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Accuracy of non-invasive stress testing in women and men with angina in the absence of obstructive coronary artery disease☆

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ABSTRACT

Objective: While >20% of patients presenting to the cardiac catheterization laboratory with angina have no obstructive coronary artery disease (CAD), a majority (77%) have an occult coronary abnormality (endothelial dysfunction, microvascular dysfunction (MVD), and/or a myocardial bridge (MB)). There are little data regarding the ability of noninvasive stress testing to identify these occult abnormalities in patients with angina in the absence of obstructive CAD.

Methods: We retrospectively evaluated 155 patients (76.7% women) with angina and no obstructive CAD who underwent stress echocardiography and/or electrocardiography before angiography. We evaluated Duke treadmill score, heart rate recovery (HRR), metabolic equivalents, and blood pressure response. During angiography, patients underwent invasive testing for endothelial dysfunction (decrease in epicardial coronary artery diameter >20% after intracoronary acetylcholine), MVD (index of microcirculatory resistance ≥25), and intravascular ultrasound for the presence of an MB.

Results: Stress echocardiography and electrocardiography were positive in 58 (43.6%) and 57 (36.7%) patients, respectively. Endothelial dysfunction was present in 96 (64%), MVD in 32 (20.6%), and an MB in 83 (53.9%). On multivariable logistic regression, stress echo was not associated with any abnormality, while stress ECG was associated with endothelial dysfunction. An abnormal HRR was associated with endothelial dysfunction and MVD, but not an MB.

Conclusion: Conventional stress testing is insufficient for identifying occult coronary abnormalities that are frequently present in patients with angina in the absence of obstructive CAD. A normal stress test does not rule out a non-obstructive coronary etiology of angina, nor does it negate the need for comprehensive invasive testing.

1. Introduction

More than 20% of patients undergoing coronary angiography (CA) have no significant obstructive coronary artery disease (CAD) despite anginal symptoms [1]. Several occult coronary abnormalities can be identified in these patients, including endothelial dysfunction, microvascular dysfunction (MVD), and/or a myocardial bridge (MB), which may explain their symptoms [2]. Previous studies have reported worse outcomes in this patient population [3], with a higher burden of hospitalization, repeat CA, and higher healthcare cost [4,5]. Current clinical practice guidelines are also not helpful in the management of these patients since current diagnostic criteria for CAD are not met [6]. Invasive cardiac catheterization including endothelial function testing, coronary physiology measurements, and intravascular ultrasound (IVUS) are suggested to be the gold standard tests for identifying these occult coronary abnormalities [7–9].

Stress echocardiography (echo) and stress electrocardiography (ECG) are non-invasive tests considered integral in the evaluation of patients with known or suspected CAD [10]. The diagnostic value of these

Abbreviations: CA, coronary angiography; CAD, coronary artery disease; DTS, duke treadmill score; ECG, electrocardiogram; FFR, fractional flow reserve; HRR, heart rate recovery; IMR, index of microcirculatory resistance; IVUS, intravascular ultrasound; METs, metabolic equivalents; MVD, microvascular dysfunction; MB, myocardial bridge; NPV, negative predictive value; PPV, positive predictive value; SNS, sympathetic nervous system; Tmn, mean transit time; WMSI, wall motion score index.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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tests has been proven in identifying obstructive CAD, but little data are available regarding their ability to evaluate the source of angina in patients with non-obstructive CAD. A previous study by Cassar et al. reported that noninvasive stress tests have limited diagnostic accuracy for identifying coronary vasomotor dysfunction in patients with no obstructive CAD [11]. Specifically, they found that stress echo, stress ECG, and stress nuclear imaging were not helpful in identifying endothelium-dependent dysfunction (decrease in coronary blood flow ≤50% after intracoronary acetylcholine (Ach)), as well as endothelium-independent dysfunction (coronary flow reserve (CFR) ≤2.5 after intracoronary adenosine). This study has never been replicated, nor has it been evaluated using more contemporary invasive methods and more comprehensive non-invasive measures.

Our aim was to investigate the diagnostic value of comprehensive noninvasive stress testing, including stress echo, stress ECG, and non-ECG stress testing parameters in identifying symptomatic women and men with non-obstructive CAD who underwent contemporary invasive testing for an occult coronary abnormality as a cause of their angina.

2. Methods

2.1. Study population

We retrospectively analyzed 155 adult patients (133 stress echo, 22 exercise treadmill tests) with typical (64.9%) or atypical (35.1%) angina who had been found to have non-obstructive CAD (stenosis <50%) on CA. Patients were electively referred to the cardiac catheterization for CA because of a clinical suspicion of coronary ischemia based on persistent anginal symptoms for at least three months despite medical therapy with or without an abnormal stress test. A baseline coronary angiogram was performed via the femoral artery to rule out obstructive CAD in the right and left coronary arteries. These patients additionally underwent invasive testing to evaluate for an underlying coronary pathophysiology as a cause of their angina, including endothelial dysfunction, MVD, or an MB [2]. We excluded those with an acute coronary syndrome, prior heart transplantation, coronary artery bypass grafting, renal insufficiency (creatinine >1.5 mg/dL), EF <55%, or another likely explanation of angina such as pulmonary hypertension, hypertrophic cardiomyopathy, or valvular heart disease.

Stress tests were ordered at the discretion of the treating physician as an evaluation for angina. The stress tests included an exercise or dobutamine stress echo, or an exercise treadmill test, according to standard laboratory protocols. All stress tests were performed before invasive coronary testing. All patients ultimately underwent CA, either because of a positive stress test or because of persistent anginal symptoms despite a negative stress test. The study was approved by the Stanford Institutional Review Board, and informed, written consent was obtained from all patients.

2.2. Invasive coronary testing

After CA, patients underwent further invasive evaluation for endothelial dysfunction, MVD, and an MB, as described previously [2]. In brief, we tested coronary endothelial function by administering up to 200 μg of intracoronary Ach into the left main coronary artery. Endothelial dysfunction was diagnosed if the epicardial coronary artery diameter decreased by >20% compared with baseline on quantitative coronary angiography [12].

Next, we measured the index of microcirculatory resistance (IMR) in the left anterior descending artery (LAD) using a pressure-temperature sensor guidewire (Certus Pressure Wire, St. Jude, St. Paul, MN). Resting mean transit time (Tmn) and hyperemic Tmn were

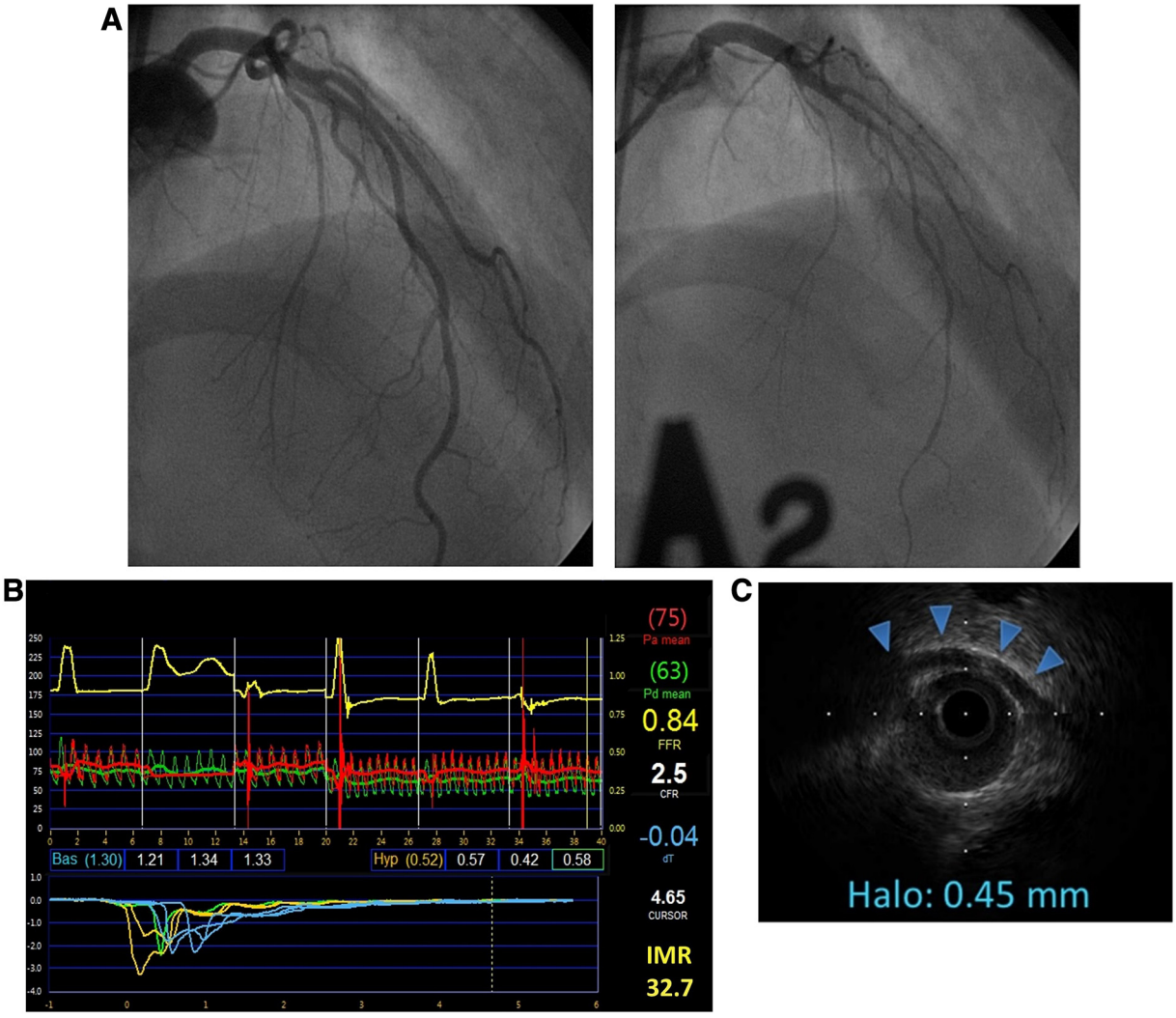

Fig. 1. Demonstrative example of occult coronary abnormalities in patients with angina in the absence of obstructive CAD. (A) Coronary angiogram with diffuse vasoconstriction after 100 μg intracoronary acetylcholine demonstrating diffuse epicardial endothelial dysfunction. (B) Coronary physiology measurements demonstrating microvascular dysfunction with an IMR of 32.7. (C) Still frame of intravascular ultrasound (IVUS) inside a myocardial bridge. Arrows point to characteristic echolucent half-moon sign (halo), with a thickness of 0.45 mm.

calculated by administering 3 ml of intracoronary saline. Maximal hyperemia was achieved using intravenous adenosine. Simultaneous measurements of mean aortic pressure (Pa, by guiding catheter) and mean distal coronary pressure (Pd, by pressure wire) were also made during maximal hyperemia. IMR was calculated as the Pd at maximal hyperemia divided by the inverse of the hyperemic Tmn [13]. MVD was defined as an IMR ≥25 [14]. IMR was chosen over CFR in defining the presence of MVD because it has been shown to be a more accurate measure of the coronary microvasculature and is not affected by sex differences in resting coronary flow [14,15].

IVUS was performed with a 40-MHz mechanical transducer ultrasound catheter (Boston Scientific, Marlborough, MA) in the LAD. All measurements were performed offline by the Stanford IVUS Core Laboratory, blinded to other testing. The presence of an MB was defined by the presence of an echolucent half-moon sign and systolic compression ≥10% [16]. Fig. 1 shows an example of endothelial dysfunction, MVD, and an MB.

2.3. Stress echocardiography testing

Stress echocardiography was performed according to the American Society of Echocardiography recommendations [17]. A standard Bruce protocol was used for exercise testing [18]. Patients exercised until their heart rate reached 85% of maximum predicted for age or until the development of exercise-limiting symptoms. For dobutamine stress echo, dobutamine was administered starting at a dose of 5 μg/kg/min and increased to up to 50 μg/kg/min, with up to 1 mg of atropine given as needed to reach target heart rate [17].

Echocardiography was performed using a commercially available echo system (Philips Healthcare, Andover, MA). An average of 5 to 10 beats per loop was recorded at rest and post-stress. All standard echocardiographic views were obtained when possible and analyzed on an offline Xcelera workstation at normal speed, in slow motion, and frame-by-frame. The left ventricle was divided into 16 segments [19]. Segmental wall motion was scored as: normal = 1; hypokinetic = 2; akinetic = 3; and dyskinetic = 4. Inadequately visualized segments were not scored. Stress echo was considered positive when one ventricular segment score increased by ≥ one grade at peak stress. The wall motion score index (WMSI) was derived by dividing the sum of individual visualized segment scores by the number of visualized segments [20].

We also analyzed a subgroup of stress echocardiograms for the presence of focal septal buckling with apical sparing during end-systole to early-diastole [21]. These images were analyzed by a senior echocardiologist (I.S.), who was blinded to other testing.

2.4. Stress electrocardiography testing

A 12 lead ECG was obtained at each stage during exercise. The PR-segment was considered as an isoelectric line and ST-segment amplitude was measured at 60 ms from the J point. A positive ECG was defined as the appearance of horizontal/downsloping ST-segment depressions of ≥1 mm for an exercise study and ≥0.5 mm for a dobutamine study in at least two contiguous leads for three consecutive beats at maximum achieved heart rate [10]. Interobserver agreement for ECG coding reached substantial, with a kappa score of 0.63.

2.5. Non-electrocardiographic exercise parameters

In patients who underwent exercise stress testing (with or without echo), we analyzed non-ECG exercise parameters, including the Duke Treadmill Score (DTS), heart rate recovery (HRR), metabolic equivalents (METs), and blood pressure response. The DTS was calculated as exercise time × (5 × ST-segment deviation) − (4 × exercise angina), with 0 = no angina, 1 = non-limiting angina, and 2 = exercise-limiting angina [22]. DTSs were categorized as low risk (≥+5), moderate risk (−10 to +4) and high risk (≤−11). HRR was defined as peak HR minus HR one minute into recovery [23,24]. Abnormal HRR was defined as a decrease in the HR of ≤12 beats per minute [23]. Abnormal blood pressure response was defined as a failure of systolic blood pressure to rise at least 10 mmHg after the first minute of exercise or initial rise in blood pressure but subsequent fall by >20 mmHg during exercise [25].

2.6. Combined interpretation of stress test parameters

We studied if combining the results of echo, ECG, and non-ECG exercise parameters into a comprehensive interpretation of stress test might improve diagnostic accuracy in identifying occult coronary abnormalities. A positive comprehensive stress test was defined as a positive stress echo and/or a positive stress ECG and/or positive non-ECG exercise parameters.

2.7. Statistical analysis

Normality of the data was verified using the Kolmogorov–Smirnov test and histogram plots. Results are expressed as mean ± standard deviation for parametric, and median (interquartile range) for non-parametric data. Chi-square tests were used for differences between categorical variables. *t*-tests or Mann-Whitney rank-sum tests were used to assess differences between continuous variables. The association between stress test variables and an occult coronary abnormality was tested using multivariable logistic regression analyses adjusted for confounding variables, including age, body mass index (BMI), and diabetes mellitus [2]. In addition, regression analysis to study the association of HRR with an occult coronary abnormality was also adjusted for beta-blocker and calcium channel blocker usage [23,26]. A *p*-value <0.05 was considered significant. Statistical analyses were performed using SPSS 22 (IBM, Armonk, NY) and NCSS 11 (NCSS, Kaysville, UT).

3. Results

Table 1 shows the clinical characteristics of the study patients. There were 119 (76.7%) women with a mean age of 54.1 ± 12.2 years and 36 (23.3%) men with a mean age of 53.7 ± 14.1 years. Women had a higher prevalence of a family history of CAD, as well as a higher total cholesterol, LDL, HDL, lipoprotein (a), and high sensitivity C-reactive protein (hs-CRP). Men had higher levels of homocysteine.

Of the 155 patients, 150 underwent endothelial function and microvascular testing, while 154 had IVUS. Endothelial dysfunction was present in 96 (64%) (74 women, 22 men), while 32 (20.6%) (25 women, 7 men) had MVD and 83 (53.9%) (61 women, 22 men) had an MB. The median duration between stress test and invasive testing was 48 (17–114) days. The stress echo was positive in 58 (43.6%) (42 women, 16 men), while 57 (36.7%) (49 women, 8 men) had a positive stress ECG. Appendix Table 1 shows the stress echo and ECG parameters in patients with endothelial dysfunction, MVD, and/or an MB. We found no significant differences between the groups.

3.1. Stress echocardiographic findings

The sensitivity and specificity of stress echo to identify the presence of any occult coronary abnormality was low to moderate in both sexes (Fig. 2(A)). On multivariable regression analysis, stress echo was not associated with the presence of any occult coronary abnormality (Table 2).

We analyzed a subset of the population consisting of 65 patients (45 women, 20 men) for the presence of focal septal buckling with apical sparing during stress echocardiography in identifying the presence of an MB. Of these patients, 44 (67.7%) had an MB by IVUS and 51 (78.5%) had focal septal buckling on stress echo. With the addition of this echocardiographic characteristic, the sensitivity and specificity of stress echo was 86.4% and 38.1%, respectively. For women, the results were similar, with a sensitivity of 84.4% and a specificity of 15.4%,

Table 1
Clinical characteristics.

Characteristic	Women $N = 119$	Men $N = 36$	*p* value
Age, yr.	54.1 ± 12.2	53.7 ± 14.1	0.97
Body mass index, kg/m^2	25.9 (24.9–28.7)	27.4 (24.9–28.9)	0.39
Hypertension	62 (52.1)	13 (36.1)	0.97
Diabetes mellitus	18 (15.3)	7 (19.4)	0.53
Dyslipidemia	69 (57.9)	21 (58.3)	0.97
Current Smoking	15 (12.6)	7 (19.4)	0.10
Family history of CAD	37 (31.1)	5 (13.9)	0.04
Medications			
Aspirin	76 (63.8)	28 (77.8)	0.27
Beta blockers	52 (43.7)	17 (47.2)	0.81
ACEI/ARB	18 (15.1)	8 (22.2)	0.53
Diuretics	17 (14.3)	1 (2.8)	0.13
Statins	66 (55.5)	23 (63.9)	0.59
CCB	22 (18.5)	10 (27.8)	0.42
Nitrates	51 (42.9)	18 (50.0)	0.66
Total cholesterol, mg/dL	168.8 ± 39.5	142.7 ± 28.2	< 0.01
Triglycerides, mg/dL	68 (53–76)	62 (45–77)	0.81
LDL, mg/dL	96.9 ± 34.5	80.5 ± 25.8	0.007
HDL, mg/dL	55 (51–58)	44 (39–53)	0.002
Lipoprotein (a), mg/dL	14.1 (10.3–16.2)	22.2 (10.8–32.7)	0.02
Fasting glucose, mg/dL	94 (90–96)	98 (91–106)	0.16
HbA1c, %	5.4 (5.4–5.7)	5.6 (5.4–5.8)	0.33
hs-CRP, mg/L	1.2 (1.0–1.9)	0.6 (0.4–1.9)	0.03
Homocysteine, μmol/L	7.3 (6.8–7.7)	8.9 (7.8–9.9)	<0.01

ACEI = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blockers; CAD = coronary artery disease; CCB = calcium channel blocker; HbA1c = hemoglobin A1c; hs-CRP = high sensitivity C-reactive protein. Variables are expressed as mean ± SD, n (%), or median (interquartile range) depending on normality criteria.

whereas for men, both the sensitivity and specificity improved to 91.7% and 75.0%, respectively. On multivariable regression analysis, focal septal buckling was associated with the presence of an MB (OR 4.08; 95% CI 1.15–14.4; $p = 0.02$).

3.2. Stress electrocardiographic findings

The specificity of stress ECG to identify any occult coronary abnormality, endothelial dysfunction, MVD, or an MB was better than that of stress echo, whereas the sensitivity was poor (Fig. 2(B)). On multivariable regression analysis, stress ECG was associated with the presence of any abnormality and endothelial dysfunction in women, but not in men. Stress ECG was not associated with the presence of MVD or an MB in either sex.

3.3. Analysis of non-electrocardiographic exercise parameters

There was no difference in the DTS, METs, or blood pressure response between those with occult coronary abnormalities vs. those without, although patients with an occult coronary abnormality had a moderately high risk DTS. Conversely, there was a significantly higher prevalence of abnormal HRR in those with endothelial dysfunction vs. those without (17 (17.7%) vs. 2 (2.1%); $p = 0.03$). This was true for women (14 (18.9%) vs. 1 (2.2%); $p = 0.041$), but not for men. Women with MVD also had a significantly higher prevalence of abnormal HRR vs. those without (49 (36%) vs. 10 (10.6%); $p = 0.02$), while men did not. There was no difference in the prevalence of abnormal HRR in patients with an MB vs. those without. On multivariable regression analysis, abnormal HRR was associated with endothelial dysfunction (OR 4.65; 95% CI 1.96–32.9; $p = 0.048$) and MVD (OR 3.85; 95% CI 1.31–17.8; p = 0.04).

3.4. Combined interpretation of stress testing parameters

The use of a comprehensive stress test to identify an occult coronary abnormality, by combining the results of echo, ECG, and non-ECG exercise parameters, greatly improved the sensitivity, although the specificity remained low to moderate (Fig. 2(C)). On multivariable regression analysis, a comprehensive stress test was associated with the presence of any occult coronary abnormality (OR 2.85; 95% CI 1.13–7.21; $p = 0.02$) and endothelial dysfunction (2.21; 95% CI 1.78–5.03; $p = 0.03$).

4. Discussion

In this study, we characterize in detail the diagnostic value of noninvasive stress testing, including stress echocardiography, electrocardiography, and non-ECG exercise parameters, in identifying occult coronary abnormalities in both women and men who have undergone comprehensive invasive testing for angina and non-obstructive CAD. Importantly, we found that stress echo was not associated with any occult coronary abnormality. However, when septal buckling with apical

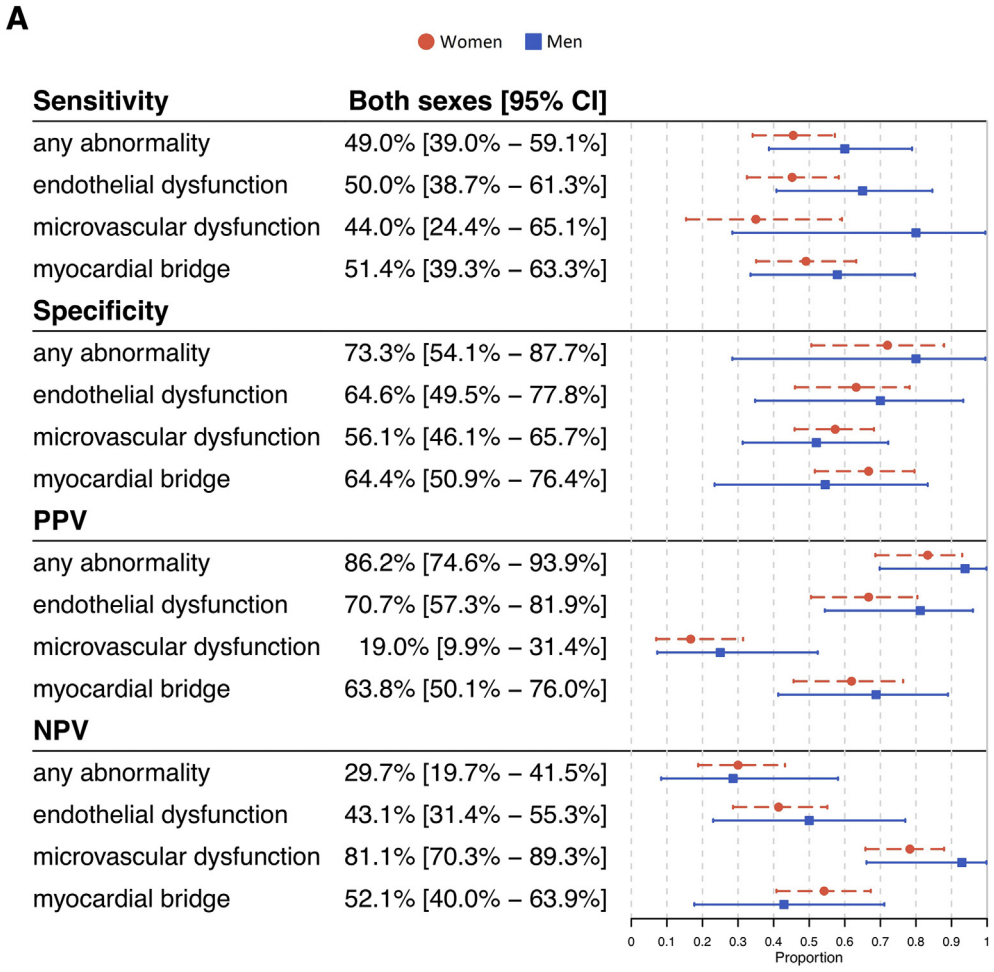

Fig. 2. (A). Sensitivity, specificity, PPV, NPV of stress echo in identifying the presence of any abnormality, endothelial dysfunction, microvascular dysfunction, and myocardial bridge. (B). Sensitivity, specificity, PPV, NPV of stress ECG in identifying the presence of any abnormality, endothelial dysfunction, microvascular dysfunction, and myocardial bridge. (C). Sensitivity, specificity, PPV, NPV of comprehensive stress test in identifying the presence of any abnormality, endothelial dysfunction, microvascular dysfunction, and myocardial bridge. CI = confidence interval, NPV = negative predictive value, PPV = positive predictive value.

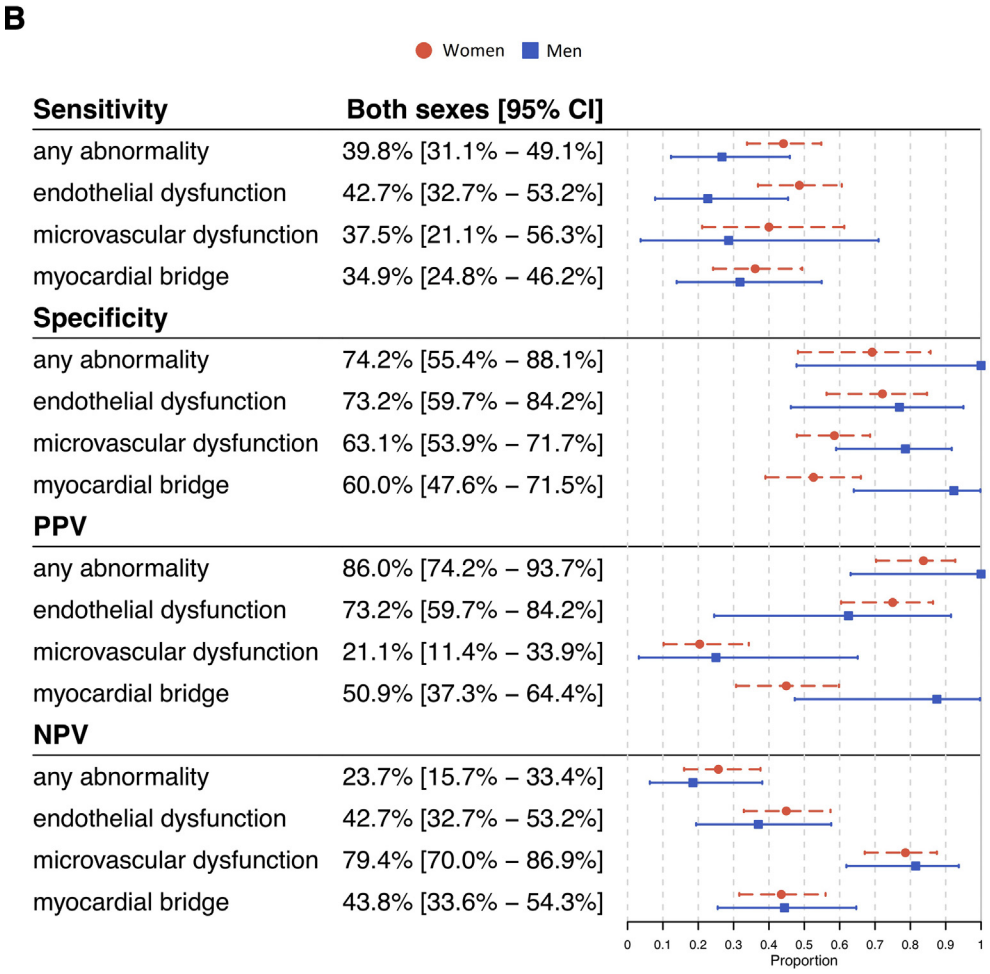

Fig. 2 (*continued*).

sparing was specifically evaluated, it was associated with the presence of an MB. Stress ECG was associated with any occult coronary abnormality, and endothelial dysfunction in women, but failed to associate with MVD or an MB in either sex. Notably, abnormal HRR was associated with endothelial dysfunction and MVD, but not with the presence of an MB. Finally, we found that the sensitivity of a stress test improved when non-ECG exercise parameters were considered along with echo and ECG. Our findings strongly suggest the need to reconsider the current approach to the evaluation and management of patients with angina in the absence of obstructive CAD.

It is not necessarily surprising that conventional stress tests were not helpful in identifying occult coronary abnormalities in patients with angina and non-obstructive CAD. These tests were validated to detect obstructive epicardial disease in large vascular territories, and have moderate sensitivity and specificity for subtler levels of ischemia, including smaller obstructed vessels that may go undetected [27]. With endothelial dysfunction, there is an imbalance between the endothelium-derived relaxing factors (nitric oxide) and endothelium-derived constrictors (endothelin), resulting in an inability to appropriately increase coronary blood flow through coronary vasodilatation during stress [28]. This imbalance in supply and demand causes ischemia, which is generally limited to the subendocardium, with preserved transmural perfusion [29]. Such ischemia may cause depolarization changes, resulting in ST-segment depression [11], but may not induce wall motion abnormalities, which requires a flow reduction >50%, and involvement of ≥20% of transmural wall thickness and ~5% of the total myocardial mass [30].

Similarly, the coronary microvasculature facilitates the supply and demand by reacting to changes in shear stress and intravascular pressure. With MVD, the coronary vascular resistance is increased, hampering the ability to preserve adequate perfusion pressure in the distal arteriolar bed [31]. Ischemia by MVD can be focal, heterogeneous, and scattered in small regions throughout the myocardium [32,33]. This type of ischemia may cause minor depolarization changes that are unable to produce significant ST-segment depression, let alone abnormal wall motion. Our results are consistent with previous studies, demonstrating the limited diagnostic accuracy of stress imaging, while stress ECG is the most specific test in identifying endothelial dysfunction [11,34].

MBs are a common anatomical variant, with a varying prevalence, ranging from 25% using invasive imaging to 85% in autopsy studies [35,36]. The rate of detection of MBs depends on the cohort studied and the imaging test performed. Although MBs are considered benign, a small subset of the population appears to have angina from a hemodynamically significant MB. The pathophysiology of ischemia caused by an MB is also considered to be different than that of obstructive CAD. With an MB, there is delay in vessel relaxation at end-systole/early-diastole, impairing coronary blood flow, particularly at stress [37]. In addition, the location of this ischemia has been proposed to be focal, located within the MB where arising septal branches may have limited perfusion [21]. Previously, we reported that this ischemia is associated with a particular motion of focal septal buckling with apical sparing during stress echo [21]. In this study we found that this abnormal motion is associated with the presence of an MB, with high sensitivity and moderate specificity.

As per our expectation, occult coronary abnormalities were associated with stress ECG changes. It has long been recognized that stress

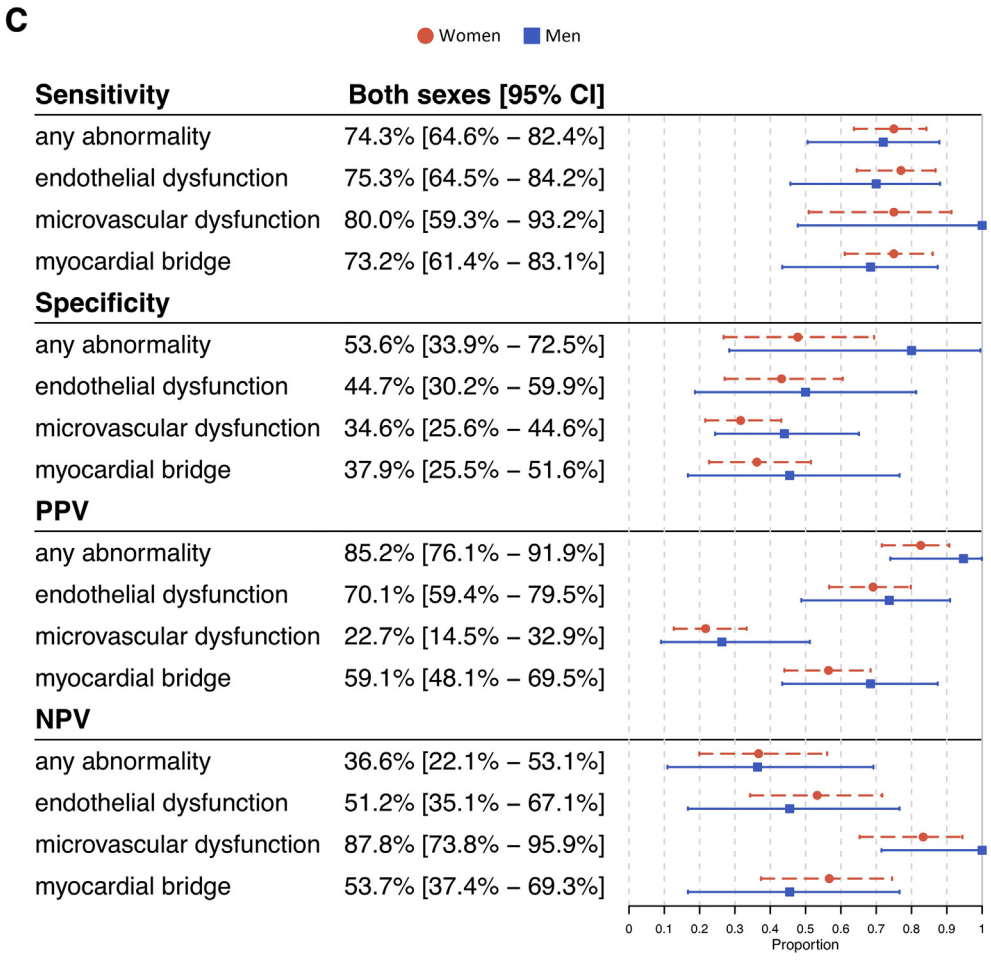

Fig. 2 (*continued*).

ECG is relatively poor at predicting obstructive CAD, and women in particular have higher rates of false positive stress ECGs than men [38,39]. We hypothesized that the false positive stress ECG changes were due to previously undetected occult coronary abnormalities, which appears to be the case. The higher specificity of stress ECG to detect occult coronary abnormalities, which may have previously gone undetected, may reduce the overall false positive rate of stress ECG.

In evaluating non-ECG exercise parameters, we found that an abnormal HRR was associated with endothelial dysfunction and MVD. This is similar to a previous study demonstrating that an attenuated HRR independently predicted the presence of endothelial dysfunction [26]. Abnormal HRR has been shown to be an independent predictor of both all-cause and cardiovascular mortality in women and men [23,24]. In addition, guidelines have recommended integrating this parameter when analyzing an exercise stress test to improve its diagnostic value [10]. The delay in early recovery of heart rate after termination of exercise is due to persistent activation of the sympathetic nervous system (SNS) and delayed/reduced activation of the parasympathetic nervous

Table 2
Multivariable logistic regression analysis for the diagnostic value of stress echo and ECG in predicting endothelial dysfunction, microvascular dysfunction, and a myocardial bridge.

Diagnostic test	Abnormality	All patients		Women		Men	
		Odds ratio[a] (95% CI)	*p* value	Odds ratio[a] (95% CI)	p value	Odds ratio[a] (95% CI)	*p* value
Stress echo	Any abnormality	2.71 (0.93–6.73)	0.06	2.10 (0.78–5.68)	0.14	3.91 (0.26–59.6)	0.32
	Endothelial dysfunction	1.66 (0.77–3.58)	0.19	1.30 (0.55–3.07)	0.54	4.23 (0.55–32.4)	0.16
	MVD	1.08 (0.44–2.69)	0.85	0.79 (0.28–2.26)	0.66	1.05 (0.37–2.96)	0.91
	MB	1.98 (0.97–4.04)	0.059	1.88 (0.82–4.29)	0.13	1.45 (0.30–6.98)	0.64
Stress ECG	Any abnormality	2.11 (1.86–5.16)	0.03	1.88 (1.35–4.83)	0.043	2.01 (0.72–5.59)	0.18
	Endothelial dysfunction	2.13 (1.01–4.49)	0.047	2.38 (1.04–5.45)	0.03	1.10 (0.17–6.99)	0.91
	MVD	1.05 (0.45–2.46)	0.90	1.00 (0.39–2.59)	0.99	0.67 (0.06–7.48)	0.75
	MB	0.85 (0.43–1.64)	0.62	0.64 (0.30–1.36)	0.24	6.70 (0.56–80.0)	0.13
Comprehensive stress test[b]	Any abnormality	2.85 (1.13–7.21)	0.02	2.29 (1.80–6.51)	0.01	7.41 (0.52–104.6)	
	Endothelial dysfunction	2.21 (1.78–5.03)	0.03	2.22 (1.88–5.59)	0.041	2.06 (0.27–15.6)	0.48
	MVD	1.82 (0.61–5.45)	0.27	1.10 (0.34–3.55)	0.87	0.57 (0.15–5.63)	0.85
	MB	1.55 (0.72–3.35)	0.26	1.56 (0.63–3.83)	0.33	0.85 (0.14–5.31)	0.86

CI = confidence interval; Echo = echocardiogram; ECG = electrocardiogram; MB = myocardial bridge; MVD = microvascular dysfunction.
[a] Adjusted for age, BMI, and diabetes mellitus.
[b] Comprehensive stress test is defined as positive stress echo and/or positive stress ECG and/or positive non-ECG stress testing parameter.

system [40,41]. This increased activation of the SNS may markedly suppress endothelium-dependent flow mediated dilatation via a specific inhibitory effect on the release of nitric oxide [42]. Likewise, animal studies have shown that chronic persistent activation of the SNS causes increased endothelial cell injury/dysfunction mediated by beta-1 adrenergic receptors [43]. HRR was associated with endothelial dysfunction and MVD in women, but not men. This may be due to the small number of men in this study or a true sex difference. Our findings support the addition of HRR to stress testing when evaluating patients with angina and non-obstructive CAD.

Finally, combining the results of echo, ECG, and non-ECG exercise parameters into a comprehensive stress test interpretation appears to improve the accuracy of diagnosing an occult coronary abnormality. Still, better non-invasive tests are needed. Promising work has been done with positron emission tomography (PET), magnetic resonance imaging (MRI), and coronary CT angiography [44–48], but comprehensive invasive coronary testing remains essential to gaining important diagnostic information that may affect treatment and outcomes in symptomatic patients with non-obstructive CAD [2]. In the future, we expect that providers will better understand that conventional stress tests are designed to evaluate for obstructive CAD, but fail to adequately rule out a coronary etiology of non-obstructive CAD. In addition, as research continues, we anticipate that improved non-invasive tests that can identify subtleties of ischemia will become available to aid providers in diagnosing these patients, which will ultimately improve and guide management. Until then, non-invasive guidelines should emphasize the inadequacy of conventional stress testing in patients with angina, but a low pre-test probability of obstructive CAD, and guidelines and appropriate use criteria for diagnostic catheterization should better reflect the need for invasive testing in this large and poorly understood population.

4.1. Limitations

This study was retrospective, but the invasive tests were done prospectively, and non-invasive testing was always performed before invasive testing, hence we do not think that the retrospective nature of this study significantly alters the results. The study had a relatively smaller sample size, with a majority of women, but this is reflective of the population with angina and non-obstructive CAD. Stress testing was limited to echocardiography and electrocardiography, and did not include alternatives, such as nuclear perfusion scanning, MRI, or PET. Likewise, invasive testing was performed in the LAD only and may have missed abnormalities in other territories. In addition, there is the risk of selection bias since our cohort of patients had persistent anginal symptoms despite medical therapy that were considered severe enough to warrant invasive testing. These results may not be generalizable to patients with mild symptoms or those controlled with medical therapy alone, although the prevalence of endothelial dysfunction and microvascular dysfunction in our study was consistent with previous studies [12,49]. In addition, there would be no reason to believe that stress testing would be any more valuable in those with less significant symptoms. Finally, outcome data was not available for this study, although previous studies have reported adverse outcomes with these abnormalities and have documented improvement with treatment in this patient population [12,49].

5. Conclusion

Conventional stress testing with echo and ECG have limited diagnostic accuracy for identifying occult coronary abnormalities that may cause angina in patients with non-obstructive CAD. Stress ECG is associated with the presence of an occult coronary abnormality in women, which may explain the high rate of false positives commonly noted in women with angina and non-obstructive CAD. Likewise, the addition of non-ECG exercise parameters, particularly heart rate recovery, in the interpretation of a stress test may provide important diagnostic information regarding an underlying occult coronary abnormality. Still, the presence of a normal noninvasive stress test does not rule out an occult coronary abnormality, and further studies are needed to clarify the best approach for the evaluation and management of patients with angina in the absence of obstructive CAD.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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Appendix A

Appendix Table 1
Stress echocardiographic and electrocardiographic parameters in patients with endothelial dysfunction, microvascular dysfunction, and a myocardial bridge.

Characteristic	All Subjects ($N = 155$)	Endothelial dysfunction ($N = 96$)	MVD ($N = 32$)	MB ($N = 83$)
Stress echo[a]				
Positive stress echo, n (%)	58 (43.6)	41 (52.9)	8 (53.3)	31 (57.4)
Rest WMSI Median (min–max)	1 (1–1.31)	1 (1–1.31)	1 (1–1.18)	1 (1–1.31)
Stress WMSI Median (min–max)	1 (1–1.56)	1 (1–1.56)	1 (1–1.56)	1 (1–1.37)
Septal buckling[b]	–	–	–	38 (86.4)
Stress ECG[c]				
Positive stress ECG, n (%)	57 (36.7)	34 (41.5)	5 (22.7)	22 (32.4)
Peak HR (bpm)	157 (142–169)	155 (142–167)	150 (130–161)	159 (143–169)
% of predicted HR	93 (87–99)	93 (87–101)	91 (81–98)	94 (88–101)
Peak SBP (mmHg)	165 (148–180)	167.6 ± 25.5	170.2 ± 25.1	164.4 ± 26.0
Peak DBP (mmHg)	78 (72–84)	79.0 ± 12.6	82.8 ± 10.1	78.5 ± 10.4

(continued on next page)

Appendix Table 1 (*continued*)

Characteristic	All Subjects ($N = 155$)	Endothelial dysfunction ($N = 96$)	MVD ($N = 32$)	MB ($N = 83$)
Exercise time (min)	9.13 (7.00–11)	9.16 (7.01–11.3)	7.7 (6.3–9.9)	9.3 (7–11)
METs	10.5 ± 3.3	10.2 ± 3.2	9.4 ± 2.8	10.6 ± 3.6
Duke Treadmill Score	−2 (−7–3)	−1 (−7–1)	−3 (−7–4)	−1 (−6–4)
Chest pain, n (%)	83 (53.5)	50 (52.1)	16 (50)	48 (57.8)

bpm = beats per minute; DBP = diastolic blood pressure; HR = heart rate; METs = metabolic equivalent term; min = minimum; max = maximum; SBP = systolic blood pressure; WMSI = wall motion score index.

[a] $n = 133$

[b] Data available for 65 patients.

[c] $n = 155$.

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