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Diagnostic performance of exercise stress testing findings and coronary microvascular dysfunction in patients with angina with non-obstructive coronary artery disease

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ABSTRACT

Background Coronary microvascular dysfunction (CMD) is common among patients with angina with non-obstructive coronary artery disease (ANOCA) and leads to poorer clinical outcomes. Exercise stress testing (EST) was shown to have a high specificity for detecting CMD. However, the relationship between diagnosing CMD using different invasive physiological parameters and thresholds and the association between EST findings and the endotype of CMD remains unknown.

Methods This multicentre, prospective cohort study enrolled 117 patients with ANOCA who underwent EST prior to invasive coronary angiography with functional assessment to measure coronary flow reserve (CFR), the index of microvascular resistance (IMR) and microvascular resistance reserve (MRR)=(CFR/FFR)×($P_{a\ rest}$/$P_{a\ hyper}$). CMD was classified using multiple criteria, including MRR <3.0, CFR <2.5 and CFR <2.0 or IMR ≥25. Diagnostic sensitivity and specificity and the accuracy of EST findings (exercise-induced chest discomfort, ischaemic ECG changes and exercise intolerance) for diagnosing CMD were assessed.

Results The prevalence of CMD was similar under all three definitions. However, structural CMD was more common using MRR <3.0. Ischaemic ECG changes during EST showed an excellent diagnostic accuracy of 86.3% (78.7–92.0%) for detecting CMD, with a sensitivity and specificity of 86.2% (68.3–96.1%) and 86.4% (77.4–92.8%), respectively. Exercise-induced chest discomfort also had a good diagnostic accuracy of 76.1% (95% CI 67.3% to 83.5%); however, it offered no additional value when added to ischaemic ECG changes. EST preferentially identified structural CMD, while functional CMD was more frequently missed.

Conclusions Ischaemic ECG changes during EST performed immediately before invasive functional assessment demonstrated excellent diagnostic accuracy for identifying patients with CMD, particularly the structural endotype.

Trial registration number NCT05841485.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Coronary microvascular dysfunction (CMD) is increasingly recognised among patients with angina with non-obstructive coronary artery disease (ANOCA) and is associated with persistent symptoms and poor outcomes.
⇒ Exercise stress test (EST) was recently shown to have a high specificity for detecting CMD; however, whether this finding is consistent when using alternative definitions of CMD (eg, with microvascular resistance reserve) or with different endotypes of CMD remains unknown.

WHAT THIS STUDY ADDS

⇒ This study showed that the overall prevalence of CMD was comparable across different definitions, while the distribution of CMD endotypes varied significantly.
⇒ During EST, the appearance of either chest discomfort or ischaemic ECG changes had excellent diagnostic accuracy for identifying CMD, with ischaemic ECG changes alone having the best performance.
⇒ Positive findings on EST predominantly identified patients with structural CMD, regardless of the diagnostic criteria.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Future studies should investigate the integration of EST into the diagnostic workflow for patients with ANOCA, examining how it can guide therapeutic decisions and potentially improve outcomes.
⇒ Studies with larger, more diverse populations should also investigate whether similar findings can be extrapolated to non-invasive diagnostic modalities.

INTRODUCTION

The traditional concept of chronic coronary syndrome (CCS) attributed myocardial ischaemia

and ischaemic chest pain (angina pectoris) to fixed, focal and flow-limiting atherosclerotic lesions that obstructed major epicardial artery(ies) or their branches. Over time, our understanding of the pathophysiology of CCS has evolved towards a more complex and dynamic model,[1] and it is now well-recognised that more than half of those with typical angina lack any epicardial coronary obstruction.[2 3] These patients, now re-labelled as having angina with non-obstructive coronary artery disease (ANOCA), exhibit impaired coronary blood flow responses to stress due to various underlying causes, with coronary microvascular dysfunction (CMD) accounting for more than half of the cases.[4–6] Importantly, despite the absence of obstructive lesions, these patients experience a reduced quality of life, frequent hospital visits and a higher risk of major cardiovascular events compared with the general population.[3 7–9]

The 2024 European Society of Cardiology (ESC) guidelines for CCS give a Class Ib recommendation for the invasive assessment of CMD as part of the comprehensive diagnostic evaluation of patients with suspected ANOCA, with the aim to identify those who could benefit from targeted pharmacological therapy, as demonstrated in the CORMICA trial and the ChaMp-CMD study.[1 10 11] However, invasive functional testing is not commonly performed in contemporary practice due to logistical difficulties, fear of complications, increased cost and lack of expertise.[12] Alternatively, non-invasive imaging with echocardiography, cardiac magnetic resonance imaging (CMR) and positron emission tomography (PET) can be used to diagnose CMD; however, significant variations exist in the prevalence of CMD among different modalities and trials. Furthermore, identifying the specific endotype of CMD, which may provide a better guide to individualised treatment strategies, still requires invasive testing.[13 14]

Due to its low sensitivity and specificity, the cardiology community has largely abandoned exercise stress testing (EST) as the default non-invasive test for diagnosing obstructive coronary artery disease (CAD). However, Sinha *et al* recently demonstrated that ischaemic ECG changes during EST in patients without obstructive CAD—previously considered 'false positive EST'—actually indicate the presence of microvascular dysfunction, as characterised by endothelial-dependent or endothelial-independent abnormalities.[15] Notably, this study used a single definition of CMD: coronary flow reserve (CFR) <2.5, leaving the complex relationships between various EST findings, CMD definitions and CMD endotypes unexplored, particularly when incorporating the novel metric microvascular resistance reserve (MRR).[16] MRR was conceptualised to directly assess the vasodilatory reserve of the coronary microcirculation.[17] Its formula incorporates adjustments for the presence of coexisting epicardial CAD and considers the haemodynamic impact of administering potent vasodilators on systemic arterial pressures, which are the main limitations of traditional metrics such as CFR and the index of microvascular resistance (IMR).

Therefore, the current study aims to investigate the relationship between the findings on EST, the diagnosis of CMD and its different endotypes.

METHODS

Study design

This is a multicentre, prospective cohort study of consecutive adult patients (aged 40–80 years) with ANOCA, which was defined as the presence of stable anginal symptoms, a clinical indication for invasive coronary angiography and no haemodynamically significant epicardial coronary artery disease, defined as fractional flow reserve (FFR) >0.80. The study was registered on clinicaltrial.gov (NCT05841485) and conducted at two university hospitals in Lithuania: Klaipeda University Hospital and the Hospital of Lithuanian University of Health Sciences Kaunas Clinics.

Using the method described by Buderer *et al*, and the observation of Sinha *et al*, assuming an expected sensitivity of 40%, specificity of 80% and a CMD prevalence of 40%, with a desired precision of ±15% and a 95% confidence level, the required sample size to reliably estimate sensitivity and specificity were 103 and 46 patients, respectively.[15 18] To account for potential dropout and withdrawal consent, we enrolled 117 patients in the current study.

Patients were excluded if they presented with acute coronary syndrome or had a history of myocardial infarction (MI), a left ventricular ejection fraction (LVEF) ≤40%, known obstructive CAD or a history of coronary artery bypass graft surgery (CABG). Additional exclusion criteria included chronic kidney disease (estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 at screening), active liver injury (aspartate aminotransferase or alanine aminotransferase levels >3 times the upper limit of normal at screening), significant valvular heart disease (ie, moderate or severe aortic or mitral valve stenosis or insufficiency), cardiomyopathy (eg, hypertrophic cardiomyopathy) or pregnancy. Patients with baseline ECG abnormalities preventing interpretation during EST, such as a left bundle branch block, and those with physical limitations preventing them from performing an EST were also excluded.

All patients underwent an EST, followed by invasive coronary angiography, and following the exclusion of obstructive CAD (<50% stenosis on quantitative coronary angiography) and FFR (>0.80), underwent further invasive coronary physiology assessment for CMD using the standardised protocols described below, and then completed the modified Seattle Angina Questionnaire (SAQ-7). Patients were blinded to the results of their EST and physiology assessment.

Exercise stress testing

ESTs were conducted on the same day before the invasive coronary angiography and physiology assessment. The EST was conducted following the American College of Cardiology/American Heart Association (ACC/AHA) guidelines and the Bruce protocol.[19 20] A 12-lead ECG, heart rate and blood pressure were recorded at regular intervals. The tests were supervised and evaluated by board-certified cardiologists. The duration of the EST was timed from the start to the cessation of the protocol. Exercise intolerance was defined as an exercise time of less than 6 min.[21] Exercise-induced chest discomfort was documented when the patient reported chest tightness or chest pain during exercise. Ischaemic ECG changes were defined as ≥0.1 mV horizontal or down-sloping ST-segment depression 80 ms from the J-point (CardioSoft V.6.7 Diagnostic System, GE Healthcare, Illinois, USA). Patients who developed ischaemic ECG changes or exercise-induced chest discomfort were classified as having a positive EST.[20] Patients who did not develop ischaemic ECG changes or chest pain after reaching their target heart rate were classified as having a negative EST, while those who did not develop ischaemic ECG changes or chest pain but did not reach their target heart rate were classified as having an inconclusive test.

Coronary physiology assessment

For all patients, coronary physiology assessments were conducted to the left anterior descending artery (LAD) with the Pressure

Table 1 Definitions of CMD and its endotypes

Definition	Definition of CMD	Definition of structural CMD	Definition of functional CMD	Definition of undetermined CMD
Boerhout *et al*	MRR <3.0	MRR <3.0 and IMR ≥25	MRR <3.0 and IMR <25	NA
EAPCI, ACC/AHA	CFR <2.0 or IMR ≥25	CFR <2.0 and IMR ≥25	CFR <2.0 and IMR <25	CFR ≥2.0 and IMR ≥25
BHF/NIHR/ESC	CFR <2.5	CFR <2.5 and IMR ≥25	CFR <2.5 and IMR <25	NA

ACC, American College of Cardiology; AHA, American Heart Association; BHF, British Heart Foundation; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; EAPCI, European Association of Percutaneous Cardiovascular Interventions; ESC, European Society of Cardiology; IMR, index of microvascular resistance; MRR, microvascular resistance reserve; NIHR, National Institute for Health and Care Research.

Wire X (Abbott Vascular, Santa Clara, California, USA), and the CoroFlow system (Coroventis Research AB, Uppsala, Sweden). CFR and IMR were measured using the standard bolus thermodilution technique.[22 23] Due to institutional protocol restrictions, acetylcholine flow reserve (AChFR) was not performed in the current study. In brief, nitro-glycerine (100 or 200 µg) was administered through the guiding catheter. The calibrated pressure wire was then positioned in the distal two-thirds of the LAD. To calculate IMR and CFR, resting mean transit time (Tmn) was determined by averaging three measurements obtained after at least three bolus injections of 3 mL room temperature saline solution into the coronary artery, with this procedure repeated under hyperaemia induced by the continuous intravenous administration of adenosine (140 µg/kg/min). FFR was also obtained under hyperaemia, with MRR then calculated using the formula: $MRR=(CFR/FFR)\times(P_{a\ rest}/P_{a\ hyper})$.[24] In this formula, $P_{a\ rest}$ and $P_{a\ hyper}$ are aortic pressure at rest and maximum hyperaemia, respectively. MRR, CFR and IMR values were then used to establish the presence of CMD and subcategorise it into structural and functional CMD as per the criteria in table 1.

Modified Seattle Angina Questionnaire

After completing the EST and CMD assessment, all patients were asked to fill out the short version of the SAQ (SAQ-7), assisted by the trained study nurse. The SAQ-7 consists of seven questions divided into three domains: quality of life, physical limitation and angina frequency.[25 26] The score of each domain, as well as the summary score, was calculated with validated formulas.

Study endpoints

The primary endpoint was to evaluate the association between EST findings—namely, ischaemic ECG changes, exercise intolerance and exercise-induced chest pain—and CMD diagnosis as defined by MRR<3.0 (Boerhout and Sinha *et al*) or defined using traditional parameters and criteria endorsed by the ESC, the ACC and AHA, the British Heart Foundation (BHF), the National Institute for Health and Care Research (NIHR), and the European Association of PCI (EAPCI; table 1).[4 16 22 27 28]

Secondary endpoints included the association between EST findings and the CMD subtypes (functional vs structural), the distribution of MRR, CFR and IMR values among patients exhibiting different EST findings and the relationship between EST results and anginal status as assessed by the SAQ-7 questionnaire.

Statistical analysis and sample size calculation

Continuous variables are presented as means (SD) or medians with IQRs according to the distribution and are compared with the Student's t-test or Mann-Whitney U test as appropriate. Categorical variables are presented as frequencies and percentages and compared with χ^2 or Fisher's exact tests as appropriate. For the comparison between EST findings and different CMD definitions, confusion matrixes were used to calculate sensitivity, specificity, positive predictive value (PPV, also known as precision), negative predictive value (NPV), accuracy and likelihood ratios. A two-sided p value <0.05 was considered statistically significant for all tests. Statistical analyses were performed using R statistical software (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study population

Between June 2023 and June 2024, a total of 117 patients with ANOCA were enrolled in the study, with a mean age of 65.95 (11.43) years and 56 (47.9%) female patients (figure 1).

Of the 117 patients, 25 (21.4%) experienced exercise-induced chest discomfort, 29 (24.8%) had ischaemic ECG changes, 75 (64.1%) had exercise intolerance (duration <6 min) and 36 (30.8%) had a positive EST.

A total of 37 patients (31.6%) exhibited an MRR <3.0, among this group were 21 patients (56.8%) having structural CMD (MRR<3.0 and IMR≥25) and 16 (43.2%) with functional CMD (MRR<3.0 and IMR<25). The demographic characteristics (age, sex, height and weight), clinical histories (eg, hypertension, diabetes) and baseline laboratory data were well-matched between patients with and without CMD (tables 2 and 3). The prevalence of CMD was similar regardless of the definition applied (figure 2); however, structural CMD was more common than functional CMD when using the MRR criteria (online supplemental figure 1).

EST findings and CMD

CMD was significantly more prevalent among patients with EST-induced chest discomfort and ischaemic ECG changes, whereas no such difference was observed in those with or without exercise intolerance (figure 3). These two EST findings were also associated with a higher incidence of structural CMD (figure 3), whereas exercise intolerance showed no such distinction (figure 3).

Table 4 shows the diagnostic performance of EST findings. Ischaemic ECG changes alone yielded the highest overall accuracy (86.3%) with a sensitivity and specificity of 86.2% and 86.4%, respectively. Adding chest discomfort improved specificity to 87.7% but reduced sensitivity (75.0%), while combining all three EST findings further lowered sensitivity (38.8%) with minimal gain in specificity (87.5%) (figure 4). Secondary analyses using alternative CMD definitions showed similar trends in diagnostic performance (online supplemental tables 1 and 2, online supplemental file 2). Across all definitions, functional CMD was more frequently missed by EST findings compared with structural CMD (figure 3, online supplemental figures 2 and 3).

EST findings and coronary physiology indices

As summarised in table 5. The median FFR was 0.89 [0.86, 0.95], with no patients having an FFR ≤0.80. The median

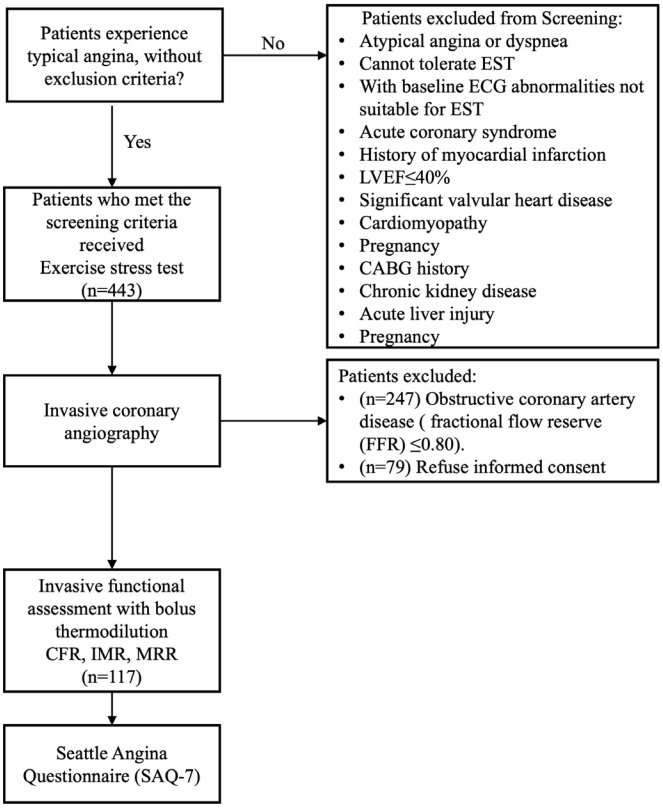

Figure 1 Flowchart of patient enrolment and assessment process. CABG, coronary artery bypass graft surgery; CFR, coronary flow reserve; LVEF, left ventricular ejection fraction; IMR, index of microvascular resistance; MRR, microvascular resistance reserve.

MRR, CFR and IMR were 3.64 [2.71, 4.2], 2.71 [1.95, 2.94] and 19.00 [14.00, 24.00], respectively. Patients with ischaemic ECG changes or EST-induced chest discomfort exhibited significantly lower CFR and MRR and higher IMR compared with those without such findings. In contrast, patients with or without exercise intolerance had similar physiological profiles.

EST findings and anginal symptoms

The results of the SAQ-7 questionnaire are presented in table 6. Patients with EST-induced chest discomfort had significantly lower SAQ summary scores and domain scores compared with those without EST-induced chest discomfort, with similar trends seen between patients with and without ischaemic ECG changes. In contrast, patients with exercise intolerance had similar SAQ-7 results to those without exercise intolerance.

DISCUSSION

In this prospective cohort study of 117 patients with ANOCA, we explored the intricate relationships between the findings on EST, the diagnosis of CMD using various criteria and parameters, and the different CMD endotypes. The key findings of our study are as follows:

1. Although the overall prevalence of CMD remained consistent across different definitions, the distribution of CMD endotypes varied.
2. Both chest discomfort and ischaemic ECG changes on EST had excellent diagnostic accuracy for identifying CMD. Notably, ischaemic ECG changes alone provided reasonable diagnostic performance for CMD, suggesting its potential as a simple, non-invasive, low-cost screening tool.
3. Positive EST findings preferentially identified structural CMD, regardless of the diagnostic criteria.

Table 2 Characteristics of angina with non-obstructive coronary arteries patients classified by CMD (MRR <3.0)

Characteristic	Overall (n=117)	No CMD (MRR ≥3.0) (n=80)	CMD (MRR <3.0) (n=37)
Sex (female)	56 (47.9%)	41 (51.3%)	15 (40.5%)
Age (years)	65.95 (11.43)	66.86 (11.53)	63.97 (11.11)
Body mass index (kg/m^2)	26.83 [25.15, 29.41]	26.79 [25.33, 29.41]	26.84 [24.54, 30.04]
Arterial hypertension	64 (54.7%)	40 (50.0%)	24 (64.9%)
History of PCI	14 (12.0%)	11 (13.8%)	3 (8.1%)
History of stroke	8 (6.8%)	4 (5.0%)	4 (10.8%)
History of diabetes mellitus	22 (18.8%)	12 (15.0%)	10 (27.0%)
History of dyslipidaemia	71 (60.7%)	51 (63.8%)	20 (54.1%)
Smoker (former/current)	62 (53.0%)	44 (55.0%)	15 (40.5%)
History of alcohol abuse	7 (6.0%)	6 (7.5%)	1 (2.7%)
CCS			
I	28 (23.9%)	16 (20.0%)	12 (32.4%)
II	65 (55.6%)	43 (53.8%)	22 (59.5%)
III	24 (20.5%)	21 (26.3%)	3 (8.1%)
IV	0 (0.0%)	0 (0.0%)	0 (0.0%)
Medication prior to admission			
Beta-blocker	48 (41.0%)	30 (37.5%)	18 (48.7%)
ACEi/ARB	55 (47.0%)	33 (41.3%)	22 (59.5%)
CCB	49 (41.9%)	32 (40.0%)	17 (46.0%)
Mineralocorticoid antagonist	5 (4.3%)	2 (2.5%)	3 (8.1%)
Statin	73 (62.4%)	52 (65.0%)	21 (56.8%)
Aspirin	51 (43.6%)	35 (43.8%)	16 (43.2%)
Nitrate	22 (18.8%)	14 (17.5%)	8 (21.6%)

Values are presented as n (%) for categorical variables and as mean (SD) or median [first quartile, third quartile] for numeric variables.
ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; CCS, Canadian Cardiovascular Society grading of angina pectoris; CMD, coronary microvascular dysfunction; MRR, microvascular resistance reserve; PCI, percutaneous coronary intervention.

Table 3 Laboratory, echocardiographic and exercise stress test parameters of patients with angina with non-obstructive coronary arteries, categorised by CMD status

Parameters	Overall (n=117)	No CMD (MRR ≥3.0) (n=80)	CMD (MRR <3.0) (n=37)
Laboratory parameters			
Haemoglobin (g/L)	135.51 (18.99)	135.82 (18.2)	134.84 (20.83)
White blood cell count (10^9/L)	8.94 [7.59, 11.25]	9.02 [7.59, 11.44]	8.61 [7.59, 10.95]
Platelets (10^9/L)	241.00 [200.00, 264.00]	241 [195.5, 263]	251 [213, 268]
Creatinine clearance (mL/min)	46.10 [38.70, 54.70]	45.7 [39.45, 54.33]	46.1 [37.5, 57.1]
Hs-CRP (mg/L)	3.55 [2, 6.34]	3.66 [2.33, 6.16]	2.81 [1.36, 6.71]
Echocardiographic parameter			
Left ventricular ejection fraction (%)	55.00 [51.00, 55.00]	55 [54.00, 55.25]	55 [50.00, 55.00]
Exercise stress test parameters			
Duration of stress test (min)	5.00 [4.00, 6.00]	5.00 [4.00, 6.00]	5.00 [5.00, 6.00]
Exercise-induced chest discomfort	25 (21.8%)	8 (10.0%)	17 (46.0%)
Ischaemic ECG changes	29 (24.8%)	4 (5.0%)	25 (67.6%)
Exercise intolerance	75 (64.1%)	49 (61.3%)	26 (70.3%)
Exercise stress test results			
Positive	36 (30.8%)	9 (11.3%)	27 (73.0%)
Negative	58 (49.6%)	55 (68.8%)	3 (8.11%)
Inconclusive	23 (19.7%)	16 (20.0%)	7 (18.9%)

Values are presented as n (%) for categorical variables and mean (SD) or median [first quartile, third quartile] for continuous variables.
CMD, coronary microvascular dysfunction; Hs-CRP, hight sensitivity C-reactive protein; MRR, microvascular resistance reserve.

Collectively, these findings challenge the traditional perception of EST being a poor diagnostic tool for obstructive CAD by highlighting its potential role in identifying CMD in patients with ANOCA, who may then warrant invasive functional assessment.

Prevalence of CMD diagnosis and the distribution of CMD endotypes with different definitions

The inability to directly visualise the coronary microvasculature has prompted the development of multiple invasive and non-invasive modalities,[29] which, due to their inherent differences, has led to a wide variation in the criteria used to define CMD, as well as in its reported prevalence.[30] In a large meta-analysis, the median prevalence of CMD was 41%, which is consistent with our findings.[31] CFR with bolus thermodilution (CFR_{thermo}) is the most commonly used invasive method to assess CMD, and this has received a Class Ib recommendation in the 2024 ESC CCS guidelines.[1] In the absence of obstructive epicardial disease, a CFR_{thermo} ≥2.5 is considered normal, while a CFR_{thermo} <2.0 is abnormal[30]; consequently, the EAPCI consensus and the ACC/AHA chest pain guidelines define CMD by a CFR_{thermo} <2.0 or an IMR ≥25.[22 27] Notably, Rahman *et al* showed that patients having a CFR_{thermo} within the grey zone (ie, 2.0–2.5) are physiologically indistinguishable from those with a CFR_{thermo} <2.00.[13] Additionally, Demir *et al* demonstrated that when compared with Doppler-derived CFR ($CFR_{Doppler}$), the optimal CFR_{thermo} threshold for CMD was <2.50.[32] Thus, the BHF/NIHR and the 2024 ESC guidelines endorsed the threshold of CFR_{thermo} <2.50.[33]

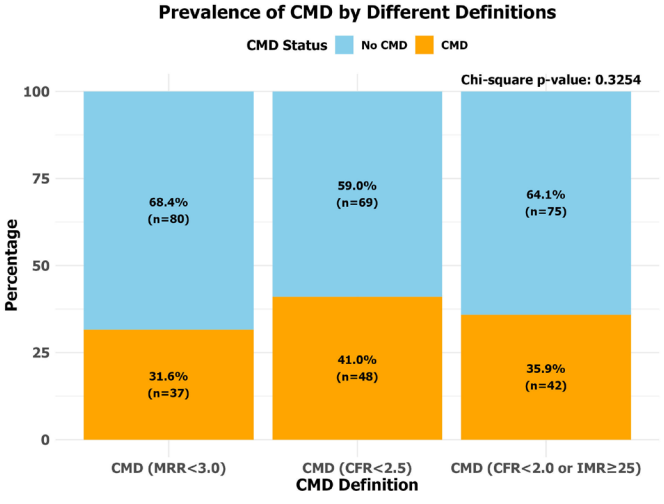

Figure 2 Prevalence of CMD by different definitions (from left to right: with MRR <3.0, with CFR <2.5, and with CFR <2.0 or IMR ≥25, respectively). CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; IMR, index of microvascular resistance; MRR, microvascular resistance reserve.

Our study was the first to compare the prevalence of CMD defined using MRR and CFR, and while we showed similar prevalence, MRR tended to classify fewer patients as having CMD, while the use of CFR identified more patients with the functional endotype of CMD. The optimal threshold of MRR to identify CMD has been increasingly established by recent literature. Boerhout *et al* demonstrated the prognostic value of MRR <3.0 in the ILIAS registry, which, similar to our study, used bolus thermodilution to derive MRR rather than the continuous thermodilution method.[16] Recently, Sinha *et al* demonstrated that an MRR <3.0 accurately predicted maladaptive exercise physiology and response to anti-anginal therapy in patients with ANOCA. Specifically, an MRR <3.0 showed high diagnostic accuracy for exercise-related coronary perfusion abnormalities (sensitivity 75%, specificity 95%), and an MRR <3.2 was predictive of ischaemia on stress perfusion CMR. While an MRR <3.0 has been shown to be prognostically important and corroborates with the validation study of de Vos *et al*,[16 24 34] the cut-off value still needs to be adapted in specific conditions. As demonstrated by Eerdekens *et al*, the optimal cut-off for MRR obtained immediately after ST-segment elevation MI was 1.25.[35]

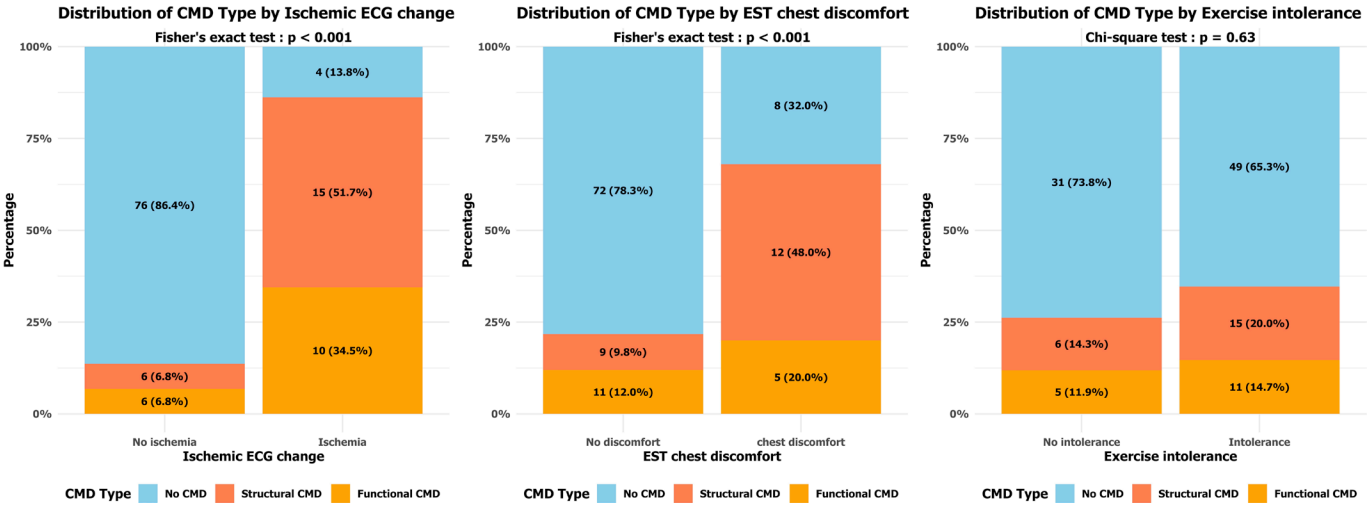

Figure 3 Distribution of coronary microvascular dysfunction (CMD) endotype among patients with different exercise stress testing (EST) findings.

Diagnostic performance of EST findings for CMD

The association between EST and microvascular dysfunction has long been investigated, but diagnostic performance varies widely, with sensitivities ranging from 20% to 60% and specificities from 50% to 100%.[15 36–39] Compared with the recent work of Sinha *et al*, our study similarly demonstrated a high specificity (76% vs 77%) of ischaemic ECG changes during EST for detecting endothelium-independent CMD (defined as CFR <2.5), while showing a notably higher sensitivity (93% vs 40%). It is important to note that in Sinha *et al*, when CMD was defined more broadly to include both endothelium-independent and/or endothelium-dependent dysfunction (CFR <2.5 and/or AChFR ≤1.5), the sensitivity and specificity were 41% and 100%, respectively.[15] Several factors likely explain the divergence in findings across studies. First, diagnostic modality matters: for example, Lopez *et al* reported low sensitivity (22.5%) yet high specificity (76.2%) when using PET-defined global CFR <2.0. Lopez *et al*'s[39] definitions of CMD vary. Early studies often defined CMD broadly as impaired hyperaemic flow with no epicardial stenosis—potentially confounding microvascular disease with epicardial vasospasm.[40] More recent approaches differentiate endothelium-independent CMD (reduced CFR) from endothelium-dependent CMD (reduced acetylcholine-induced flow reserve), yet CFR thresholds between 2.0 and 2.5 remain a 'grey zone,' and some definitions incorporate IMR as a criterion.[22 38]

Nevertheless, for endothelium-independent CMD, most studies using invasive functional tests report consistently high specificity for EST, especially when ischaemic ECG changes alone define a positive test, echoing our findings.[15 36] By contrast, results for endothelium-dependent CMD are more heterogeneous: Ong *et al* reported moderate sensitivity (57.5%) and specificity (62%), while Cassar and Sinha *et al* found lower sensitivity but higher specificity.[15 36 41] This discrepancy likely reflects not only the underlying physiological differences of endothelium-dependent CMD but also substantial variations in diagnostic methodology. Ong *et al* diagnosed CMD based solely on clinical symptoms and ischaemic ECG changes during acetylcholine bolus infusions without directly measuring coronary flow. In contrast, Cassar and Sinha *et al* employed quantitative flow assessments, defining CMD as a <50% increase in coronary blood flow during graded acetylcholine infusions—a method more widely endorsed in current guidelines.

Unlike ischaemic ECG changes, the diagnostic utility of other EST findings—such as exercise-induced chest pain and exercise intolerance—remains far less well-defined. Miner *et al* showed that exercise intolerance can aid CMD diagnosis; however, protocol-specific factors may influence results.[21] In our cohort, over 60% of patients exhibited exercise intolerance, possibly reflecting the steep workload increments of the Bruce protocol. Such abrupt increases may limit diagnostic discrimination, and future studies using alternative protocols may offer clearer

Table 4 The diagnostic performance of EST findings for CMD

	Ischaemic ECG changes Value (95% CI)	Exercise-induced chest discomfort value (95% CI)	Exercise intolerance value (95% CI)	Positive EST value (95% CI)	All three combined value (95% CI)
Sensitivity	86.2% (68.3% to 96.1%)	68.0% (46.5% to 85.1%)	34.7% (24.0% to 46.5%)	75.0% (57.8% to 87.9%)	38.8% (28.4% to 50.0%)
Specificity	86.4% (77.4% to 92.8%)	78.3% (68.4% to 86.2%)	73.8% (58.0% to 86.1%)	87.7% (78.5% to 93.9%)	87.5% (71.0% to 96.5%)
PPV	67.6% (50.2% to 82.0%)	45.9% (29.5% to 63.1%)	70.3% (53.0% to 84.1%)	73.0% (55.9% to 86.2%)	89.2% (74.6% to 97.0%)
NPV	95.0% (87.7% to 98.6%)	90.0% (81.2% to 95.6%)	38.8% (28.1% to 50.3%)	88.8% (79.7% to 94.7%)	35.0% (24.7% to 46.5%)
Accuracy	86.3% (78.7% to 92.0%)	76.1% (67.3% to 83.5%)	48.7% (39.4% to 58.1%)	83.8% (75.8% to 89.9%)	52.1% (42.7% to 61.5%)
PLR	6.32% (3.83% to 12.15%)	3.13% (1.89% to 5.26%)	1.32% (0.69% to 2.52%)	6.08% (3.36% to 12.21%)	3.11% (1.23% to 10.81%)
NLR	0.16% (0.04% to 0.34%)	0.41% (0.19% to 0.69%)	0.89% (0.70% to 1.16%)	0.29% (0.14% to 0.48%)	0.70% (0.57% to 0.89%)

Positive EST is defined as either ischaemic ECG changes or exercise-induced chest discomfort; all three combined is defined by the combination of ischaemic ECG changes, exercise-induced chest discomfort and exercise intolerance.
CMD, coronary microvascular dysfunction; EST, exercise stress testing; NLR, negative likelihood ratio; NPV, negative predictive value; PLR, positive likelihood ratio; PPV, positive predictive value.

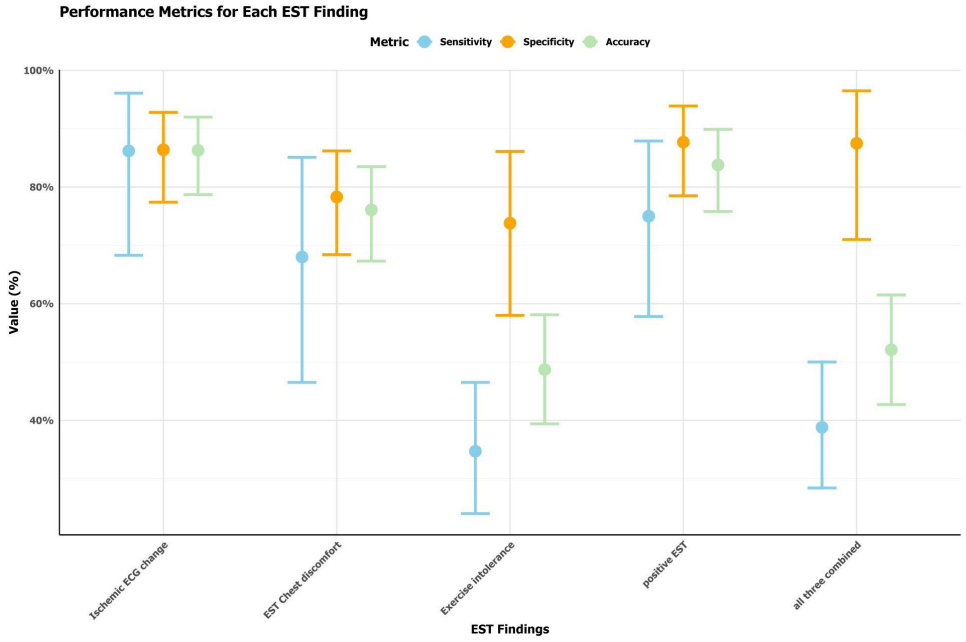

Figure 4 Diagnostic performance of EST findings. EST, exercise stress test, positive EST is defined as either having exercise-induced chest discomfort or ischaemic ECG changes.

stratification between CMD endotypes. Third, patient populations differ; for instance, Pargaonkar *et al* noted higher sensitivity but lower specificity in women, and patients' comorbidities and symptomology could also influence diagnostic performance.[21 38] Lastly, the timing between EST and invasive assessment significantly impacts sensitivity. In Cassar *et al*, with a 6 month delay, sensitivity was 20%, whereas specificity remained 80%, while in Sinha *et al* (median 29 days' 'after' invasive tests) sensitivity was 40% and specificity 77%.[15 36] In our study, conducted on the same day as the invasive assessment, sensitivity reached 93% while specificity was 76%.

Differential identification of CMD endotypes with EST findings

Although PET is generally considered the gold standard for assessing coronary microvascular function, CMD endotypes (functional vs structural) can only be differentiated invasively. Functional CMD is characterised by increased resting flow with enhanced nitrous oxide (NO) synthase activity at rest and impaired vasodilatory reserve, whereas structural CMD is marked by reduced coronary flow during exercise due to endothelial dysfunction. Boerhout *et al* showed that both endotypes have an equivalent risk for major adverse cardiac events at 5 years, while Lee *et al* and Hong *et al* showed a worse outcome in patients with structural CMD.[16 42 43] Of note, while both endotypes of CMD are commonly treated with the same pharmacologic agents, recent data from the randomised, phenotype-blinded crossover ChaMP-CMD trial suggest that treatment response may vary.[10 11] In this study, only patients with CMD (CFR <2.5) showed clinically meaningful improvements in exercise time and SAQ, while patients with normal CFR did not. Among patients with CMD, functional CMD responded equally well to amlodipine and ranolazine, whereas structural CMD showed a trend towards greater benefit with amlodipine. These findings support an endotype-stratified treatment strategy, which may help personalise anti-anginal therapy. Further studies exploring device-based therapies (eg, coronary sinus reducers) in larger CMD populations are warranted. In the current study, ischaemic ECG changes and chest discomfort during EST were more frequently identified with structural CMD, while functional CMD was more likely to be missed. This disparity may reflect the underlying pathophysiological continuum of CMD. In line with the bimodal model proposed by Sezer *et al* in their study of the diabetic population, early-stage CMD typically presents as functional CMD, whereas longer disease duration and vascular remodelling give rise to structural CMD.[44] These more advanced alterations likely increase susceptibility to ischaemia during exertion. Additionally, the low workload achieved during our study may be insufficient to provoke the same level of myocardial stress as pharmacological agents that are required

Table 5 Physiological parameters in patients with different EST findings

	Ischaemic ECG changes			Exercise-induced chest discomfort			Exercise intolerance		
Metrics	No	Yes	P value	No	Yes	P value	No	Yes	P value
FFR	0.89 (0.86–0.95)	0.87 (0.84–0.94)	0.242	0.9 (0.86–0.95)	0.86 (0.83–0.94)	0.049	0.88 (0.85–0.94)	0.9 (0.86–0.97)	0.142
CFR	2.85 [2.6–3)	1.73 (1.44–1.95)	<0.001	2.81 (2.19–2.97)	1.98 (1.58–2.64)	<0.001	2.76 (2–2.88)	2.66 (1.91–2.97)	0.952
IMR	18 (12–22.25)	35 (15–47)	<0.001	18 (13–23)	35 (15–47)	0.011	17.5 (12–23)	20 (14–29)	0.341
MRR	3.92 (3.31–4.34)	2.36 (2.14–2.83)	<0.001	3.89 (3.2–4.28)	2.66 (2.28–3.12)	<0.001	3.68 (3.01–4.17)	3.62 (2.57–4.31)	0.787

Positive EST is defined as either ischaemic ECG changes or exercise-induced chest discomfort; all three combined is defined by the combination of ischaemic ECG changes, exercise-induced chest discomfort and exercise intolerance.
CFR, coronary flow reserve; FFR, fractional flow reserve; IMR, index of microvascular resistance; MRR, microvascular resistance reserve .

Table 6 SAQ-7 scores in patients with different EST findings

	Ischaemic ECG changes			Exercise-induced chest discomfort			Exercise intolerance		
Metrics	No	Yes	P value	No	Yes	P value	No	Yes	P value
SAQ7	69.44 (63.06–72.5)	48.33 (45.56–52.78)	<0.001	67.78 (56.53–72.08)	51.11 (45.56–63.06)	<0.001	65 (53.89–71.11)	66.39 (52.08–71.94)	0.927
SAQ7PL	75 (66.67–83.33)	50 (41.67–66.67)	<0.001	75 (66.67–83.33)	58.33 (50–66.67)	<0.001	75 (66.67–81.25)	75 (58.33–83.33)	0.524
SAQ7AF	70 (70–80)	70 (60–70)	<0.001	70 (70–80)	70 (60–70)	0.008	70 (70–80)	70 (70–80)	0.462
SAQ7QL	62.5 (50–62.5)	25 (25–37.5)	<0.001	62.5 (37.5–62.5)	25 (25–50)	<0.001	50 (28.12–62.5)	50 (25–62.5)	0.964

EST, exercise stress testing; SAQ, Seattle Angina Questionnaire.

to detect functional CMD.[45] Using alternative protocols that involve a more gradual increase in workload (eg, the Naughton protocol) may improve the diagnostic performance in identifying functional CMD.[46] Differential diagnostic performance would be an issue when endotype-specific therapies become available.

Limitations

Our study has several limitations. First, our population was small and limited to patients presented with typical angina, which represents only 10–25% of patients with chest pain and has been shown to have a higher prevalence of CMD, limiting the generalisability of the findings.[1 37] Second, we could not assess acetylcholine-induced vessel spasm despite knowing its strong correlation with exercise tests due to strict regulatory constraints, which prevented a comprehensive assessment of endothelial-dependent CMD and epicardial vasospasm. In clinical practice, CMD and epicardial vasospasm often overlap, and categorising patients into endothelial-dependent CMD, endothelial-independent CMD, and mixed types should be pursued. Third, we could not fully process the vast amounts of data from the EST; factors such as blood pressure changes, oxygen consumption and metabolic equivalents need to be further investigated. Fourth, the SAQ was performed after the ANCOA diagnosis and inclusion in the study; thus, it may be influenced by procedure-related anxiety. Lastly, there are no data available regarding the relationship between EST and coronary microvascular function (MRR and CFR) derived from continuous thermodilution, which, in a head-to-head comparison study by Jansen *et al*, was only modestly associated with the data derived from bolus thermodilution.[47]

CONCLUSION

Ischaemic ECG changes during EST performed immediately before invasive functional assessment demonstrated excellent diagnostic accuracy for identifying patients with CMD, particularly structural CMD. However, the complexities surrounding the timing of EST and the extrapolation to other diagnostic modalities require further investigation. Future studies should focus on whether integrating EST into ANOCA management workflows could enhance diagnostic efficiency and improve patient outcomes.

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