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SHORT REPORT

Prognostic significance of myocardial ischaemia during exercise echocardiography in the absence of angiographic evidence of obstructive coronary disease

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Abstract

Aims We studied the prognostic significance of myocardial ischaemia during exercise stress echocardiography (ExE) in the absence of angiographic evidence of obstructive coronary artery disease (CAD) in a contemporary cohort of patients.

Methods and results We retrospectively enrolled 84 patients who underwent ExE and had exercise-induced myocardial ischaemia followed by angiographic coronary evaluation. Fifty-one (61%) patients had non-obstructive CAD (iNOCAD), and 33 (39%) had normal coronaries (iNC). iNC and NOCAD patients were propensity matched to 99 and 153 patients with non-ischaemic ExE, respectively. Compared to iNOCAD, iNC patients were younger (60.9 ± 10.4 vs. 68 ± 8.9 years, $P = 0.002$) and predominantly women (76% vs. 47%, $P = 0.009$). Ejection fraction (57 ± 9.4 vs. 56.4 ± 6, $P = 0.776$) as well as other clinical and demographic variables were similar. During median follow-up of 3.2 years, there were 27 composite adverse cardiovascular events (1 death, 10 acute chest pain events, 2 strokes, and 21 cardiac hospitalizations). iNC was associated with a higher risk of acute chest pain (HR: 19.0, 95% CI: 3.7–93) and the composite adverse outcome (HR: 3.3, 95% CI: 1.7–6.6), compared to matched patients. Similarly, iNOCAD was associated with a higher risk of the composite outcome (HR: 2.2, 95% CI: 1.2–4.2).

Conclusion Ischaemic ExE in the absence of angiographically obstructive CAD carries an elevated risk of adverse cardiovascular events necessitating medical optimization and close follow-up for progression.

Keywords iNOCA • myocardial ischaemia • exercise stress test

Introduction

Myocardial ischaemia in the absence of obstructive coronary artery disease (CAD) is a heterogeneous condition with elevated clinical risk.[1] While patients with obstructive CAD represent the highest clinical risk group, ischaemia in the absence of obstructive CAD is not benign. This condition is associated with an elevated cardiovascular risk compared to the general population, including persistent symptoms and recurrent hospitalizations.[2] Management of these patients is a challenge, and the use of anti-anginal and anti-atherosclerosis medications in these

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patients seems to be less frequent compared to patients with obstructive CAD. Ischaemia in the absence of obstructive CAD occurs in both women and men, however, studies have shown that it is more frequent in women who are also more likely to have recurrent hospitalizations due to angina. While all predisposing factors are not clearly understood, myocardial ischaemia in these patients seem to be related to the traditional cardiometabolic risk factors, with mechanisms that can be 'atherosclerotic' due to progression of CAD, or 'non-atherosclerotic' due to myocardial disease, microvascular dysfunction,[3] abnormal coronary flow reserve and vasomotor dysfunction.[1] As a result, this condition remains under-recognized, underdiagnosed, and undertreated due to the heterogeneity of patient populations and underlying mechanisms. This underscores the need for further demographic, clinical, and mechanistic studies to enhance understanding, identify potential risks, and develop targeted therapeutics.

We studied the prognostic significance of myocardial ischaemia during exercise stress echocardiography (ExE) in the absence of angiographic evidence of obstructive CAD in a contemporary cohort of patients.

Methods

We retrospectively enrolled patients who underwent ExE at Mount Sinai Morningside Hospital, New York, NY, between June 2017 and December 2020 and had exercise-induced myocardial ischaemia followed by angiographic coronary evaluation.

All echocardiographic images were obtained on commercially available systems (GE Vivid 7, 9, and E95, GE Healthcare, Wauwatosa, WI). Resting and exercise echocardiography studies were performed by standard methodology as has been previously described.[4] Echocardiographic images were acquired at baseline (rest images) and immediately after treadmill exercise. The sonographers obtained the standard 2D echocardiographic views in the left lateral decubitus position for the assessment of post-exercise wall motion abnormalities suggestive of exercise-induced myocardial ischaemia immediately after transition from treadmill to bed. Exercise-induced myocardial ischaemia was defined as new post-exercise wall motion abnormalities and was assessed using the traditional 17-segment model (see Supplementary data online, table *S1*). All studies were reported by a single reader blinded to the study, who is level 3 trained in echocardiography and has extensive experience with stress echocardiography. Subsequently, mitral inflow velocities and e' velocity at the septal mitral annulus were obtained, with the goal of obtaining mitral inflow velocities with a pulsed-wave Doppler placed at the tip of the mitral valve at heart rates of 100–110 beats per minute to avoid E- and A-wave fusion.

After obtaining diagnostic coronary angiographic images, patients were divided into ischaemic with non-obstructive CAD (iNOCAD, < 50% left main and <70% non-left main disease with negative invasive coronary indices) and ischaemic with angiographically normal coronaries (iNC). Patients were followed for a median of 3.2 years for death, acute chest pain events (ACP), stroke, and non-ACP cardiac hospitalization. ACP was defined as in-hospital evaluation for acute chest pain with at least 2 of the following: typical or possibly cardiac chest pain, ischaemic dynamic electrocardiographic (EKG) changes, and elevation of cardiac troponin I level. ACP was categorized as non-infarction ACP if no troponin elevation was detected, myocardial infarction with non-obstructive CAD (MINOCA) if troponin showed a typical rise and fall pattern, and acute coronary syndromes (ACS) if any 2 criteria were accompanied by angiographically significant CAD. Our study was conducted in accordance with the Declaration of Helsinki. The study was approved by our institutional review board (IRB) number 21-01009.

Statistical analysis

Continuous variables and nominal variables were expressed as mean ± SD and number(%) and compared using Student's *t*-test and χ^2 test, respectively. Outcomes were tested using Cox-regression models and Kaplan–Meier survival curves; 3:1 propensity score matching was conducted to match iNC and iNOCAD patients, separately, with symptomatic patients who had a non-ischaemic ExE. We computed the propensity score by using logistic regression with the dependent variable being the presence of ischaemia during ExE, and the independent variables (covariates) being age, sex, risk factors (diabetes, hypertension, hyperlipidaemia, and smoking), major comorbidities (congestive heart failure and renal disease), medications (aspirin, lipid-lowering agents, renin angiotensin aldosterone antagonists, beta blockers, and nitrates), resting diastolic Doppler variables (e' velocity, E/e' ratio and tricuspid regurgitation velocity), and exercise performance. A 3:1 propensity score matching was done using the nearest neighbour classification and resulted in 99 matched patients for the iNC group and 153 patients for the iNOCAD group. A *P*-value <0.05 was considered statistically significant. All analyses were performed with SPSS version 23.0 (SPSS, Inc).

Results

We identified 33 iNC patients and 51 iNOCAD patients (matched with 99 and 153 non-ischaemic patients, respectively). All patients had new post-exercise wall motion abnormalities suggestive of myocardial ischaemia. In addition, during treadmill exercise, chest pain or EKG evidence of ischaemia occurred in 50(60%) patients [19(58%) with iNC and 31(61%) with iNOCAD, $P = 0.770$]. Of these, 8(10%) patients had both chest pain and EKG changes suggestive of ischaemia [3(9%) with INC and5(10%) with INOCAD], 27(32%) patients had only chest pain [10(30%) with iNC and17(33%) with iNOCAD], and 15(18%) patients had only EKG changes suggestive of ischaemia [6(18%) with iNC and9(18%) with iNOCAD].

The indications for studies, as well as the ischaemic segments according to the 17-segment model, are summarized in Supplementary data online, table *S1*.

Table 1 summarizes comparisons between iNC and iNOCAD patients as well as comparisons with matched patients. Compared to iNOCAD, iNC patients were younger (60.9 ± 10.4 vs. 68 ± 8.9 years, $P = 0.002$), predominantly women [25(76%) vs. 24(47%), $P = 0.009$], and less likely to receive antihyperlipidaemic medications [15(46%) vs. 37(73%), $P = 0.013$]. Risk factors, comorbidities, other medications, resting and exercise blood pressure and heart rate, resting ejection fraction (57 ± 9.4 vs. 56.4 ± 6, $P = 0.776$), resting diastolic measures, and exercise capacity were similar between both groups. Interestingly, iNC patients had lower septal mitral annular e' velocity (8.0 ± 2.9 vs. 9.5 ± 3 cm/s, $P = 0.029$), and E/A ratio (0.9 ± 0.31 vs. 1.1 ± 0.45, $P = 0.023$) post exercise. Other exercise diastolic function measures were similar.

Cardiac coronary computed tomography and calcium scoring were done for 29 patients (14 iNC and 15 iNOCAD), and all iNC had a calcium score of 0 Hounsfield units while iNOCAD had a calcium score of 109 ± 260 Hounsfield ($P < 0.001$).

During follow-up, there were 1 death, 10 ACP events (3 MINOCA, 6 non-infarction ACP, and 1 ACS), 2 strokes, 21 cardiac hospitalizations, and 27 composite outcomes. Compared to iNOCAD, iNC patients showed no differences for death (0 vs. 1, $P = 0.418$), ACP (6 vs. 4, $P = 0.153$), stroke (2 vs. 0, $P = 0.075$), cardiac hospitalizations (9 vs. 12, $P = 0.699$), or the composite outcome (12 vs. 15, $P = 0.505$). All iNC with ACP (3 MINOCA and 3 non-infarction ACP) continued to have normal coronaries at follow-up invasive coronary studies, although among iNOCAD patients, 1 patient had non-ST elevation myocardial infarction (NSTEMI) with 1 vessel obstructive CAD treated with coronary stenting, and 2 had non-infarct ACP and continued to show non-obstructive CAD.

Kaplan–Meier curves and Cox-regression models suggested that, compared to iNOCAD, iNC patients had a non-significantly elevated risk of both ACP (HR: 3.3, 95% CI: 0.84–13.5, $P = 0.069$, *Figure 1*) and the composite outcome (HR: 1.6, 95% CI: 0.73–3.4, $P = 0.078$, *Figure 1*).

Among the matched patients (n = 252), during follow-up, there were 4 deaths, 2 ACS (1 unstable angina and 1 NSTEMI), 22 cardiac hospitalizations, and 28 composite outcome events. Kaplan–Meier curves suggested that, compared to matched patients, iNC patients had an elevated risk of both ACP and the composite outcome (both $P < 0.001$,

Table 1 Comparisons between study patients as well as matched patients

	iNC ($n = 33$)	iNOCAD ($n = 51$)	Matched with iNC ($n = 99$)	Matched with iNOCAD ($n = 153$)
Age, years	60.9 ± 10.4	68 ± 8.9 [a]	59.7 ± 11.4	64.5 ± 11.7
Body mass index, kg/m^2	28.3 ± 7.7	29.4 ± 5.6	29.8 ± 6.6	29.4 ± 7
Women, *n*(%)	25(76)	24(47) [a]	76(77)	66(43)
Hypertension, *n* (%)	24(73)	43(84)	68(69)	129(84)
Diabetes mellitus, *n*(%)	9(27)	20(39)	32(32)	52(34)
Smoking history, *n*(%)	13(39)	23(45)	43(43)	70(46)
Hyperlipidaemia, *n*(%)	19(58)	34(67)	56(57)	109(71)
Family history, *n*(%)	3(9)	11(22)	8(8)	34(22)
Percutaneous coronary intervention, *n*(%)	0(0)	11(22) [a]	3(3)	31(20)
Atrial arrhythmia, *n*(%)	2(6)	3(6)	6(6)	6(4)
Chronic kidney disease, *n*(%)	1(3)	1(2)	4(4)	8(5)
Shortness of breath, *n*(%)	13(39)	12(24)	30(30)	40(26)
Chest pain, *n*(%)	20(61)	39(76)	54(55)	79(52)
Medications				
Aspirin, *n*(%)	14(42)	32(63)	34(34)	85(56)
Statin, *n*(%)	15(46)	37(73) [a]	48(49)	103(67)
Angiotensin converting enzyme inhibitors, *n*(%)	5(15)	17(33)	22(22)	46(30)
Angiotensin receptor blockers, *n*(%)	6(18)	9(18)	16(16)	39(26)
Beta blockers, n(%)	11(33)	27(53)	28(28)	65(43)
Calcium channel blockers, *n*(%)	15(46)	21(41)	29(29)	60(39)
Diuretics, *n*(%)	6(18)	20(39) [a]	25(25)	45(29)
Nitrates, *n*(%)	4(12)	6(12)	5(5)	13(9)
Warfarin, *n*(%)	1(3)	0(0)	0(0)	1(1)
Direct oral anticoagulants, *n*(%)	2(6)	3(6)	5(5)	5(3)
Any anti-ischaemic medication, *n*(%)	21(64)	45(88) [a]	63(64)	122(80)
Resting heart rate, b/m	76.2 ± 14.4	74.6 ± 20.8	76.4 ± 15.7	73.2 ± 15.2
Resting systolic blood pressure, mmHg	133.9 ± 16.1	139 ± 15.1	135.5 ± 16.6	137.5 ± 17.4
Resting diastolic blood pressure, mmHg	78.7 ± 14.8	76.6 ± 8.8	77.7 ± 12.1	76.4 ± 10.4
Exercise heart rate, b/m	154.7 ± 14.7	148.5 ± 18.6	154.4 ± 16	150.5 ± 16.7
Exercise systolic blood pressure, mmHg	160.9 ± 18.9	160.8 ± 18.8	160 ± 17.7	160.7 ± 19.3
Exercise diastolic blood pressure, mmHg	87.1 ± 13.2	79.1 ± 12.2 [a]	84.6 ± 12.2	82.3 ± 12.6
Metabolic equivalent of tasks	8.1 ± 2.7	9.7 ± 13.6	8.4 ± 2.8	9.2 ± 6.7
Percentage of maximum age predicted heart rate (%)	97.4 ± 9	97.3 ± 12.6	96.5 ± 8.7	97.2 ± 10.8
Resting echocardiogram				
Ejection fraction, %	57 ± 9.4	56.4 ± 6	58.6 ± 7.1	59.3 ± 6.5 §
Left atrial volume index, mL/m^2	28.3 ± 8.9	30.3 ± 10.9	28.2 ± 8.9	28.6 ± 9.9
E-wave velocity, cm/s	65.5 ± 20.9	72.2 ± 21	70.8 ± 17.8	70.8 ± 20.3
A-wave velocity, cm/s	71.4 ± 23	78.3 ± 22.6	73.5 ± 21.3	79 ± 22.8
e' velocity, cm/s	6.5 ± 2.4	6.8 ± 2	6.9 ± 2.5	6.8 ± 2.1
E/A ratio	0.99 ± 0.38	0.99 ± 0.42	1.08 ± 0.7	0.95 ± 0.35
E/e' ratio	10.8 ± 4.1	11.2 ± 3.8	11.1 ± 4.1	11.8 ± 7.2
Tricuspid regurgitation velocity, m/s	2.28 ± 0.51	2.31 ± 0.48	2.30 ± 0.46	2.26 ± 0.46
Diastolic dysfunction (No/Yes/Indeterminate), *n*(%)	16(49)/7(21)/ 10(30)	26(50)/10(20)/ 15(30)	55(56)13(13)/31(31)	104(68)/17(11)/32(21)
Post-exercise echocardiogram				
E-wave velocity, cm/s	87.9 ± 28	104.8 ± 30.4 [a]	95.6 ± 25.4	98.2 ± 31.4
A-wave velocity, cm/s	103.9 ± 31.7	104.8 ± 30.1	103.4 ± 26.6	105.9 ± 26.7
e' velocity, cm/s	8 ± 2.9	9.5 ± 3 [a]	8.5 ± 3.1	8.9 ± 2.9
E/A ratio	0.9 ± 0.31	1.1 ± 0.45 [a]	0.99 ± 0.43	0.99 ± 0.47

Continued

Table 1 ***Continued***

	iNC ($n = 33$)	iNOCAD ($n = 51$)	Matched with iNC ($n = 99$)	Matched with iNOCAD ($n = 153$)
E/e' ratio	12.1 ± 5.6	12 ± 4.2	12.6 ± 4.6	12 ± 6.1
Tricuspid regurgitation velocity, m/s	2.67 ± 0.79	2.89 ± 0.57	2.62 ± 0.69	2.61 ± 0.69 §
Death, n(%)	0(0)	1(2)	1(1)	3(2)
Acute chest pain episodes, *n*(%)	6(18)	4(8)	1(1) [b]	1(1) [c]
Cerebrovascular events, *n*(%)	2(6)	0(0)	0(0) [b]	0(0) [c]
Non-chest pain cardiac hospitalizations, *n*(%)	9(27)	12(24)	9(9)	13(9) [c]
Composite outcome, *n*(%)	12(36)	15(29)	10(10)	17(11) [c]

[a]$P < 0.05$ between iNC and iNOCAD.
[b]$P < 0.05$ between iNC and iNC-matched patients.
[c]$P < 0.05$ between iNOCAD and iNOCAD-matched patients.

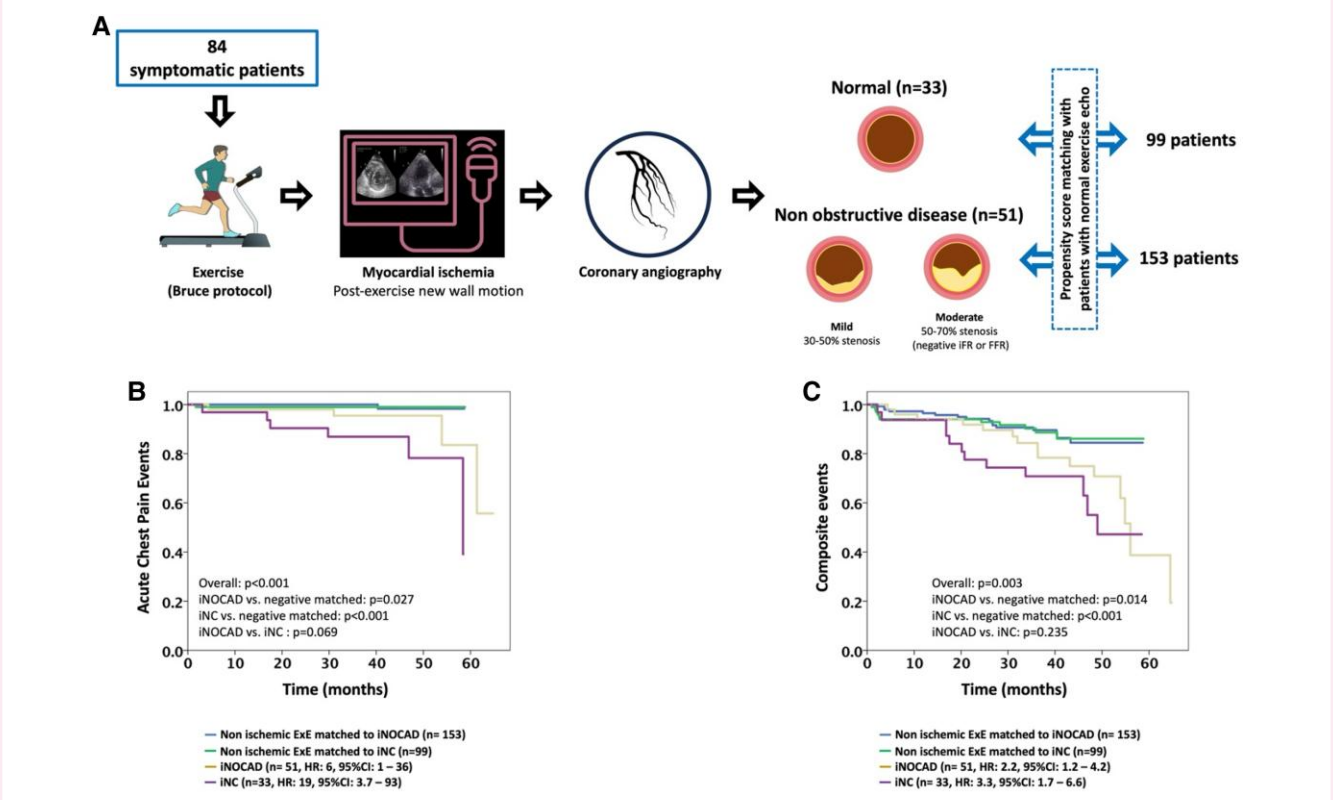

Figure 1 Prognostic significance of myocardial ischaemia in patients without obstructive coronary disease. *A*, study flow chart, *B*, acute chest pain events in patients with myocardial ischaemia and normal coronaries (iNC) and non-obstructive coronary disease (iNOCAD) compared to matched patients with non-ischaemic exercise stress test. *C*) composite outcomes events in patients with myocardial ischaemia and iNC and iNOCAD compared to matched patients with non-ischaemic. Lower panels represent patients at risk per group for acute chest pain events and composite outcomes.

Figure 1). Similarly, iNOCAD patients had an elevated risk of ACP ($P = 0.027$, *Figure 1*) and the composite outcome ($P = 0.014$, *Figure 1*). Cox-regression showed that, compared to matched patients, iNC patients had a higher risk of ACP (HR: 19.0, 95% CI: 3.7–93) and the composite outcome (HR: 3.3, 95% CI: 1.7–6.6). Among iNOCAD patients, there was an increased risk for the composite outcome (HR: 2.2, 95% CI: 1.2–4.2) but not ACP (HR: 6.0, 95% CI: 1 to 36).

Discussion

Myocardial ischaemia seen as new wall motion abnormalities during ExE despite non-obstructive or normal coronary arteries has been reported previously,[2,5] and it has been largely labelled as a false-positive test result. The possible explanations for false-positive ExE include pathological processes such as hypertensive heart disease,[6] conduction abnormalities,

coronary vasospasm,[7] endothelial dysfunction, and small-vessel disease.[8] In addition, inter-reader variability and issues of overinterpretation of the echocardiographic results have also been reported.[9] In clinical settings, it is generally assumed that a false-positive result is a low-risk finding for future cardiovascular outcomes, however, the aforementioned pathological mechanisms associated with 'false-positive' results suggest that these patients may be at a higher risk for adverse events. The prognostic significance of symptoms suggestive of myocardial ischaemia in patients with non-obstructive or normal coronaries both in the presence and absence of ExE evidence of myocardial ischaemia has not been well studied.

The presence of angina with or without non-obstructive coronary artery disease is reportedly associated with exercise pathophysiology and myocardial ischaemia.[10]

In the current study, in a group of symptomatic patients with echocardiographic evidence of myocardial ischaemia yet either iNOCAD or iNC on invasive angiography, women were more likely to have iNC compared to iNOCAD. Moreover, iNC patients were less likely to be treated with anti-ischaemic medications and lipid-lowering agents. Similar findings have been previously reported.[11]

As suggested by the types of coronary-specific outcomes, the mechanism of myocardial ischaemia in iNC patients seems to be non-atherosclerotic, while in iNOCAD patients, the mechanism seems to be more heterogeneous and includes both non-atherosclerotic and progressive atherosclerotic mechanisms.

Non-atherosclerotic mechanisms contributing to ischaemia and adverse outcomes include coronary microvascular dysfunction, which leads to abnormal coronary flow reserve due to endothelial dysfunction, as well as impaired vascular smooth muscle reactivity, resulting in epicardial and/or microvascular vasospasm. Additional non-atherosclerotic contributors include an impaired supply/demand ratio secondary to myocardial hypertrophy and dysfunction, anaemia, pulmonary hypertension, thromboembolism, and microembolism. Other potential mechanisms encompass spontaneous coronary artery dissection, myocardial bridging, and inflammatory or autoimmune conditions.[12]

Microvascular dysfunction is a relevant mechanism in our study, as both myocardial ischaemia and exercise-induced diastolic dysfunction —evidenced by lower post-exercise e' velocity—was observed. Both ischaemia iNOCAD and iNC were associated with adverse cardiac outcomes. However, these outcomes were more prevalent in iNC, a group predominantly composed of women, suggesting an under-recognized sex-specific, non-atherosclerotic mechanism of myocardial ischaemia in the presence of normal coronary arteries. Ischaemia in the absence of obstructive coronary artery disease is reportedly more prevalent in women, associated with an increased risk of major cardiovascular events, and linked to a higher likelihood of developing diastolic dysfunction and heart failure.[13] Notably, this condition may not correlate strongly with the extent of atherosclerotic burden.[14] Prior studies have suggested a potential link between oestrogen loss, stress-related hormonal dysregulation, and ischaemia in the absence of obstructive coronary disease.[15] Furthermore, women presenting with myocardial ischaemia without obstructive coronary disease frequently experience persistent chest pain, often accompanied by diminished quality of life. Additionally, microvascular dysfunction in women has been associated with greater diastolic dysfunction and increased myocardial fibrosis, as detected by cardiac magnetic resonance imaging, compared to women without microvascular dysfunction.[16] These findings may provide a mechanistic explanation for our study findings.

It is also important to note that microvascular dysfunction can coexist with obstructive CAD, potentially contributing to persistent angina despite percutaneous coronary intervention.[12] However, in such cases, aggressive anti-anginal and anti-atherosclerotic therapies should be initiated promptly. In contrast, as observed in our study, similar treatment strategies appear to be underutilized in patients with ischaemia but no obstructive coronary disease, potentially contributing to persistent and recurrent symptoms.

Our study is limited by its single-center, retrospective design, which introduces the potential for selection bias, missing data, and confounding factors. Additionally, the small sample size and limited number of outcome events may reduce statistical power and limit the generalizability of our findings. The study population may not fully represent the broader patient population, as significant differences in age and sex distribution were observed, potentially introducing bias. However, coronary microvascular dysfunction is well-documented to be prevalent among women with chest pain in the absence of obstructive coronary artery disease, which may explain this observed distribution.[13,17] Furthermore, invasive assessments of coronary flow reserve and vasospasm were not performed, limiting our ability to definitively confirm or refute the presence of microvascular dysfunction or vasospasm. The absence of advanced imaging modalities such as cardiac MRI and PET further restricts our ability to characterize microvascular dysfunction or non-obstructive ischaemia comprehensively. Consequently, while our findings are suggestive, they require validation through future studies incorporating both invasive and non-invasive assessments of microvascular function.

Conclusions

The findings of our study suggest that ischaemic ExE in the absence of angiographically obstructive CAD may be associated with an elevated risk of adverse cardiac events. Potential underlying mechanisms include myocardial dysfunction, coronary vasospasm, endothelial dysfunction, and small-vessel disease. These observations underscore the importance of medical optimization and close follow-up to monitor disease progression. Notably, our study indicates that patients—particularly women—with normal coronary arteries are at an increased risk for chest pain and cardiac events, likely driven by non-atherosclerotic mechanisms such as microvascular dysfunction.

Consent

This manuscript is a retrospective analysis and patients' consent to participate does not apply.

Supplementary data

Supplementary data are available at *European Heart Journal - Imaging Methods and Practice* online.

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Data availability

The data in this manuscript are not publicly available due to the privacy of the research participants' data.

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