstable angina

Coronary pressure-derived FFR is the current standard of care for the functional assessment of lesion severity for patients with intermediate-grade stenosis (50–70% stenosis) without evidence of ischemia in noninvasive testing or for those with multivessel disease [4, 6–8, 10]. Interestingly, the hemodynamic relevance, as defined by FFR ≤ 0.80, correlates poorly with diameter stenosis by visual estimation [5, 6]. Thus, in the FAME Study (Fractional Flow Reserve versus Angiography for Multivessel Evaluation), in only 35% of the cases of 50–70% diameter stenosis was the stenosis hemodynamically relevant, and in 20% of the cases of 71–90% stenosis the FFR finding was negative [8]. These results are consistent with our findings in the present study. Valid estimation of intermediate coronary stenosis is an advantage in routine clinical practice, and, importantly, a potential misjudgment is of prognostic relevance.

Assessment of FFR is applied routinely irrespective of specific patient characteristics such as systolic or diastolic heart failure, diabetes mellitus-related microvascular disease, AF, or ACS; however, FFR has not been validated under all of these conditions since such patients were excluded in previous randomized controlled trials [4, 8, 17, 18]. In the present study, pathological FFR values were most frequently documented in the LAD followed by the RCA and the LCX. This observation might be partly explained by factors such as the mass of the myocardial territory that is supplied by the epicardial coronary vessel and the amount of collateral blood flow. Importantly, this order of FFR values was also confirmed for all degrees of diameter stenosis in the present study.

Considering a possible impact of myocardial mass and microvascular circulation on FFR values, patient comorbidities such as diabetes mellitus, LVH, and heart failure may influence FFR; however, such potential confounders were not considered in previous trials [4, 5, 8, 9, 17, 18]. The validity of FFR measurements is associated with the vasodilatory capacity of the coronary system, and thus the presence of microvascular dysfunction may affect the required maximal hyperemia. In particular, patients with diabetes mellitus are characterized by microvascular dysfunction and impaired vasodilatory capacity with increased microvascular resistance [10]. Therefore, diabetic patients may display an abnormal response to coronary vasodilators used in FFR assessment, and FFR interpretation is still controversial in this specific cohort [10, 19–21]. In the present study, there were no differences between patients with and without type two diabetes mellitus in the frequency of pathological FFR values among patients with intermediate coronary stenosis. Thus, our findings suggest that FFR measurement conducted under maximal hyperemia is a valid method for assessing coronary hemodynamic properties in patients with diabetes mellitus. The presence of LVH in a subgroup of patients likewise did not influence the frequency of pathological FFR values, suggesting that LVH also has a negligible impact on FFR assessment. Nevertheless, the results of the present study have to be validated in a larger trial of FFR measurements that takes the aspect of microvascular dysfunction into account.

In heart failure patients, the increased left ventricular end-diastolic pressure influences the coronary blood flow and may thus impact FFR assessment [9]. In previous randomized controlled trials, patients with reduced left ventricular function were excluded, and therefore FFR assessment was also not validated in these patients [4, 5, 8–10]. However, in the present study, FFR values obtained in patients with intermediate coronary stenosis under maximal hyperemia were not more frequently pathological in patients with systolic (HFrEF) or diastolic (HFpEF) heart failure compared with patients having a normal systolic or diastolic left ventricular function. Therefore, the results of the present study confirm the validity of FFR assessment in heart failure patients.

Acute coronary syndrome, with extended catecholamine secretion and ischemic injury, is associated with microvascular dysfunction that may influence FFR assessment [22–24]. Current evidence, however, suggests that FFR assessment is also valid in patients with NSTE-ACS, and it is used under this specific condition in routine clinical practice [22–24]. The evidence from previous trials was supported by results from the present study [22–24]. Thus, there were no differences in the frequency of pathological FFR values between patients with NSTE-ACS and those with stable coronary artery disease. Further larger-scale studies will be necessary to confirm the results of the present study in patients with ACS.

Limitations

The results of the present study were based on a retrospective analysis and are therefore exploratory in nature. This must be considered as a major limitation of the present study. No additional invasive measurements of vasodilatory capacity with increased microvascular resistance were made in addition to FFR analysis in patients with diabetes mellitus. Further prospective studies are required to confirm the results of the present study.

Conclusion

The present study demonstrates that fractional flow reserve (FFR) measurement is a valid and reliable method of evaluating coronary artery stenosis in routine clinical practice. Pathological FFR values were most frequently documented in the left anterior descending artery followed by the right coronary artery and the left circumflex artery. The results also indicate that the presence of heart failure with reduced ejection fraction, heart failure with preserved ejection fraction, diabetes mellitus, atrial fibrillation, and left ventricular hypertrophy does not influence FFR values; thus, measurement of FFR is valid in assessing the indication for percutaneous coronary intervention in patients with these comorbidities.

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Compliance with ethical guidelines

Conflict of interest O. Dörr, C. Liebetrau, M. Weferling, F. Hoffmann, N. Forderer, T. Keller, N. Boeder, F. Blachutzik, S. Keranov, P. Bauer, T. Bauer, C.W. Hamm, and H. Nef declare that they have no competing interests.

For this article no studies with human participants or animals were performed by any of the authors. All studies performed were in accordance with the ethical standards indicated in each case.

References

1. Adjedj J, Toth GG, Johnson NP, Pellicano M, Ferrara A, Flore V et al (2015) Intracoronary adenosine: dose-response relationship with Hyperemia. JACC Cardiovasc Interv 8:1422–1430
2. De Bruyne B, Baudhuin T, Melin JA, Pijls NH, Sys SU, Bol A et al (1994) Coronary flow reserve calculated from pressure measurements in humans. Validation with positron emission tomography. Circulation 89:1013–1022
3. Park SJ, Kang SJ, Ahn JM, Shim EB, Kim YT, Yun SC et al (2012) Visual-functional mismatch between coronary angiography and fractional flow reserve. JACC Cardiovasc Interv 5:1029–1036
4. Fearon WF, Nishi T, De Bruyne B, Boothroyd DB, Barbato E, Tonino P et al (2018) Clinical outcomes and cost-effectiveness of fractional flow reserve-guided Percutaneous coronary intervention in patients with stable coronary artery disease: three-year follow-up of the FAME 2 trial (fractional flow reserve versus Angiography for Multivessel evaluation). Circulation 137:480–487
5. Jeremias A, Kirtane AJ, Stone GW (2017) A test in context: fractional flow reserve: accuracy, prognostic implications, and limitations. J Am Coll Cardiol 69:2748–2758
6. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U et al (2019) ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 40(2):87–165. https://doi.org/10.1093/eurheartj/ehy394
7. Pijls NH, van Schaardenburgh P, Manoharan G, Boersma E, Bech JW, van't Veer M et al (2007) Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. J Am Coll Cardiol 49:2105–2111
8. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M et al (2009) Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 360:213–224
9. Leonardi RA, Townsend JC, Patel CA, Wolf BJ, Todoran TM, Fernandes VL et al (2013) Left ventricular end-diastolic pressure affects measurement of fractional flow reserve. Cardiovasc Revasc Med 14:218–222
10. Reith S, Battermann S, Hellmich M, Marx N, Burgmaier M (2014) Impact of type 2 diabetes mellitus and glucose control on fractional flow reserve measurements in intermediate grade coronary lesions. Clin Res Cardiol 103:191–201
11. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H et al (2018) 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 39:119–177
12. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U et al (2018) ESC/EACTS Guidelines on myocardial revascularization. EuroIntervention 14:1435–1534
13. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ et al (2016) ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European society of cardiology (ESC). Developed with the special contribution of the heart failure association (HFA) of the ESC. Eur J Heart Fail 18:891–975
14. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F et al (2016) 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European society of cardiology (ESC). Eur Heart J 37:267–315
15. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A et al (2013) ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 34:2949–3003
16. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M et al (2018) ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 39(33):3021–3104
17. Bech GJ, De Bruyne B, Pijls NH, de Muinck ED, Hoorntje JC, Escaned J et al (2001) Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: a randomized trial. Circulation 103:2928–2934
18. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z et al (2012) Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med 367:991–1001
19. Dominguez-Franco AJ, Jimenez-Navarro MF, Munoz-Garcia AJ, Alonso-Briales JH, Hernandez-Garcia JM, de Teresa Galvan E (2008) Long-term prognosis in diabetic patients in whom revascularization is deferred following fractional flow reserve assessment. Rev Esp Cardiol 61:352–359
20. Sahinarslan A, Kocaman SA, Olgun H, Kunak T, Kiziltunc E, Ozdemir M et al (2009) The reliability of fractional flow reserve measurement in patients with diabetes mellitus. Coron Artery Dis 20:317–321
21. Yanagisawa H, Chikamori T, Tanaka N, Usui Y, Takazawa K, Yamashina A (2004) Application of pressure-derived myocardial fractional flow reserve in assessing the functional severity of coronary artery stenosis in patients with diabetes mellitus. Circ J 68:993–998
22. Layland J, Rauhalammi S, Watkins S, Ahmed N, McClure J, Lee MM et al (2015) Assessment of fractional flow reserve in patients with recent non-ST-segment-elevation myocardial infarction: comparative study with 3-T stress perfusion cardiac magnetic resonance imaging. Circ Cardiovasc Interv 8:e2207
23. Ntalianis A, Sels JW, Davidavicius G, Tanaka N, Muller O, Trana C et al (2010) Fractional flow reserve for the assessment of nonculprit coronary artery stenoses in patients with acute myocardial infarction. JACC Cardiovasc Interv 3:1274–1281
24. Sels JW, Tonino PA, Siebert U, Fearon WF, Van't Veer M, De Bruyne B et al (2011) Fractional flow reserve in unstable angina and non-ST-segment elevation myocardial infarction experience from the FAME (Fractional flow reserve versus Angiography for Multivessel Evaluation) study. JACC Cardiovasc Interv 4:1183–1189