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Prevalence of coronary microcirculatory dysfunction in patients with chronic coronary syndromes and moderate coronary stenosis

Short title: Coronary microcirculatory dysfunction in chronic coronary syndromes

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WHAT'S NEW?

Currently available data on coronary microcirculatory dysfunction (CMD) prevalence is based mainly on non-invasive testing, whereas data on its prevalence according to current European Society of Cardiology guidelines, regarding thermodilution-based coronary flow reserve and index of microcirculatory resistance methods is scarce. Overall prevalence of CMD in patients with moderate coronary stenoses was high and confirmed in 45% of cases. The presence of CMD in 34% of patients qualified for revascularization may influence persistent angina after revascularization.

ABSTRACT

Background: Coronary microcirculatory dysfunction (CMD) is an emerging topic in the contemporary treatment of patients with chronic coronary syndromes (CCS), with influence both on diagnosis and patient outcome. Data on CMD prevalence according to current guidelines is scarce.

Aims: We aimed to assess prevalence of CMD in patients with CCS and moderate lesions in coronary angiography using thermodilution method.

Methods: The study was a prospective registry including patients undergoing coronary angiography for CCS who was diagnosed with moderate coronary stenosis. Patients with significant epicardial stenosis were excluded. All patients underwent fractional flow reserve, coronary flow reserve and index of microcirculatory resistance (IMR) assessment.

Results: We enrolled a total of 101 patients. CMD was diagnosed in 45% of cases, with a particular difference between groups without any significant lesions and with at least one vessel causing significant ischemia (55% vs. 24%; $P = 0.03$). In the CMD group, there were lower coronary flow reserve and higher IMR median values compared with no CMD group (1.6 vs. 2.6; $P < 0.001$ and 29 vs. 15; $P < 0.001$ respectively). In logistic regression models, higher resting full-cycle ratio values ($P = 0.006$) and the presence of diastolic dysfunction ($P = 0.03$) were independent predictors of CMD presence.

Conclusions: In patients with CCS and moderate coronary stenosis CMD is highly prevalent, independent of the level of diameter stenosis. The presence of CMD in 34% of patients qualified for revascularization may influence persistent angina after revascularization. As there are no specific predictors of CMD, more common functional testing in these patients should be advised.

Key words: chronic coronary syndromes, coronary flow reserve, coronary microcirculatory dysfunction, fractional flow reserve, index of microcirculatory resistance

INTRODUCTION

Coronary microcirculatory dysfunction (CMD) is an emerging topic in the contemporary treatment of patients with chronic coronary syndromes (CCS). Up to 39% of patients undergoing coronary angiography (CAG) reveal no significant coronary lesions [1]. Current European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of CCS from 2024 emphasize the role of coronary functional testing in this particular group of patients [2]. The presence of CMD is a known risk factor for a worse prognosis, as well as a risk factor for a discrepancy between different functional coronary indices [2–7].

Ongoing investigations focus either on coronary dysfunction in patients without any significant coronary lesions (INOCA, ANOCA) or in a setting of acute coronary syndromes without stenosis (MINOCA), nevertheless, data on the prevalence of CMD in the population of CCS patients with moderate coronary lesions are scarce. Regardless of the 2019 ESC guidelines definition and the use of invasive coronary flow reserve (CFR) assessment with concomitant coronary resistance assessment, most available data were obtained either from non-invasive CFR assessment or Doppler-based studies inside coronary arteries [2].

MATERIAL AND METHODS

To assess the prevalence of CMD in patients with CCS and moderate lesions in CAG using a thermodilution-based method.

The study was a prospective observational registry of patients undergoing CAG for CCS, based on symptoms and non-invasive testing for ischemia between 2015 and 2017. Inclusion criteria were age over 18 years, and a presence of any 40%–90% diameter stenosis in main coronary arteries, suitable for functional fractional flow reserve (FFR) assessment. The main exclusion criteria w an acute coronary syndrome as an indication for CAG, any coronary lesions with >90% diameter stenosis (or >50% diameter stenosis in left main), and active neoplastic or inflammatory condition. Basic laboratory tests were performed in all patients before CAG, as well as echocardiography with left ventricular ejection fraction and geometry assessment. Diastolic dysfunction assessment was performed according to the guideline [8]. Coronary angiography was recorded after a bolus injection of 200 µg of nitroglycerin i.c. Quantitative coronary angiography (QCA) was performed by an independent core lab analyst blinded to the results of FFR/resting full-cycle ratio (RFR). Using the guide catheter for calibration and an edge detection system (CAAS 5.7 QCA system, PieMedical, Maastricht, The Netherlands), the reference vessel diameter and minimum lumen diameter were measured, and the percent diameter stenosis (% DS) was calculated. All study procedures were approved by Jagiellonian University Bioethics Committee (approval number 122.6120.262.2015 with further extensions).

Coronary physiology assessment

In all coronary arteries both resting (P_d/P_a, RFR) and hyperemic FFR indices were assessed using a pressure wire (PressureWire X, Abbott, US) placed in the distal part of a tested vessel. Hyperemia was induced by intravenous continuous iv infusion of 140 µg/kg/min of adenosine [9–11]. Guiding catheter wedging was prevented and pressure drift was checked after each

measurement. Calculations of RFR, defined as the lowest filtered P_d/P_a value, were performed using CoroFlow ver 3.0 software (Abbott, US) [12]. Values of FFR ≤0.80 and RFR ≤0.89 were assumed hemodynamically significant.

Coronary microcirculatory assessment and definitions

Thermodilution-derived CFR was calculated as a mean transit time ratio of repeated intracoronary injections of 3–5 ml of saline solution, measured both in resting condition and during full stable hyperemia [13, 14]. Index of microcirculatory resistance (IMR) values were calculated using hyperemic mean transit time and P_d on hyperemia, Yong formula was used for correction of the epicardial stenosis effect [15–17]. Additionally, baseline resistive index (BRI) and resistive reserve ratio (RRR) were calculated according to published methodology, to reflect the reactivity of coronary microcirculation [18].

The patient was diagnosed with CMD implementing chronic coronary syndrome 2024 ESC guideline definition, when either IMR ≥25 units in any vessel or CFR <2.0 in a vessel with no significant lesion, i.e. FFR >0.80, was measured [2].

Statistical analysis

Continuous data were presented as a mean with a standard deviation or as a median with an interquartile range according to the normality of distribution, checked with the Shapiro–Wilk test. Continuous variables were compared using the t-Student test or the U-Mann–Whitney test for non-normally distributed data. Quantitative data were compared using the χ^2 test. Correlation were calculated using Spearman Rho or Pearson correlation coefficient according to normality of distribution. Univariate and step-wise logistic regression analysis was performed to find predictors of coronary microcirculatory dysfunction, Akaike information criterion was used for model selection. Model performance was assessed using c-statistic. Further sensitivity analysis using mixed-effect logistic regression models, with vessel tested as a random effect, was implemented [19]. All calculations were performed using R ver. 4.0.3 (R-core team, Vienna) statistical language with easystats ecosystem packages, a *P*-value <0.05 was considered significant in all analyses [20].

RESULTS

Patients' characteristic

The study included 101 patients, 25.7% female, with a mean age of 66.2 years. Most patients were treated for arterial hypertension and dyslipidemia, 41.6% had a history of diabetes and

over 44% were current or prior smokers. Detailed characteristics of the patients included are presented in Table 1.

Prevalence of CMD

CMD was diagnosed in 45% of patients overall, with a difference between groups without any significant lesions and with at least one vessel causing significant ischemia (55 vs. 24%,;*P* = 0.03). Results were illustrated in Figure 1.

Per patient analysis — clinical and echocardiographic factors

All patients were similar in terms of demography, prior medical history of coronary intervention, fasting glucose, and low-density lipoprotein (LDL) cholesterol levels. On the contrary, higher diastolic pressure and lower pulse pressure were recorded in the CMD group compared to patients without CMD (*P* = 0.039 and *P* = 0.029, respectively). Table 1 presents detailed clinical and laboratory characteristics of patients.

Both groups were also similar in terms of left ventricular ejection fraction (LVEF), chamber diameters, or right ventricle systolic pressure (RVSP), however, left ventricular hypertrophy was more common in the CMD group (55% vs. 24% in no CMD group; *P* = 0.012), with a different pattern of left ventricular geometry. The detailed echocardiographic analysis is presented in Table 2.

Per vessel analysis — angiographic and functional factors

Angiographic analysis

The analysis included 157 vessels. The median % diameter stenosis (% DS) was 45%, predominantly the left anterior descending artery was tested. Gensini score was similar in both, CMD and no-CMD groups (*P* = 0.07). No difference was observed in terms of TIMI frame count (TFC) or slow flow phenomenon prevalence.

Functional measurements

In a group of CMD patients compared to no CMD group, higher values of FFR and RFR were recorded, 0.84 [interquartile range (IQR) 0.82–0.91] vs. 0.83 (IQR 0.74–0.90), *P* = 0.03 and 0.92 (IQR 0.86–0.94) vs. 0.89 (IQR 0.81–0.94), *P* = 0.045, respectively.

In the CMD group, lower values of CFR and higher IMR levels were recorded [1.6 (IQR 1.2–2.0) vs. 2.6 (IQR 2.1–3.4), *P* <0.001 and 29 (IQR 21–37) vs. 15 (IQR 12–20), *P* <0.001 respectively]. Resistive reserve ratio levels were also lower in the CMD group [1.9 (IQR 1.4–

2.7) vs. 3.4 (IQR 2.7–4.4), *P* <0.001]. Detailed QCA and functional measurement results are presented in Table 3.

Correlation between functional coronary indices

There was no significant correlation between epicardial and microcirculatory specific indices, nevertheless, there was a positive correlation between P_d/P_a, RFR and CFR, RFR as well as between IMR and BRI. A negative correlation was present between IMR and both, CFR and RRR (*P* <0.05). Only a pair of CFR and FFR revealed no correlation. Detailed results of correlation analysis are presented in matrix Figure 2.

Logistic regression results

Only higher RFR levels and the presence of diastolic dysfunction remained predictors of CMD presence, with OR 1.13 (95% CI, 1.05–1.21; *P* = 0.004) and OR 4.0 (95% CI, 1.5–11.44, *P* = 0.007), respectively. Sensitivity analysis with a multivariable mixed-effect regression model incorporating the random effect of vessel tested confirmed higher RFR and diastolic dysfunction as a potential risk factor of CMD presence, with OR 1.11 (95% CI, 1.03–1.19; *P* = 0.006) and OR 3.19 (95% CI, 1.09–9.30; *P* = 0.03). Detailed regression results are presented in Tables 4 and 5.

DISCUSSION

Currently, available data on CMD prevalence is based mainly on non-invasive testing, whereas data on its prevalence according to current ESC guidelines, regarding thermodilution-based CFR and IMR methods, is scarce [2]. The main findings of our study are a relatively high prevalence of CMD, present in 45% of patients with CCS, particularly in over 55% of patients without any significant coronary artery stenosis, and in 34% of patients with at least one significant coronary stenosis. Apart from the higher age, there were no clinical predictors of CMD presence, nevertheless, higher RFR values and the presence of left ventricular hypertrophy or diastolic LV dysfunction were independent risk factors of the CMD diagnosis.

Prevalence of CMD

We provide data showing a high prevalence of CMD, present in 45% of patients with chronic coronary syndromes, present in either patient without significant coronary lesions (55%) or patients with concomitant epicardial stenosis (34%). Currently available data derived from PET studies show a similar, 50%–53% prevalence of CMD in patients suspected of coronary artery

disease [21]. When using a different methodology, where CMD was defined as decreased coronary flow velocity reserve (CFVR <2.0 or 2.5), its prevalence was reported in a broader range, between 26% to over 64% of patients, depending on the source [5, 22]. Invasive studies, based on IMR measurement show results similar to presented in our analysis, as Kobayashi et al. [23] reported CMD in over 40% of patients. Data on CMD prevalence in the Polish population, according to ESC 2024 guidelines definition, is still scarce [2]. Nonetheless, Corcoran et al. [24] enforcing the ESC definition reported the prevalence of CMD in 61% of patients, which is slightly higher than reported in our study.

Clinical and echocardiographic predictors of CMD

Our research did not reveal any clinical risk factors of CMD presence in chronic coronary syndromes and borderline coronary lesions, however, group diagnosed with CMD was slightly older without a statistically significant difference. Currently, available data on CMD risk factors provide robust and sometimes contradictory results [5, 25–27]. For instance, Taquetti et al. [25] reported no difference between CMD and control groups in terms of age, sex, hypertension, or dyslipidemia prevalence, which is similar to our observation. On the other hand, various authors report higher age as a typical risk factor for CMD diagnosis. In our study, higher age was a significant risk factor of CMD in univariate logistic regression analysis, however, this effect was diminished in a multivariable model, as age may be rather a covariate to other pathologies present in older patients.

Our data suggest an association between the presence of CMD and left ventricular hypertrophy as well as diastolic dysfunction, which in our regression analysis were independent, statistically significant risk factors of CMD presence. However, our analysis was limited to a subgroup of only 68 patients, due to lack of proper myocardial imaging in transthoracic echocardiography in a significant number of patients, therefore this particular result may be uncertain. Escaned et al. reported in 2009 an association between measurements of diastolic dysfunction and elevated IMR values [28]. On the contrary, Dykun et al. [26] in their analysis of 379 patients found no difference in terms of E/e', left atrium volume nor left ventricular mass index between the CMD group and controls. Similarly, Lam et al. [29] in a group of 149 patients (of which 37% were diagnosed with CMD by contrast echocardiography), showed no association between diastolic dysfunction parameters and the presence of microvascular dysfunction.

Functional differences and mechanisms of CMD in CCS

There are numerous postulated mechanisms of coronary microcirculatory dysfunction, regarding both, structural abnormalities and vascular tone dysregulation [30–33].

In our study, apart from obviously lower CFR values with higher IMR values in the CMD group, lower RRR values were also observed. In general, CFR values reflect the global epicardial and microcirculatory ability to increase coronary flow during hyperaemia, whereas decreased RRR may suggest the decreased vasoactive capacity of coronary microcirculation, even though RRR and CFR values are strongly correlated [24]. In our cohort, a similarly strong positive correlation between CFR and RRR values was observed.

Noteworthy, higher RFR levels in the CMD group were observed, however, resting measurements of BRI, TFC or slow low phenomenon prevalence was similar to the no-CMD group. This may be associated with a more complex mechanism, than just increased baseline microcirculatory, which may be associated with the extent of ischemia territory and viability of the myocardium involved.

Similarly, no correlation between TFC nor slow flow phenomenon and coronary microvascular dysfunction were present in our analysis. In a series of 15 cases, Fineschi et al. [34] suggested that the slow flow phenomenon was associated with higher baseline resistance in coronary arteries, whereas there was no significant correlation with either CFR or IMR values, which is similar to our observation. On the other hand, in a larger cohort of 152 patients, the sensitivity and specificity of TFC to detect CMD were poor [35].

The lack of reliable angiographic features suggesting CMD presence is a strong argument in favour of the broad use of functional assessment to detect microcirculatory abnormalities.

Study limitations

Only over 100 patients were included in the study, however, analyses included 157 vessels, which is a good population to assess CMD prevalence, regarding data from non-invasive studies.

Our study included typical CCS patients with symptoms of stenocardia but not all of them had prior ischemia non-invasive testing, which is strongly recommended by current guidelines, however, all the patients underwent invasive FFR testing to detect possible ischemic lesions during CAG.

CONCLUSION

The prevalence of CMD in CCS patients with moderate coronary lesions is high, and CMD is present in 45% of cases, independently from the grade of artery stenosis visualized in CAG. Moreover, the presence of CMD in over 34% of patients qualified for revascularization, may account for persistent angina after apparently successful PCI. As there are only a few factors to predict CMD and none is a fully specific marker, more common use of functional testing is needed and may improve patients' symptoms.

Article information

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Table 1. Patient characteristics

	All patients n = 101	No CMD n = 56	CMD n = 45	*P*-value
Demography and medical history				
Age, years, mean (SD)	66.2 (9.04)	65.4 (8.57)	67.3 (9.58)	0.30[a]
Age >65 years, n (%)	50 (50.0)	26 (47.3)	24 (53.3)	0.69[b]
Sex, n (%)				0.62[b]
Female	26 (25.7)	16 (28.6)	10 (22.2)	
Male	75 (74.3)	40 (71.4)	35 (77.8)	
Weight, kg, mean (SD)	79.5 (14.8)	79.4 (14.5)	79.6 (15.3)	0.95[a]
Height, cm, mean (SD)	166 (10.0)	166 (9.94)	166 (10.2)	0.96[a]
BMI, kg/m^2, mean (SD)	28.8 (4.30)	28.8 (4.28)	28.8 (4.39)	0.96[a]
Arterial hypertension treated, n (%)	97 (96.0)	52 (92.9)	45 (100)	0.13[b]
Dyslipidemia treated, n (%)	99 (98.0)	55 (98.2)	44 (97.8)	1.00[b]
Diabetes, n (%)	42 (41.6)	25 (44.6)	17 (37.8)	0.62[b]
Prior AMI, n (%)	25 (27.8%)	14 (28.0%)	11 (27.5%)	1.00[b]
Tabacco use, n (%)				1.00[b]

Never	52 (55.9%)	30 (56.6%)	22 (55.0%)	
Current or former	41 (44.1%)	23 (43.4%)	18 (45.0%)	
Clinical symptoms				
Character of symptoms, n (%)				
Non-typical	41 (45.1)	22 (44.0)	19 (46.3)	0.99[b]
typical	50 (54.9)	28 (56.0)	22 (53.7)	
CCS scale, n (%)				
0	21 (20.8)	7 (12.5)	14 (31.1)	
1	30 (29.7)	21 (37.5)	9 (20.0)	0.035[b]
2	36 (35.6)	18 (32.1)	18 (40.0)	
3	14 (13.9)	10 (17.9)	4 (8.89)	
NYHA scale, n (%)				
0	50 (54.9)	29 (58.0)	21 (51.2)	
1	10 (11.0)	8 (16.0)	2 (4.88)	0.15[b]
2	29 (31.9)	12 (24.0)	17 (41.5)	
3	2 (2.20)	1 (2.00)	1 (2.44)	
Clinical and laboratory assessment				
Invasive pressure assessment				
SBP, mm Hg, mean (SD)	136 (22.1)	134 (21.9)	139 (22.5)	0.36[a]
DBP, mm Hg, mean (SD)	65.5 (13.5)	62.9 (12.8)	68.9 (13.9)	0.04[a]
PP, mm Hg, mean (SD)	70.6 (18.5)	71.3 (16.8)	69.6 (20.7)	0.69[a]
Non-invasive pressure treatment				
SBP, mm Hg, mean (SD)	132 (13.4)	133 (13.8)	129 (12.8)	0.16[a]
DBP, mm Hg, mean (SD)	72.2 (10.4)	71.1 (9.26)	73.6 (11.6)	0.24[a]
PP, mm Hg, mean (SD)	59.3 (14.4)	62.1 (14.3)	55.8 (14.0)	0.03[a]
LDL cholesterol, mmol/l, median (IQR)	2.22 (1.79–2.86)	2.20 (1.77–2.71)	2.29 (1.83–3.14)	0.42[a]
LDL cholesterol according to level, n (%)				
<1.4 mmol/l	7 (7.1)	4 (7.4)	3 (6.8)	
<1.8 mmol/l	18 (18.4)	11 (20.4)	7 (15.9)	0.94[c]
<2.5 mmol/l	38 (38.8)	21 (38.9)	17 (38.6)	
≥2.5 mmol/l	35 (35.7)	18 (33.3)	17 (38.6)	
HDL cholesterol, mmol/l, median (IQR)	1.20 (1.05–1.40)	1.23 (1.07–1.36)	1.19 (1.00–1.40)	0.66[a]
Glucose fasting, mmol/l, median (IQR)	5.80 (5.20–7.23)	5.80 (5.10–7.60)	6.00 (5.25–6.80)	0.97[a]

HbA1c, mmol/l, median (IQR)	5.80 (5.50–6.50)	5.90 (5.50–6.90)	5.80 (5.40–6.20)	0.24[a]
Serum creatinine, µmol/l, median (IQR)	82.0 (73.0–94.0)	82.5 (73.8–93.0)	82.0 (70.0–95.0)	0.73[a]
eGFR-CKD, median (IQR)	78.0 (65.0–90.0)	78.0 (66.2–87.2)	81.0 (65.0–95.0)	0.45[a]
Pharmacotherapy				
Acetylsalicylic acid, n (%)	91 (90.1)	53 (94.6)	38 (84.4)	0.11[b]
Beta adrenolytic, n (%)	86 (85.1)	49 (87.5)	37 (82.2)	0.65[b]
Non dihidypiridydne Ca-blocker, n (%)	9 (9.0)	7 (12.7)	2 (4.4)	0.18[b]
Dihidpropiridine Ca-blocker, n (%)	33 (32.7)	14 (25.0)	19 (42.2)	0.11[b]
ACEI/ARB, n (%)	91 (91.0)	52 (92.9)	39 (88.6)	0.50[b]
Statin, n (%)	99 (98.0)	55 (98.2)	44 (97.8)	1.00[b]

[a]U Mann–Whitney. [b]t-Student test. [c]χ_2

Abbreviations: ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; AMI, acute myocardial infarction; BMI, body mass index; CCS, Canadian Cardiovascular Society; CKD, chronic kidney disease; CMD, coronary microcirculatory dysfunction; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rhigh-densityigh density lipoprotein; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; NYHA, New York Heart Association; PP, pulse pressure; SBP, systolic blood pressure; SD, standard deviation

Table 2. Echocardiographic results

	All patients n = 101	No CMD n = 56	CMD n = 45	*P*-value
LVEF, %, median (IQR)	55 (50–60)	59 (50–60)	55 (50–60)	0.19[a]
LVIDd, mm, median (IQR)	48 (44–53)	47 (44–52)	50 (46–56)	0.06[a]
IVSd, mm, median (IQR)	12 (10–13)	11 (10–12)	12 (11–13)	0.15[a]
E/A, median (IQR)	0.80 (0.77–1.00)	0.80 (0.70–0.98)	0.90 (0.77–1.20)	0.47[a]
Diastolic dysfunction, n (%)				
Normal	52 (51)	34 (61)	17 (37)	0.05[b]
Impaired	49 (49)	22 (39)	28 (63)	
RVSP, mm Hg, median (IQR)	25.0 (20.0–30.0)	23.0 (20.0–28.0)	27.0 (23.0–34.0)	0.13[a]

LVMI, g/m^2, median (IQR)	105 (88.8–126)	101 (80.9–114)	121 (90.4–134)	0.03[1]
LVH, n (%)	28 (28%)	11 (20%)	17 (38%)	0.01[b]
Left ventricular geometry, n (%)				
Normal geometry	23 (29.9)	16 (34.8)	7 (22.6)	
Concentric remodeling	26 (33.8)	19 (41.3)	7 (22.6)	0.04[b]
Eccentric hypertrophy	15 (19.5)	5 (10.9)	10 (32.3)	
Concentric hypertrophy	13 (16.9)	6 (13.0)	7 (22.6)	

[a]U Mann–Whitney test; [b]χ^2 test

Abbreviations: CMD, coronary microcirculatory dysfunction; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVIDd, left ventricular end-diastolic diameter; IQR, interquartile range; IVSd, end-diastolic interventricular septum diameter; RVSP, right ventricle systolic pressure; LVMI, indexed left ventricular mass index

Table 3. Quantitative coronary angiography and functional measurement results

	All vessels n = 157	**no CMD n = 83**	**CMD n = 74**	***P*-value**
Vessel, n (%)				
LAD	88 (57.1)	51 (63.7)	37 (50.0)	0.15[b]
LCx	39 (25.3)	19 (23.8)	20 (27.0)	
RCA	27 (17.5)	10 (12.5)	17 (23.0)	
Percent diameter stenosis, %, median (IQR)	45 (40–50)	45 (39–50)	45 (40–49)	0.92[a]
Lesion length, mm, median (IQR)	17.5 (11.0–25.0)	18.4 (11.0–25.0)	16.7 (10.6–25.6)	0.70[a]
Percentage of >20 mm lesions, n(%)	55 (39.3)	31 (43.1)	24 (35.3)	0.44[a]
Reference diameter, median (IQR)	2.67 (2.38–2.97)	2.67 (2.44–2.97)	2.67 (2.33–2.99)	0.75[a]
Gensini, median (IQR)	9.5 (6.5–14.5)	9.25 (7.0–16.0)	10.0 (6.0–13.0)	0.60[a]
TFC, frames/s, median (IQR)	36 (27–45)	36 (27–45)	36 (27–45)	0.65[a]

Slow flow phenomenon, n(%)	32 (20.6)	16 (19.5)	16 (21.9)	0.87
FFR, median (IQR)	0.84 (0.78–0.91)	0.83 (0.74–0.90)	0.84 (0.82–0.91)	0.03[a]
Vessel status according to FFR, n(%)				0.003[b]
FFR >0.80	108 (68.8)	48 (57.8)	60 (81.1)	
FFR ≤0.80	49 (31.2)	35 (42.2)	14 (18.9)	
P_d/P_a, median (IQR)	0.92 (0.89–0.95)	0.92 (0.88–0.94)	0.93 (0.90–0.95)	0.15[a]
RFR, median (IQR)	0.89 (0.84–0.94)	0.89 (0.81–0.94)	0.92 (0.86–0.94)	0.045[a]
IMR_{corr}, median (IQR)	19(13–29)	15(12–20)	29(21–37)	<0.001[a]
CFR, median (IQR)	2.1(1.5–2.7)	2.6(2.1–3.4)	1.6(1.2–2.0)	<0.001[a]
RRR, median (IQR)	2.7(1.8–3.7)	3.4(2.7–4.4)	1.90(1.40–2.68)	<0.001[a]
BRI, median (IQR)	56.3(34.5–81.0)	56.3(38.3–74.6)	57.2(31.0–103)	0.60[a]
Vessel status according to IMR, n(%)				<0.001[b]
IMR <25	107 (68.2)	83 (100)	24 (32.4)	
IMR ≥25	50 (31.8)	0 (0.00)	50 (67.6)	
Vessel status according to CFR, n(%)				<0.001[b]
CFR ≥2.0	88 (56.1)	67 (80.7)	21 (28.4)	
CFR <2.0	69 (43.9)	16 (19.3)	53 (71.6)	
Vessel status according to RRR, n(%)				<0.001[b]
RRR ≥2.0	108 (68.8)	74 (89.2)	34 (45.9)	
RRR <2.0	49 (31.2)	9 (10.8)	40 (54.1)	

[a]U Mann–Whitney. [b]χ^2

Abbreviations: BRI, baseline resistive ratio; CFR, coronary flow reserve; CMD, coronary microcirculatory dysfunction; FFR, fractional flow reserve; IMR, index of microcirculatory resistance; IQR, interquartile range; LAD, left anterior descending; LCx, left circumflex artery; QCA, quantitative coronary angiography; RCA, right coronary artery; RFR, lowest filtered P_d/P_a; RRR, relative resistance ratio; TFC, TIMI frame count

Table 4. Logistic regression results of CMD predictors

	Multivariable baseline model			Multivariable model — stepwise regression		
CMD predictors	**OR**	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**
RFR, per 0.01	1.12	1.04–1.20	0.002	1.13	1.05–1.21	0.004

Age, per 1 year	1.02	0.95–1.09	0.595	NA		
Sex, male	1.65	050–5.40	0.410	NA		
LDL cholesterol, per 1 mmol/l	1.05	0.74–1.48	0.795	NA		
Central SBP, per 10 mm Hg	1.02	1.00–1.04	0.057	1.02	1.00–1.04	0.09
LVMI, per10 g/m^2	1.03	0.85–1.24	0.79	NA		
Diastolic LV dysfunction	3.70	1.19–11.50	0.02	4.00	1.50–11.44	0.007
c-statistic	0.786 (95% CI, 0.699–0.874)			0.784 (95% CI, 0.696–0.873)		

Abbreviations: OR, odds ratio; CI, confidence interval; CMD, coronary microcirculatory dysfunction; LDL, low-density lipoprotein; LV, left ventricle; LVMI, left ventricular mass index; NA, not applicable; RFR, resting full-cycle ratio; SBP, Systolic blood pressure

Table 5. Uni and multivariable mixed effect logistic regression results with the tested vessel as a random effect

	Univariable model			Multivariable model		
Predictor	**OR**	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**
RFR, per 0.01	1.09	1.02–1.16	0.016	1.11	1.03–1.19	0.006
Left ventricular hypertrophy	3.00	1.21–7.47	0.018	2.06	0.71–5.96	0.18
Diastolic dysfunction	3.02	1.25–7.35	0.014	3.19	1.09–9.30	0.03

Abbreviations: CI, confidence interval, OR, odds ratio; RFR, resting full-cycle ratio

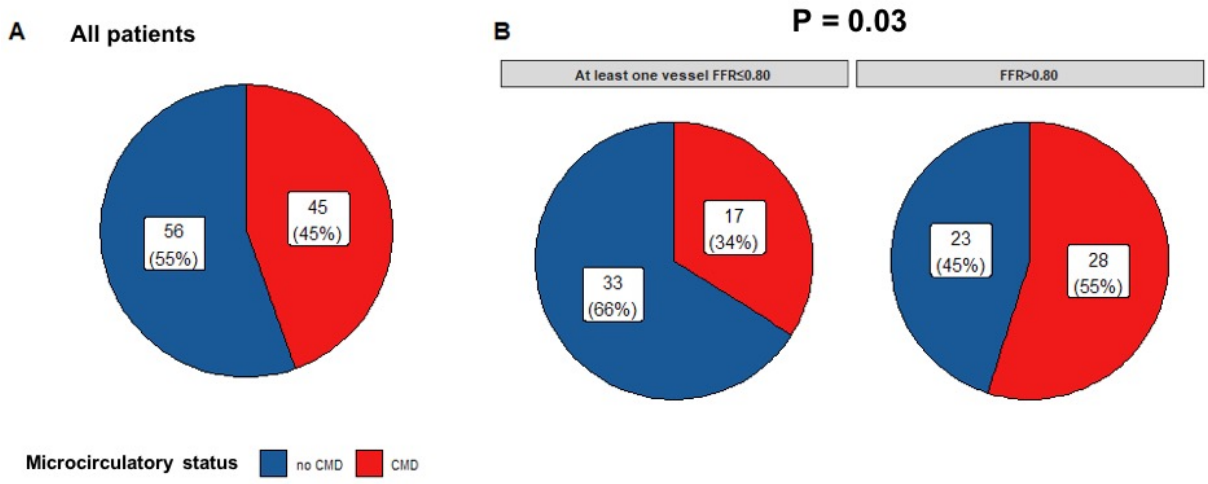

Figure 1. Coronary microcirculatory dysfunction prevalence according to the presence of fractional flow reserve <0.80

Abbreviations: CMD, coronary microcirculatory dysfunction; FFR, fractional flow reserve

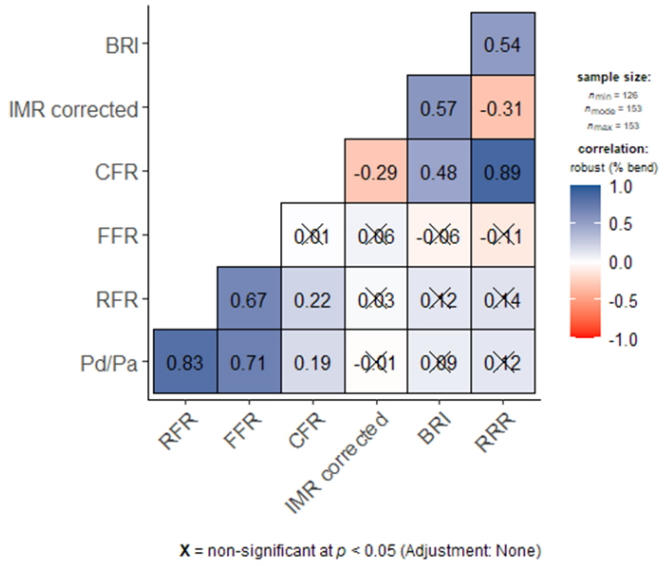

Figure 2. Spearman rho for pairs of epicardial indices

X, lack of significant correlation

Abbreviations: BRI, baseline resistive index; CFR, coronary flow reserve; FFR, fractional flow reserve; IMR, index of microcirculatory resistance; RFR, resting full-cycle ratio; RRR, resistive reserve ratio