Coronary microvascular disease in patients referred to coronary angiography following coronary computed tomography angiography

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ABSTRACT

BACKGROUND: Ischaemia without obstructive epicardial coronary artery disease (CAD) is common and is often related to coronary microvascular disease (CMD). Previous studies primarily focused on functional assessment in patients with established ischaemia without obstructive epicardial CAD.

AIMS: We sought to assess the prevalence of CMD and compare clinical and procedural characteristics including myocardial perfusion imaging, as derived from rubidium-82 positron emission tomography ([82]Rb-PET), and health status according to CAD classification.

METHODS: We conducted a prospective, observational study of symptomatic patients with suspected obstructive epicardial CAD on coronary computed tomography angiography. All patients were referred to [82]Rb-PET and invasive coronary angiography with bolus thermodilution. CMD was defined as the absence of obstructive epicardial CAD (fractional flow reserve >0.80 or diameter stenosis <90%) combined with coronary flow reserve <2.5 and/or index of microvascular resistance ≥25. Main analyses included myocardial perfusion characteristics by [82]Rb-PET and health status at baseline and at 3-month follow-up according to CAD classification (no disease, obstructive epicardial CAD, isolated CMD or combined obstructive epicardial CAD and CMD).

RESULTS: Among 561 patients, isolated CMD was diagnosed in 131 patients (prevalence 0.23, 95% confidence interval [CI]: 0.20-0.27). Vessel territories with isolated CMD were characterised by similar perfusion characteristics to non-diseased vessels (mean difference in hyperaemic myocardial blood flow 0.03 [95% CI: –0.13 to 0.06] mL/min/g). Patients with isolated epicardial disease on both patient and vessel levels had reduced stress myocardial blood flow compared to patients without disease. The probability of being angina-free at 3 months tended to be lower for the CMD group (odds ratio [OR] 0.56, 95% CI: 0.31-1.00) and higher for the revascularised epicardial disease group (OR 1.52, 95% CI: 0.94-2.48) compared to the group classified as not diseased.

CONCLUSIONS: CMD, as identified with bolus thermodilution, is common in patients referred to invasive coronary angiography based on suspected obstructive epicardial CAD even in patients with normal stress myocardial blood flow by [82]Rb-PET. (ClinicalTrials.gov: NCT02264717 and NCT04707859)

Current European and North American guidelines on chronic coronary syndrome emphasise the use of coronary computed tomography angiography (CTA) as a first-line diagnostic test in patients with symptoms suggestive of obstructive epicardial coronary artery disease (CAD)[1,2]. However, a sizeable proportion of patients with suspected obstructive epicardial CAD on coronary CTA do not have obstructive epicardial disease on the downstream invasive coronary angiography (ICA)[3,4].

Previous studies report that up to 1 in 2 patients with relevant anginal symptoms but without obstructive epicardial CAD show evidence of coronary microvascular disease (CMD)[5]. Diagnosing CMD may help guide personalised treatment strategies and optimise patient outcomes. Guidelines currently recommend the use of invasive coronary flow reserve (CFR) and the index of microvascular resistance (IMR) to identify CMD[2]. However, previous studies mainly focused on functional assessment in patients with established angina but without obstructive epicardial CAD among populations referred to ICA based on multiple diagnostic strategies[6,7].

In a population of symptomatic patients referred to ICA following coronary CTA, we aimed to evaluate and compare clinical and procedural characteristics, including myocardial perfusion imaging as derived from rubidium-82 positron emission tomography ([82]Rb-PET), and health status for patients with no disease, those with CMD only, those with obstructive epicardial CAD only or those with both CMD and obstructive epicardial CAD.

Methods

STUDY POPULATION

This was a substudy of the Danish Study of Non-Invasive Diagnostic Testing in Coronary Artery Disease (Dan-NICAD) 2 and 3. The trial designs were previously published[8,9]. This substudy included all patients that were referred for ICA based on suspected obstructive epicardial CAD (>50% diameter stenosis [DS]) on index coronary CTA. All patients were referred to myocardial perfusion imaging including [82]Rb-PET and ICA. All patients provided informed written consent. The Central Denmark Region Committees on Health Research Ethics approved the study. The study was registered at ClinicalTrials.gov: NCT03481712 and NCT04707859.

RUBIDIUM-82 POSITRON EMISSION TOMOGRAPHY

A detailed description of the scanning protocol was previously reported[8,9]. Adenosine was administered continuously for 7 minutes (140 µg/kg/min). Quantitative analyses were performed to derive the global and territory-specific (left anterior descending artery [LAD], left circumflex artery [LCx], and right coronary artery [RCA]) resting and stress myocardial blood flow (MBF) and subsequent MBF reserve

Impact on daily practice

Our findings underscore that routine bolus thermodilution in patients referred to coronary angiography following coronary computed tomography angiography will lead to a coronary microvascular disease diagnosis in up to 1 in 2 patients, often despite normal perfusion as assessed with rubidium-82 positron emission tomography.

(MBFR), according to a cardiovascular imaging expert panel statement[10]. Findings were reported as averaged values and as the lowest mean value for two adjacent segments, both on a patient and a territory level.

INVASIVE CORONARY ANGIOGRAPHY AND FUNCTIONAL ASSESSMENT

According to guideline recommendations and the study protocol, all coronary stenoses with visually estimated 30-90% DS in vessels >2 mm were considered for physiological assessment[8]. Additionally, for patients included as part of Dan-NICAD 3, full 3-vessel physiological assessment was applied, with the only exception being visually high-grade stenoses (>90% DS)[9]. In short, the pressure wire (PressureWire X Guidewire [Abbott]) was advanced distally in the target vessel (>2 mm distal to all visible disease or 2/3 of the vessel length), and its position was recorded during contrast injection. Resting pressure waveforms were recorded for at least 10 seconds when the effects of contrast and nitrate were considered negligible. For thermodilution, a total of 3 mL of saline was administered manually three times before and three times after administration of intravenous adenosine (140 µg/min/kg) to obtain mean baseline and hyperaemic transit times using the Coroventis CoroFlow system (Coroventis AB). All pressure waveforms, flow data and three-dimensional quantitative coronary angiograms (3D-QCA) underwent blinded review and analysis for artefacts in a core lab setting (Interventional Imaging Core Laboratories, Institute of Clinical Medicine, Aarhus University, Denmark). For the thermodilution measurements, cutoffs were applied according to guidelines, with fractional flow reserve (FFR) ≤0.80, CFR <2.5, and IMR ≥25[3]. IMR was adjusted according to Yong's formula[11]. We further calculated microvascular resistance reserve (MRR), which was recently introduced as a measure of the microvasculature that eliminates the influence of epicardial disease. We applied a cutoff of 3.0 for MRR[12].

HEALTH STATUS

All patients were invited to complete the 19-item Seattle Angina Questionnaire (SAQ) at baseline and after 3 months. We included angina stability score, quality of life (QoL), angina frequency score, physical limitation score, and treatment satisfaction score. A summary score was calculated

Abbreviations

[82]Rb-PET	rubidium-82 positron emission tomography	CMD	coronary microvascular disease	IMR	index of microvascular resistance
CAD	coronary artery disease	CTA	computed tomography angiography	MBF	myocardial blood flow
CFR	coronary flow reserve	FFR	fractional flow reserve	MBFR	myocardial blood flow reserve
		ICA	invasive coronary angiography		

as the mean of the angina frequency, physical limitation, and QoL scores. The SAQ score ranged from 0-100 with higher scores indicating better health status. Freedom of angina was defined as an angina frequency score of 100.

ANALYSIS STRATEGY

CAD classification was performed based on ICA findings and the thermodilution measurements as follows: (1) no disease: defined as no lesions with >30% DS and/or normal FFR, CFR and IMR; (2) CMD: defined as a vessel with FFR >0.80 and CFR <2.5 and/or IMR ≥25; (3) obstructive epicardial disease: defined as high-grade coronary artery stenosis (>90% DS) or FFR ≤0.80; and (4) concomitant disease: defined as vessels with FFR ≤0.80 and IMR ≥25. The prevalence of CMD was calculated with a predefined stratification according to selective assessment of vessels with visually estimated 30-90% DS, as performed in Dan-NICAD 2, versus complete 3-vessel assessment, as performed in Dan-NICAD 3. Main analyses included the following: (1) characterisation of quantitative perfusion characteristics (global and territorial MBF and MBFR) using ^{82}Rb-PET according to stratification by CAD classification; and (2) the influence of CAD classification on the probability of being angina-free after 3 months. Vessel-level analyses were stratified according to whether bolus thermodilution was performed in vessels with <30% DS (non-stenosed vessels) or vessels with >30% DS (stenosed vessels), as part of the 3-vessel protocol.

STATISTICAL ANALYSES

Continuous variables are presented as means with standard deviations or medians with interquartile ranges (IQR). Categorical baseline data are presented as a number with percentages. Differences in procedural and clinical characteristics across CAD classification groups were tested for statistical significance with one-way analysis of variance or the Kruskal-Wallis test and the chi-squared test or Fisher's exact test as appropriate. Bonferroni correction was applied in case of multiple comparisons. Logistic regression ("glm" package in R) was used to assess and illustrate the probability of being angina-free after 3 months depending on CAD classification and as a function of the baseline angina frequency score. Applicable tests were two-tailed, and p<0.05 was considered statistically significant. R version 3.5.2 (R Foundation for Statistical Computing) was used for all statistical analyses.

Results

A total of 713 patients underwent ICA. Following the exclusion of patients and vessels who lacked physiological assessment for 30-90% DS, or had lost pressure/thermodilution waveform data, or had insufficient quality of FFR pressure or thermodilution data, 561 patients and 1,682 vessels were included for analyses **(Figure 1)**.

Our study included 357 (64%) patients from Dan-NICAD 2, which involved functional evaluation of moderately stenosed vessels, and 204 (36%) patients from Dan-NICAD 3, in which a protocolled 3-vessel physiological assessment was performed regardless of lesion severity. Baseline and procedural characteristics are summarised stratified by CAD classification in **Table 1** and **Table 2**. The mean age was 63±8 years, and 174 (31%) were female.

Patients with obstructive epicardial CAD or concomitant obstructive epicardial CAD and CMD more frequently had typical chest pain **(Table 1)**. The mean FFR, CFR and IMR were 0.89±0.10, 3.6±2.3, and 19±16, respectively. Median values are listed according to vessel and stratified by stenosed/non-stenosed vessels in **Supplementary Table 1**.

PREVALENCE OF CMD ACCORDING TO MEASURING STRATEGY AND VESSEL TERRITORY

On a patient level, a 3-vessel measuring strategy resulted in a lower prevalence of patients being classified as disease-free (0.28 [95% confidence interval {CI}: 0.22-0.34] vs 0.44 [95% CI: 0.39-0.49]) or as having obstructive epicardial CAD (0.27 [95% CI: 0.21-0.33] vs 0.35 [95% CI: 0.30-0.40]), and the prevalence
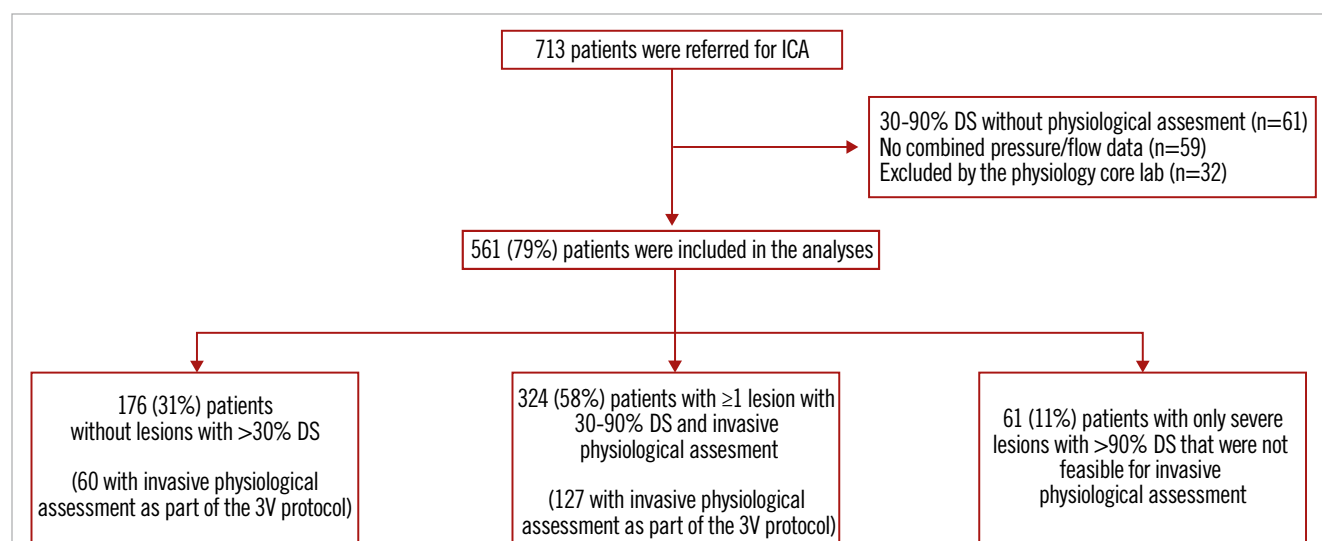

Figure 1. *Study flowchart. The 3V protocol refers to the 3V functional assessment protocol that was applied in Dan-NICAD 3. 3V: three-vessel; DS: diameter stenosis; ICA: invasive coronary angiography*

Table 1. Baseline characteristics.

	No disease	Microvascular disease	Epicardial disease	Concomitant epicardial and microvascular disease	*p*-value
n	212 (38)	131 (23)	179 (32)	39 (7)	
Demographics					
Age, years	63.4±8.3	64.1±7.6	63.0±8.0	63.0±7.0	1.00
Female	83 (39.2)	53 (40.5)	30 (16.8)	8 (20.5)	<0.01
Risk factors					
Diabetes	20 (9.4)	9 (7.6)	27 (15.1)	4 (10.3)	0.90
Hypertension	111 (52.4)	72 (55.0)	101 (56.4)	27 (69.2)	1.00
Smoking					1.00
Active smoker	71 (33.5)	41 (31.3)	67 (37.4)	15 (38.5)	
Former smoker	28 (13.2)	23 (17.6)	28 (15.6)	4 (10.3)	
Never	113 (53.3)	67 (51.1)	84 (46.9)	20 (51.3)	
Hyperlipidaemia	74 (35.1)	55 (42.0)	64 (36.2)	13 (33.3)	1.00
Family history of CAD	77 (36.5)	54 (41.2)	63 (35.4)	17 (44.7)	1.00
Clinical presentation					
Symptoms					<0.01
Typical chest pain	46 (21.7)	21 (16.0)	69 (38.5)	16 (41.0)	
Atypical chest pain	78 (36.8)	51 (38.9)	52 (29.1)	15 (38.5)	
Dyspnoea	32 (15.1)	20 (15.3)	28 (15.6)	2 (5.1)	
Non-specific	56 (26.4)	39 (29.8)	30 (16.8)	6 (15.4)	
Clinical likelihood (risk-factor weighted)					**<0.01**
<5%	44 (21.0)	28 (21.4)	18 (10.2)	3 (7.9)	
5-15%	91 (43.3)	54 (41.2)	59 (33.5)	14 (36.8)	
>15%	75 (35.7)	49 (37.4)	99 (56.2)	21 (55.3)	
Imaging					
CACS	173.0 [50.0, 383.0]	368.5 [110.5, 805.3]	363.0 [108.5, 1,231.0]	704.0 [104.0, 1,319.0]	<0.01
[82]Rb-PET					
[82]Rb-PET global resting MBF, mL/min/g					
Averaged	1.13±0.24	1.19±0.27	1.05±0.24	1.05±0.22	<0.01
Mean of lowest 2 adjacent segments	0.94±0.24	0.98±0.26	0.88±0.25	0.85±0.21	0.03
[82]Rb-PET global stress MBF, mL/min/g					
Averaged	2.84±0.60	2.88±0.64	2.17±0.64	2.36±0.53	<0.01
Mean of lowest 2 adjacent segments	2.35±0.57	2.40±0.60	1.68±0.73	1.76±0.72	<0.01
[82]Rb-PET global MBF reserve, mL/min/g					
Averaged	2.59±0.58	2.52±0.62	2.15±0.63	2.39±0.73	<0.01
Mean of lowest 2 adjacent segments	2.39±0.63	2.33±0.60	1.71±0.73	1.96±0.93	<0.01
[82]Rb-PET perfusion defect					
Stress MBF <2	14 (7.3)	6 (4.7)	67 (41.4)	22 (62.9)	<0.01
SSS ≥4	19 (9.8)	9 (7.0)	95 (58.0)	7 (20.0)	<0.01

Values are mean±standard deviation, median [interquartile range], or n (%). Patient-level clinical and procedural characteristics stratified by CAD classification. P-values are adjusted for multiple comparisons with Bonferroni correction. CACS: coronary artery calcium score; CAD: coronary artery disease; MBF: myocardial blood flow; MBFR: myocardial blood flow reserve; [82]Rb-PET: rubidium-82 positron emission tomography; SAQ: Seattle Angina Questionnaire; SSS: summed stress score

of patients classified with isolated CMD was higher (0.35 [95% CI: 0.28-0.42] vs 0.17 [95% CI: 0.13-0.21]) than with a selective measuring strategy. In the subgroup of vessels where a 3-vessel invasive physiological assessment protocol was applied (n=322), the prevalence of CMD was 0.35 (95% CI: 0.30-0.40), and this did not differ between the RCA (0.31 [95% CI: 0.22-0.40]), LAD (0.37 [95% CI: 0.27-0.48]), and LCx (0.37 [95% CI: 0.29-0.46]). For the subgroup of vessels with invasive assessment of

Table 2. Vessel characteristics.

	No disease	Microvascular disease	Epicardial disease	Concomitant epicardial and microvascular disease	p-value
n	1,135 (67)	231 (14)	291 (17)	25 (2)	
Anatomy					
Vessel					<0.01
RCA	413 (36.4)	67 (29.0)	76 (26.1)	4 (16.0)	
LAD	290 (25.6)	90 (39.0)	161 (55.3)	20 (90.0)	
LCx	432 (28.1)	74 (32.0)	54 (18.6)	1 (4.0)	
Diameter stenosis, %	27.3 [18.8, 36.8]	35.8 [24.1, 44.1]	60.7 [45.0, 88.3]	53.5 [41.4, 60.6]	<0.01
Pressure					
FFR	0.93 [0.87, 0.97]	0.93 [0.87, 0.97]	0.75 [0.70, 0.78]	0.71 [0.65, 0.78]	<0.01
bPa, mmHg	92.2 (11.1)	93.5 (11.8)	91.4 (12.5)	94.7 (15.6)	1.00
hPa, mmHg	85.1 (12.2)	85.9 (14.1)	82.9 (12.1)	88.5 (17.7)	1.00
bPd, mmHg	90.1 (11.6)	90.8 (12.3)	81.8 (13.1)	79.8 (18.0)	<0.01
hPd, mmHg	78.4 (12.5)	78.1 (13.6)	61.6 (12.2)	62.0 (18.5)	<0.01
dPr	0.98 [0.95, 1.01]	0.97 [0.93, 1.00]	0.88 [0.84, 0.91]	0.88 [0.81, 0.90]	<0.01
Flow/resistance					
CFR	4.2 [3.2, 5.8]	2.0 [1.6, 2.4]	2.5 [1.9, 3.5]	1.5 [1.1, 2.5]	<0.01
Transit time rest, s	0.74 [0.51, 0.98]	0.53 [0.33, 1.08]	0.56 [0.38, 0.76]	0.99 [0.52, 1.45]	<0.01
Transit time stress, s	0.17 [0.12, 0.22]	0.29 [0.19, 0.44]	0.22 [0.16, 0.31]	0.54 [0.45, 0.70]	<0.01
IMR	13.0 [9.5, 18.0]	24.0 [13.0, 34.0]	14.0 [10.0, 19.0]	32.0 [27.0, 37.0]	<0.01
[82]Rb-PET (vessel territory)					
PET territory resting MBF, mL/min/g					
Averaged	1.10±0.27	1.16±0.28	1.02±0.24	1.02±0.27	<0.01
Mean of lowest 2 adjacent segments	0.93±0.24	0.97±0.26	0.83±0.23	0.80±0.22	<0.01
PET territory stress MBF, mL/min/g					
Averaged	2.76±0.66	2.79±0.66	1.88±0.70	2.30±0.68	<0.01
Mean of lowest 2 adjacent segments	2.28±0.59	2.27±0.59	1.49±0.61	1.84±0.61	<0.01
PET territory MBF reserve, mL/min/g					
Averaged	2.59±0.70	2.50±0.73	1.91±0.71	2.46±1.27	<0.01
Mean of lowest 2 adjacent segments	2.32±0.61	2.21±0.66	1.61±0.71	2.11±1.04	<0.01
PET territory perfusion defect					
Stress MBF <2	130 (11.4)	24 (10.3)	150 (51.5)	7 (28)	<0.01
SSS ≥4	43 (3.8)	14 (6.0)	137 (47.0)	4 (16)	<0.01

Values are mean±standard deviation, median [interquartile range] or n (%). Vessel-level procedural characteristics stratified by CAD classification. P-values are adjusted for multiple comparisons with Bonferroni correction. bPa: baseline aortic pressure; bPd: baseline distal pressure; CAD: coronary artery disease; dPR: diastolic pressure ratio; hPa: hyperaemic aortic pressure; hPd: hyperaemic distal pressure; IMR: index of microvascular resistance; LAD: left anterior descending artery; LCx: left circumflex artery; MBF: myocardial blood flow; PET: positron emission tomography; [82]Rb: rubidium-82; RCA: right coronary artery; SSS: summed stress score

30-90% lesions (n=385), CMD prevalence was 0.31 (95% CI: 0.26-0.36), and this was highest for the RCA (0.42 [95% CI: 0.31-0.54]) compared to the LAD (0.25 [95% CI: 0.20-0.32]) and the LCx (0.37 [95% CI: 0.26-0.49]) **(Figure 2)**.

PERFUSION CHARACTERISTICS ACCORDING TO CAD CLASSIFICATION

Complete [82]Rb-PET data were available in 520 patients (93%). Territories with invasively assessed isolated CMD were characterised by a higher resting MBF (mean difference 0.06 [95% CI: −0.10 to −0.02]), while stress MBF (mean difference 0.03 [95% CI: −0.13 to 0.06]) and MBFR (mean difference −0.09 [95% CI: −0.02 to 0.19]) were similar **(Table 2, Figure 3, Supplementary Figure 1)** compared to territories without invasively assessed disease. Only territories with isolated obstructive epicardial CAD had, on average, reduced stress myocardial blood flow and myocardial blood flow reserve **(Figure 3, Central illustration)**. Anatomical lesion severity as assessed by 3D-QCA was more severe for vessels with CMD compared to vessels without disease **(Table 2)**.
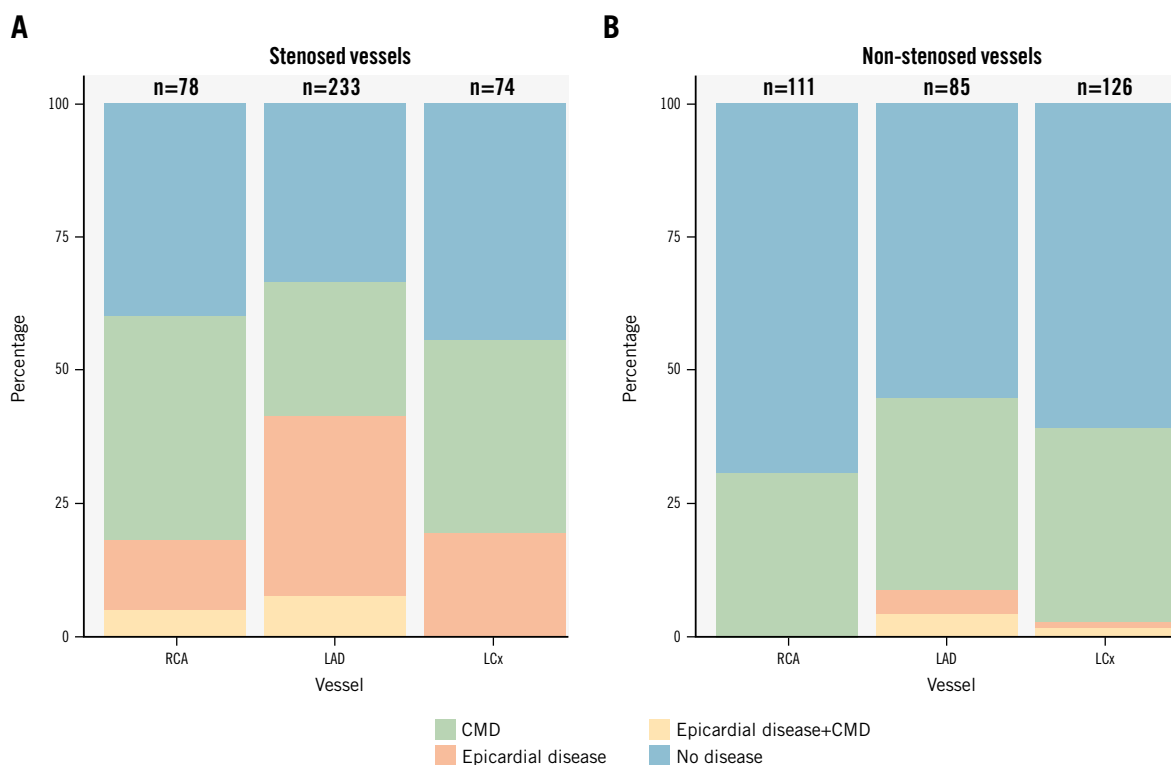
Figure 2. *CAD classification stratified by coronary artery. Coronary microvascular disease, epicardial disease, and concomitant disease according to the evaluated coronary artery, stratified by stenosed vessels (>30% diameter stenosis by visual assessment (A) and non-stenosed vessels (B). CAD: coronary artery disease; CMD: coronary microvascular disease; LAD: left anterior descending artery; LCx: left circumflex artery; RCA: right coronary artery*
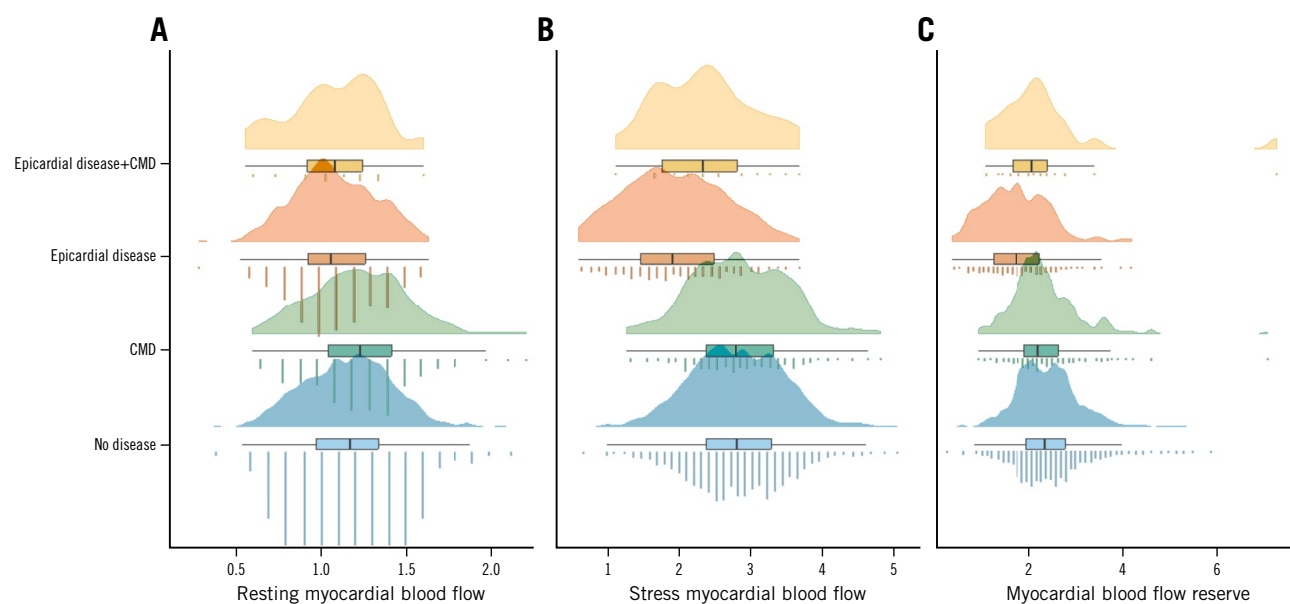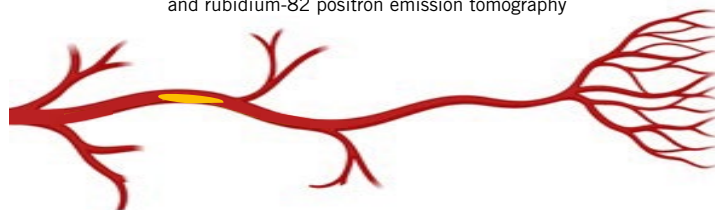

Figure 3. *Perfusion characteristics according to CAD classification. Myocardial perfusion by ^{82}Rb-PET illustrated with raincloud plots (combined density plot, boxplot and jittered point) according to resting myocardial blood flow (in mL/min/g; A), stress myocardial blood flow (in mL/min/g; B) and myocardial blood flow reserve (as a ratio of stress myocardial blood flow/resting myocardial blood flow; C) according to the 4 groups of invasive CAD classification). CAD: coronary artery disease; CMD: coronary microvascular disease; ^{82}Rb-PET: rubidium-82 positron emission tomography*
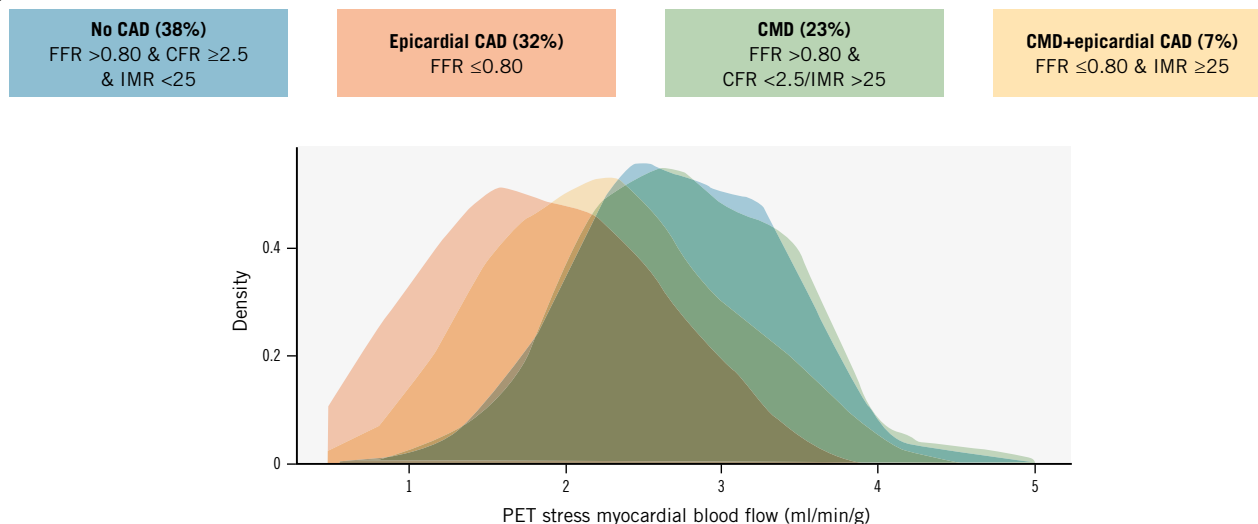
EuroIntervention — Central **Illustration**

Stress myocardial blood flow according to CAD classification.

A

Study population: 562 patients with suspected CAD on coronary CTA underwent paired bolus thermodilution and rubidium-82 positron emission tomography

B

| No CAD (38%) FFR >0.80 & CFR ≥2.5 & IMR <25 | Epicardial CAD (32%) FFR ≤0.80 | CMD (23%) FFR >0.80 & CFR <2.5/IMR >25 | CMD+epicardial CAD (7%) FFR ≤0.80 & IMR ≥25 |

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A) Study population; (B) stress myocardial blood flow as assessed with ^{82}Rb-PET according to CAD classification following routine bolus thermodilution assessment. CAD: coronary artery disease; CFR: coronary flow ratio; CMD: coronary microvascular disease; CTA: computed tomography angiography; FFR: fractional flow reserve; IMR: index of microvascular resistance; PET: positron emission tomography; ^{82}Rb: rubidium-82

INFLUENCE OF CFR, IMR, AND MRR ON CMD DIAGNOSIS

In the subgroup of patients with isolated CMD, 117 patients were classified as having disease based solely on CFR, 46 based solely on IMR, and 68 based on abnormal CFR in combination with abnormal IMR **(Supplementary Table 2)**. Resting MBF was higher and stress MBF lower for the CFR group compared to the IMR group. No differences were seen in perfusion characteristics following stratification by MRR **(Supplementary Table 2)**.

SYMPTOMS AND HEALTH STATUS AT BASELINE AND THREE MONTHS ACCORDING TO CAD CLASSIFICATION

Patients with isolated obstructive epicardial CAD or concomitant obstructive epicardial CAD and CMD more often described typical chest pain compared to patients with isolated CMD or no disease **(Table 1)**. A total of 427 had complete baseline and 3-month follow-up SAQ data. No significant differences were found in key SAQ parameters between the groups at baseline and 3 months of follow-up **(Supplementary Table 3, Supplementary Table 4)**. The probability of being

angina-free at 3 months tended to be lower for the CMD group and higher for the revascularised epicardial disease group compared to the group without disease **(Supplementary Table 4, Supplementary Table 5, Figure 4)**.

Discussion

This is, to our knowledge, the largest study to date with consecutive invasive physiological lesion assessment in patients referred to ICA based on coronary CTA with suspected obstructive CAD. The main findings were as follows: (1) similar to previous studies focusing solely on patients with angina with no obstructive coronary artery disease (ANOCA), CMD was common in this cohort, with its prevalence dependent on complete assessment of all main coronary arteries; (2) only isolated obstructive epicardial CAD was associated with reduced stress myocardial perfusion, as assessed with ^{82}Rb-PET; (3) patients with isolated CMD were less likely to be angina-free after 3 months compared to those who underwent revascularisation for obstructive epicardial disease.
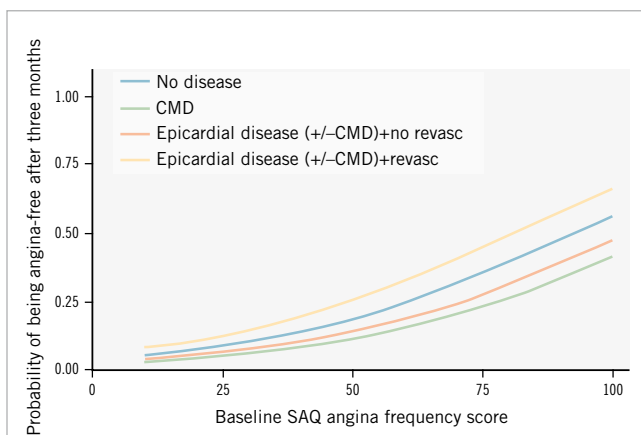
Figure 4. *Influence of CAD phenotype on the probability of being angina-free. The probability of being angina-free as a function of the baseline SAQ angina frequency score including the effect of CAD phenotype. CAD: coronary artery disease; CMD: coronary microvascular disease; revasc: revascularisation; SAQ: Seattle Angina Questionnaire*

PREVALENCE OF CORONARY MICROVASCULAR DYSFUNCTION

Previous studies found various CMD prevalence estimates ranging from 0.16 to 0.72, with an average of 0.41 in a recent meta-analysis that included patients with non-obstructive epicardial CAD[13]. Overall, we found a lower prevalence, likely due to patient selection driven by our study design, which involved referral to ICA based on suspected obstructive epicardial CAD on coronary CTA. However, the prevalence of CMD increased when all 3 major epicardial vessels were assessed, leading to identification of almost 1 in 2 with isolated CMD or concomitant CMD and epicardial disease. The increasing yield of multivessel assessment is in line with a recent study comparing a single-vessel protocol with multivessel invasive coronary functional testing[7]. While the latter study was performed in patients referred to an expert ANOCA testing centre, our findings underscore the diagnostic impact of microcirculatory assessment even in early stages, when there is still a primary suspicion of obstructive epicardial CAD. Our findings are important because coronary CTA is gaining international traction as a first-line diagnostic strategy in patients presenting with symptoms suggestive of CAD. Additionally, our findings illustrate that patients can have CMD, defined by bolus thermodilution, despite fairly normal perfusion on [82]Rb-PET. This may explain persistent angina symptoms following percutaneous coronary intervention (PCI) that may be caused by undiagnosed CMD, with the need for supplementary medical treatment. Indeed, we showed that patients with isolated CMD were less likely to be angina-free after 3 months compared to patients who underwent revascularisation for obstructive epicardial CAD **(Supplementary Table 5)**. Furthermore, our findings underscore uncertainties related to the diagnosis of CMD.

CLINICAL INDICATION FOR DIAGNOSING CMD

The importance of CMD is increasingly acknowledged[14]. Its identification, including patient-specific treatment, has been shown to be related to improved quality of life[6]. However, accurate assessment of CMD is challenging, with a lack of reproducible and accurate techniques. While invasive CAD classification of patients with ischaemia with no obstructive CAD (INOCA) using bolus thermodilution and acetylcholine improves treatment satisfaction, it did not seem to improve patient outcomes in a randomised clinical study[15]. On the contrary, CMD diagnosed with CFR (Doppler flow, cutoff 2.0) is associated with increased rates of major cardiac events and target vessel failure compared to patients/vessels with FFR >0.80 and normal CFR[16]. However, wire-based CFR, unlike FFR, does not appear to have a continuous relationship with clinical outcomes[17]. Unlike CFR, the evidence underlying IMR is strongest for prognostication following PCI in acute coronary syndrome[18]. In stable patients, a high IMR is mainly associated with a poor outcome when combined with a low CFR[19]. We found that patients with isolated CMD had a similar symptom profile and similar myocardial perfusion characteristics by [82]Rb-PET as patients without obstructive epicardial CAD or CMD, both on a patient and vessel level. The latter underscores the need for further research into diagnostic pathways that include CMD diagnosis.

OPTIMAL INVASIVE DIAGNOSES OF CMD

Assessment of coronary physiology with bolus thermodilution has several technical limitations, including but not limited to manual injection of saline and wire positioning. The latter affects transit times and thus inherently IMR, which has been shown to have a broad span of normal values in previous reports, limiting clinical interpretation and reproducibility[20-22]. Microvascular resistance assessment with continuous thermodilution theoretically accounts for epicardial atherosclerosis and is far more reproducible than bolus thermodilution[23,24]. Furthermore, increased microvascular resistance measured with continuous thermodilution correlates to physical limitations and angina in patients without obstructive epicardial CAD[25]. This paper documents that bolus thermodilution identifies CMD in a substantial number of patients with normal myocardial perfusion by [82]Rb-PET, thus questioning its value **(Figure 3)**. Our findings add to the previous Dan-NICAD analysis describing poor correlation between CFR derived from bolus thermodilution and myocardial blood flow reserve measured by [82]Rb-PET (rho 0.11 for RCA, rho 0.34 for LCx, and rho 0.24 for LAD on a per-vessel level in Dan-NICAD 3)[26]. Aside from potential limitations related to bolus thermodilution, the clinical importance of discordant bolus thermodilution and [82]Rb-PET is not well understood but may in part be attributed to applied [82]Rb-PET definitions where small subendocardial defects with intact flow may still be present[27]. Furthermore, a suspicion regarding the presence of functional CMD could be raised from elevated basal flow on [82]Rb-PET, but no clear-cut value for clinical use has been established[10].

CLINICAL IMPLICATIONS

Assuming that bolus thermodilution is a gold standard for invasive assessment of CMD, routine assessment may be

warranted in patients referred to ICA following coronary CTA. The latter includes patients with a normal [82]Rb-PET, as a substantial proportion of patients will have CMD following bolus thermodilution assessment if the current European guideline recommendations are followed. A full 3-vessel assessment with bolus thermodilution may be necessary for a complete diagnostic evaluation for CMD identification, but if CMD is demonstrated in the first interrogated vessel, selective assessment seems sufficient.

Limitations

We were not able to differentiate and identify subendocardial perfusion characteristics using relative subendocardial stress-to-rest ratios as proposed by Gould et al[28]. However, from a theoretical point of view, we would not expect bolus thermodilution to correlate better to stress-to-rest ratios. We did not include vasospasm evaluation with acetylcholine testing. However, our findings still apply to a broad population as acetylcholine testing is not widely adopted. Female sex was underrepresented in our study, which may be of importance as female sex is associated with angina without obstructive epicardial CAD. On the contrary, we included a slightly larger proportion of females compared to the INOCA subanalysis of the ISCHEMIA trial[29]. A distal wire position may lead to a false-positive IMR, and it cannot be excluded that three-vessel interrogation could lead to a false-positive diagnosis of CMD[20]. It cannot be ruled out that epicardial CAD with FFR >0.80 may impact the transit times and thus the CFR- and IMR-related analyses despite adjusting the IMR with Yong's formula. Conversely, IMR and CFR are used in clinical practice independent of epicardial CAD. The latter is in accordance with a preclinical investigation of IMR measurements in porcine models documenting that IMR was not influenced by epicardial stenosis[30]. We only included patients with suspected obstructive disease on coronary CTA, which may have impacted the CMD prevalence. While the variation in study protocol, with guided physiological assessment versus complete 3-vessel assessment, was useful to assess the difference in prevalence of CMD, it may have impacted the remaining presented analyses.

Conclusions

Up to 1 in 2 symptomatic patients referred to invasive coronary angiography based on suspected obstructive epicardial CAD on coronary computed tomography angiography have coronary microvascular disease, as assessed with bolus thermodilution, often with normal myocardial blood flow, as assessed with [82]Rb-PET myocardial perfusion imaging.

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Conflict of interest statement

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Supplementary data

Supplementary Table 1. Invasive parameters stratified by vessel.

Supplementary Table 2. CFR- vs IMR-based CMD diagnosis: ^{82}Rb-PET perfusion according to CMD type.

Supplementary Table 3. SAQ scores at baseline and three months.

Supplementary Table 4. Tabulated angina frequency scores.

Supplementary Table 5. Logistic regression on freedom from angina at 3 months.

Supplementary Figure 1. Stress myocardial blood flow according to CAD classification, stratified by vessel/territory.

The supplementary data are published online at: https://eurointervention.pcronline.com/ doi/10.4244/EIJ-D-24-01155

Supplementary data

Supplementary Table 1. Invasive parameters stratified by vessel.

	RCA	LAD	LCx	p
Bolus thermodilution results when performed in vessels with greater than 30% diameter stenosis				
	RCA	LAD	LCx	*p*
n	78	233	74	
FFR	0.90 [0.83, 0.93]	0.82 [0.75, 0.86]	0.91 [0.87, 0.95]	<0.001
CFR	2.55 [1.52, 3.70]	2.80 [2.00, 3.70]	2.70 [2.00, 3.50]	0.271
IMR	18.00 [13.00, 33.75]	16.00 [10.00, 22.00]	15.50 [11.00, 20.00]	0.006
Bolus thermodilution results when performed in all three vessels routinely				
	RCA	LAD	LCx	*P*
n	111	85	126	
FFR	0.96 [0.94, 0.98]	0.90 [0.86, 0.92]	0.98 [0.96, 1.00]	<0.001
CFR	4.40 [2.75, 6.55]	3.00 [2.00, 4.70]	3.30 [2.22, 4.57]	<0.001
IMR	14.00 [11.00, 20.00]	15.00 [10.00, 23.00]	14.00 [10.00, 21.00]	0.963

Abbreviations as in table 2.

Supplementary Table 2. CFR vs IMR based CMD diagnosis: ^{82}Rb-PET perfusion according to CMD type.

	Coronary flow reserve and index of microvascular resistance				Microvascular resistance reserve		
	CFR<2.5 and IMR<25	CFR$\geq$2.5 and IMR$\geq$25	CFR<2.5 and IMR$\geq$25	p	MRR$\leq$3	MRR>3	P
n	117	46	68		228	477	
PET rest-MBF	1.21 (0.27)	1.07 (0.28)	1.15 (0.31)	0.03	1.16 (0.29)	1.12(0.26)	0.07
PET stress-MBF	2.65 (0.67)	2.79 (0.58)	3.02 (0.64)	<0.01	2.72 (0.69)	2.71 (0.66)	0.78
PET MBFR	2.26 [1.84, 2.59]	2.60 [2.22, 2.95]	2.50 [2.20, 3.09)	0.17	2.34 [2.00, 2.71)	2.40 [2.05, 2.85]	0.12
Stress-MBF <2.0	18 (16.4)	3 (6.7)	3 (4.5)	0.03	29 (13)	66 (14)	0.87

Abbreviations as in table 2.

Supplementary Table 3. SAQ scores at baseline and three months.

	No disease (n=153)	Microvascular disease (n=93)	Epicardial disease (n=150)	Concomitant epicardial and microvascular disease (n=31)	p
Baseline SAQ					
Summary score	71 (15)	72 (14)	71 (15)	66 (17)	0.31
Angina stability score	58 (25)	59 (24)	57 (24)	57 (29)	0.90
Quality of life	58 (21)	60 (21)	61 (21)	55 (22)	0.44
Angina frequency score	77 (18)	79 (18)	76 (19)	73 (21)	0.43
Physical limitations score	76 (20)	78 (15)	77 (16)	72 (20)	0.50
Treatment satisfaction score	73 (9)	74 (8)	73 (9)	75 (8)	0.61
3-months follow-up SAQ					
Summary score	77 (16)	77 (16)	75 (17)	73 (17)	0.58
Angina stability score	62 (21)	63 (23)	62 (25)	61 (23)	0.96
Quality of life	67 (22)	70 (20)	63 (23)	66 (21)	0.12
Angina frequency score	84 (18)	80 (21)	83 (22)	80 (26)	0.43
Physical limitation score	80 (19)	80 (19)	80 (18)	74 (24)	0.40
Treatment satisfaction score	69 (22)	69 (12)	69 (13)	69 (14)	0.97

SAQ denotes Seattle angina questionnaire.

**Supplementary Table 4. Tabulated angina frequency scores.**

		Enrollment	**3 months**
No disease (n=153)	Daily angina	1 (0)	3 (2)
	Weekly angina	35 (23)	20 (13)
	Montly angina	86 (56)	72 (47)
	No angina	31 (20)	58 (38)
CMD (n=93)	Daily angina	2 (2)	4 (4)
	Weekly angina	20 (22)	12 (12)
	Montly angina	55 (59)	52 (56)
	No angina	16 (17)	25 (27)
Epicardial disease (n=150)	Daily angina	5 (3)	7 (5)
	Weekly angina	35 (23)	20 (13)
	Montly angina	82 (55)	58 (39)
	No angina	28 (19)	65 (43)
Concomitant epicardial and microvascular disease (n=31)	Daily angina	1 (3)	3 (10)
	Weekly angina	11 (35)	3 (10)
	Montly angina	15 (48)	13 (42)
	No angina	13 (42)	12 (39)

Abbreviations as in table 1.

Supplementary Table 5. Logistic regression on freedom from angina at 3 months.

	n	OR
No disease (ref)	153	-
CMD	93	0.56 (0.31-1.00)
Epicardial disease (+/- CMD) without revascularization	38	0.71 (0.32-1.55)
Epicardial disease (+/- CMD) with revascularization	143	1.52 (0.94-2.48)

Logistic regression assessing the influence of CAD classification on freedom of angina at 3 months. The model was adjusted for baseline SAQ angina frequency score.
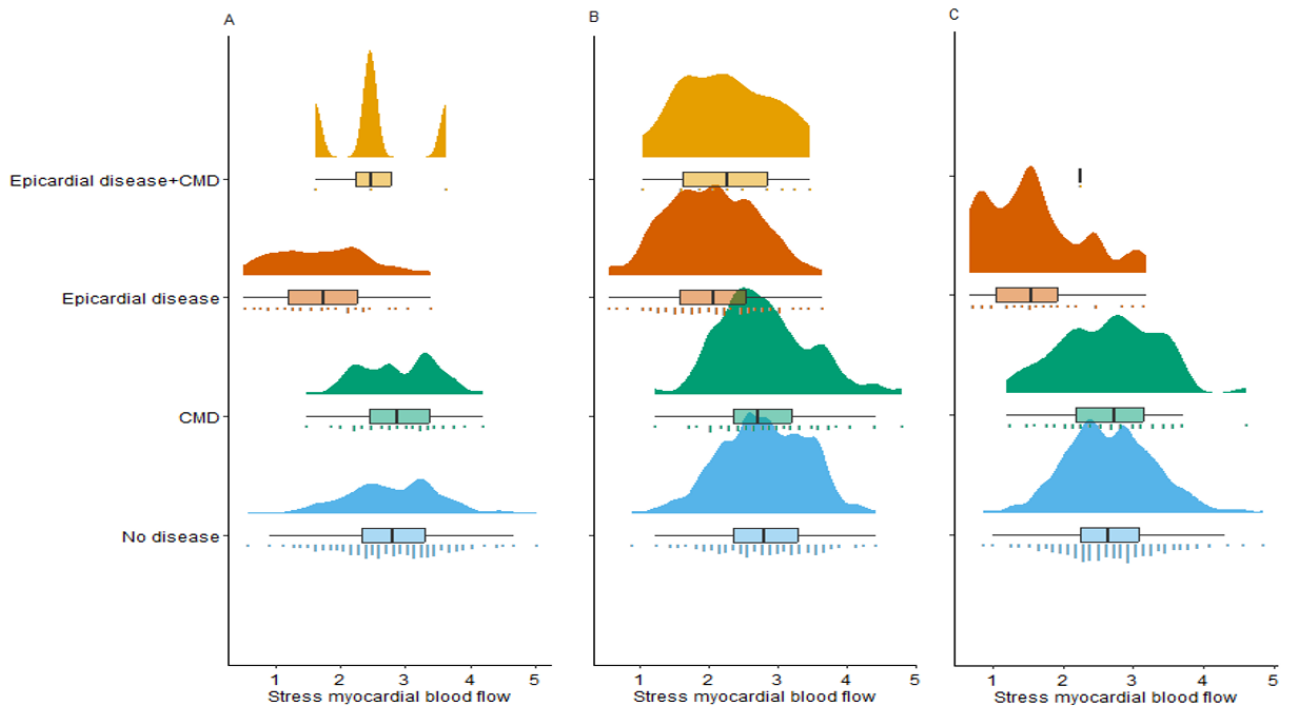
Supplementary Figure 1. Stress myocardial blood flow according to CAD classification, stratified by vessel/territory.

Stress myocardial blood flow by Rb82-PET illustrated with rain-plots (combined density plot, box-plot and jittered point) according to RCA (panel A), LAD (panel B) and LCx (panel C) according to the four groups of invasive CAD classification (y-axis).