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Research paper

Intracoronary acetylcholine for vasospasm provocation in women with ischemia and no obstructive coronary artery disease

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ABSTRACT

Objectives: To evaluate the utility of higher dose intracoronary acetylcholine (ACh) during invasive coronary function testing (CFT) in women with suspected ischemia and no obstructive coronary artery disease (INOCA) for detection of epicardial vasospasm, relation to quality of life (QoL) and the presence of scar by late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (CMRI).

Background: CFT is an established method for diagnosis of coronary microvascular dysfunction (CMD). The utility of epicardial vasospasm provocation testing with higher dose ACh infusion is not fully understood.

Methods: Women with suspected INOCA undergoing invasive CFT were enrolled in the Women's Ischemia Syndrome Evaluation-Pre-Heart Failure with Preserved Ejection Fraction (WISE Pre-HFpEF) study (NCT03876223). Incremental infusions of 0.364, 36.4 μg and 108 μg ACh were used for vasospasm provocation. Vasospasm was defined as ≥75 % artery diameter reduction compared to post-nitroglycerin diameter and related to QoL and LGE on CMRI.

Results: Among 73 women (56 ± 11 years), epicardial vasospasm was detected in 17 (23 %). Among women with vasospasm, the vast majority (94 %) had coronary endothelial dysfunction and few (12 %) had other abnormal CFT measures. Those with vasospasm had more nocturnal angina symptoms, calcium channel blocker use, poorer QoL (all $p = 0.001$) and disease perception ($p = 0.02$) than those without. LGE scar by CMRI was not associated with vasospasm ($p = 0.22$).

Conclusions: Among women with suspected INOCA, intracoronary Ach spasm testing provoked epicardial vasospasm in one fourth. Women with epicardial vasospasm overwhelmingly had concomitant endothelial dysfunction, worse QoL but not more frequent myocardial scar on CMRI.

1. Introduction

Patients with suspected ischemia and no obstructive coronary disease (INOCA) comprise a heterogeneous group. The presence of coronary vasomotor dysfunction is increasingly recognized, with coronary microvascular dysfunction (CMD), endothelial dysfunction and coronary artery vasospasm comprising pathophysiologic pathways of dysfunction [1]. Epicardial vasospasm can cause myocardial infarction in the absence of obstructive coronary artery disease (MINOCA) [2] and myocardial scar due to previous myocardial infarction can be detected

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by contrast enhanced cardiac magnetic resonance imaging (CMRI) using late gadolinium enhancement (LGE), a finding that is associated with adverse prognosis [3]. INOCA has also been associated with poorer patient reported measures of physical, mental and social quality of life (QoL) [4].

Invasive coronary function testing (CFT) is used to detect CMD and epicardial vasospasm using vasoactive agents to assess endothelial and non-endothelial dependent micro- and macrovascular function [5]. However, CFT is not commonly performed in routine clinical care, and there is a lack of standardization in procedural methods, doses, and outcomes [6]. Specifically, there is significant variability in the total number of incremental acetylcholine (ACh) doses given, the minimum and maximal doses used, and the timing of administration. Thus, differences in incremental and maximum doses ranging from 100 μg to 200 mg [7] and incidence of provoked spasm on functional testing display wide variability, with reports ranging from ~30–70 % spasm elicited by provocation [8–11]. Even with the lack of standardization, the recent 2021 Chest Pain guidelines designate a IIa recommendation for CFT, stating that it is reasonable to consider CFT for patients with persistent stable chest pain and non-obstructive CAD and at least mild myocardial ischemia on imaging, to improve the CMD diagnosis and risk stratification [12].

Despite increased awareness and recommendations of MINOCA, there is relatively little data regarding the association between detected epicardial vasospasm and clinically relevant outcomes such as quality of life (QoL), functional status and the presence of (LGE) on CMRI. We evaluated the utility of incremental ACh testing, including a higher dose for provocative vasospasm testing, during CFT for detection of vasospasm and relations to QoL and myocardial scar in women with suspected INOCA.

2. Methods

Women with signs and symptoms of INOCA enrolled from 2015 to 2019 in the ongoing Women's Ischemia Syndrome Evaluation-Mechanisms of Coronary Microvascular Dysfunction Leading to Heart Failure with Pre-Preserved Ejection Fraction (WISE-Pre-HFpEF) study (NCT03876223) undergoing clinically indicated CFT with complete data were included in this analysis. The study was approved by the site institutional review committee. All participants gave informed consent.

2.1. Coronary function testing (CFT)

CFT was performed under previously published protocols [5]. In brief, non-obstructive CAD (<50 % diameter stenosis) was confirmed by angiography and functional testing was performed using a Doppler Flowire (Philips Volcano) in the left anterior descending artery. First, graded doses of 18 mg and 100 mg intracoronary (IC) adenosine were administered, and coronary flow reserve (CFR) was calculated as the average peak velocity at maximal hyperemia divided by average peak velocity at baseline (Volcano Combomap® Software Version 1.0). Non-endothelial dependent microvascular dysfunction was defined as an abnormal CFR <2.5.

Incremental doses of IC ACh (0.364 μg, 36.4 μg and 108 μg) were

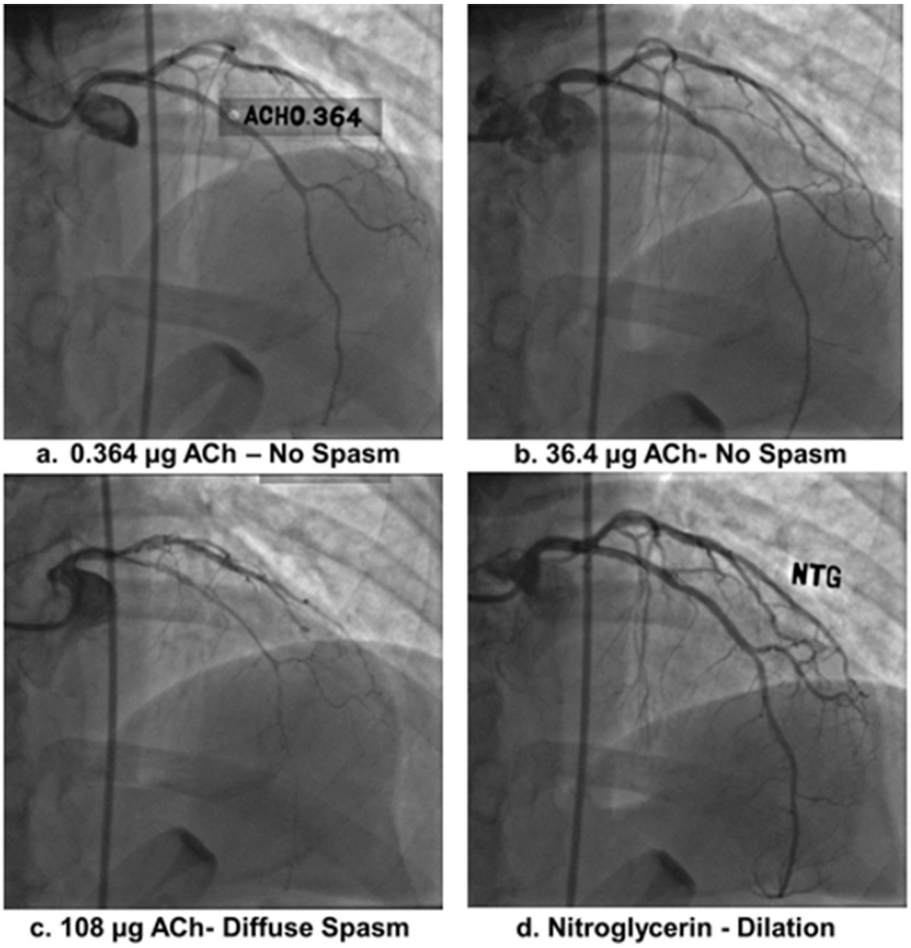

Fig. 1. Epicardial coronary spasm following incremental acetylcholine administration. Epicardial coronary spasm (≥75 %) of the mid-left anterior descending artery with intracoronary acetylcholine 108 μg (C) when compared to baseline (A) and 36.4 μg acetylcholine (B), resolved by administration of intracoronary nitroglycerin (D).

administered by infusion pump, each over 3 min. Cine images were taken between each dosage to evaluate for epicardial coronary vasospasm (Fig. 1). Subsequent doses were not administered if epicardial vasospasm was visualized (n = 1, Fig. 2). Abnormal microvascular endothelial dysfunction was defined as <50 % increase in coronary blood flow (CBF), to 36.4 μg IC Ach, and was calculated using the following formula: (Change in CBF = (CBF following 36.4 μg Ach infusion – resting CBF)/ CBF following 36.4 μg Ach infusion). Epicardial endothelial dysfunction was defined as <0 % increase in coronary artery diameter to 36.4 μg IC ACh. Epicardial vasospasm was defined as ≥75 % decrease in coronary artery diameter compared to post-nitroglycerin diameter, with ECG changes and associated chest pain, per previously established definitions [10,11]. Women who exhibited epicardial vasospasm ≥75 % at baseline or moderate dose (36.4 μg) ACh, prohibiting testing at a higher dose, were also considered to have clinically relevant spasm. Microvascular spasm was defined as <75 % decrease in coronary artery diameter to 36.4 μg or 108 μg of IC ACh with associated ischemic ECG changes and chest pain [11]. Lastly, 200 μg IC nitroglycerin was administered and a < 20 % increase in coronary artery diameter was considered abnormal. Coronary severity score, an angiographic severity score assigning points for any stenosis weighted by stenosis severity, location and collaterals and coronary diameter were measured by quantitative coronary angiography in a core laboratory masked to other clinical data. [13]

2.2. Quality of life (QoL)

Clinical symptoms and QoL were assessed with the Seattle Angina Questionnaire (SAQ), measuring five functional dimensions including (1) physical limitation, (2) angina stability, (3) angina frequency, (4) treatment satisfaction and (5) disease perception. Scores were generated for each domain and scaled 0–100, with 0 denoting the worst and 100 the best possible status. Functional status was assessed with the Duke Activity Status Index (DASI), a 12-item questionnaire that assesses a patient's ability to perform various routine activities of daily living, with a higher score corresponding to a higher functional status [14].

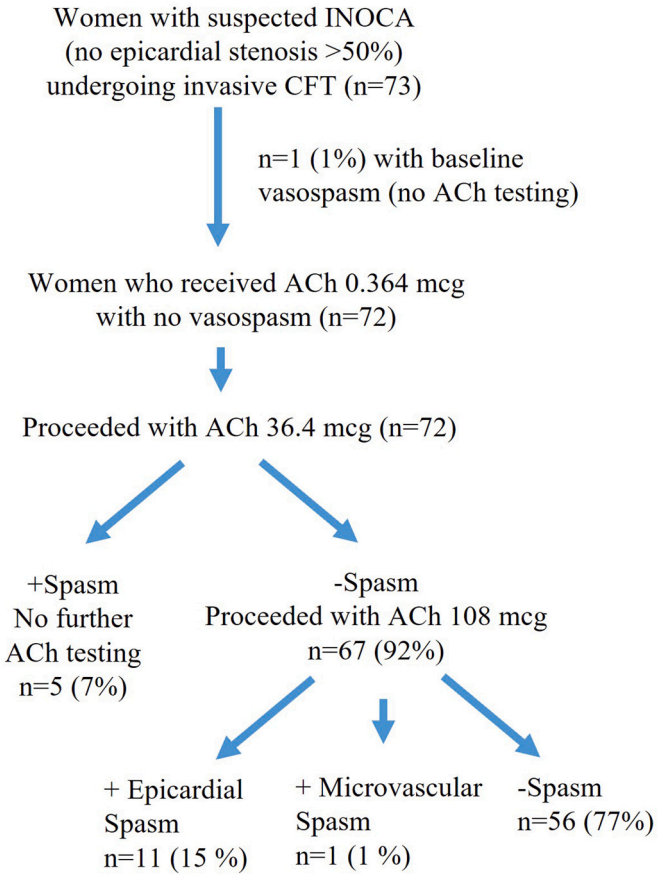

Fig. 2. Coronary function testing with incremental acetylcholine for epicardial vasospasm provocation flow diagram.

2.3. Cardiac magnetic resonance imaging (CMRI)

Participants underwent a vasodilator stress/rest CMRI for assessment of myocardial perfusion and detection of LGE pattern as described previously [15]. All studies were performed on a 3 T scanner (Magnetom Vida, Siemens Healthineers, Erlangen, Germany). A total 0.2 mmol/kg gadolinium-based contrast agent (Optimark, gadoversetamide) was used in divided doses and high resolution LGE images were acquired 12 min post-gadolinium administration, using a single shot multi-slice acquisition approach during breath hold.

LGE images were analyzed with CAAS MRV 3.3 software (Pie Medical Imaging B.V., Netherlands) or CVI42 (v.5.13.5, Circle Cardiovascular Imaging, Calgary, Canada) software by blinded core laboratory. The extent of LGE was quantified using the full-width at half-maximum method. LGE was defined as typical scar (ischemic) pattern when its location was subendocardial or transmural and localized to a coronary artery distribution. Atypical scar (non-ischemic) pattern was defined as LGE with a mid-myocardial or epicardial distribution. LGE quantification was performed by a single experienced operator using post-processing software (QMass, Medis Medical Imaging Systems, Leiden, Netherlands), by delineating regions of LGE across all the multi-slice short axis acquisitions [15].

2.4. Statistical analysis

Variables were summarized using counts and percentages for categorical variables or means and standard deviation for continuous variables. Categorical variables were compared using Fisher's Exact test and continuous variables were compared using Wilcoxon rank sum tests due to outliers or non-normal distributions. A significance level of 0.05 was used.

3. Results

A total of 73 women underwent CFT and CMRI. Overall, 17/73 (23 %) demonstrated epicardial vasospasm (Fig. 2). Of the 17 women with vasospasm, 1 (6 %) had spasm at baseline, 5 (29 %) had spasm with the medium 36.4 mg IC ACh dose and 11 (65 %) had spasm with the higher dose 108 mg IC ACh (Fig. 2). Only one (1 %) woman had microvascular spasm. No CFT-related adverse events occurred.

There was substantial overlap of CFT measured abnormalities and epicardial coronary vasospasm (Fig. 3). Overall, 35/73 (48 %) had microvascular endothelial dysfunction, as evidenced by abnormal CBF and 32 (44 %) had epicardial coronary endothelial dysfunction, as evidenced by abnormal vasodilation. In total, 16/17 of the women with vasospasm (94 %) also had confirmed coronary microvascular endothelial dysfunction (testing with Ach was not performed in one woman due to vasospasm at baseline) while 2/17 (12 %) with spasm also had abnormal CFR (Fig. 4).

Age, cardiovascular risk factors, medications at baseline, and coronary artery severity score were similar in women with and without spasm (Table 1). Women with epicardial vasospasm more frequently reported angina causing nighttime awakening, were more likely to be treated with nitroglycerin, calcium channel blockers and hormone therapy, had lower functional capacity measured by DASI and poorer SAQ disease perception scores compared to those without.

Myocardial scar measured by LGE was identified in 9 (13 %) women—4 women with epicardial coronary spasm and 5 without (p = 0.224) (Table 1). One woman had an ischemic LGE pattern in the LAD territory

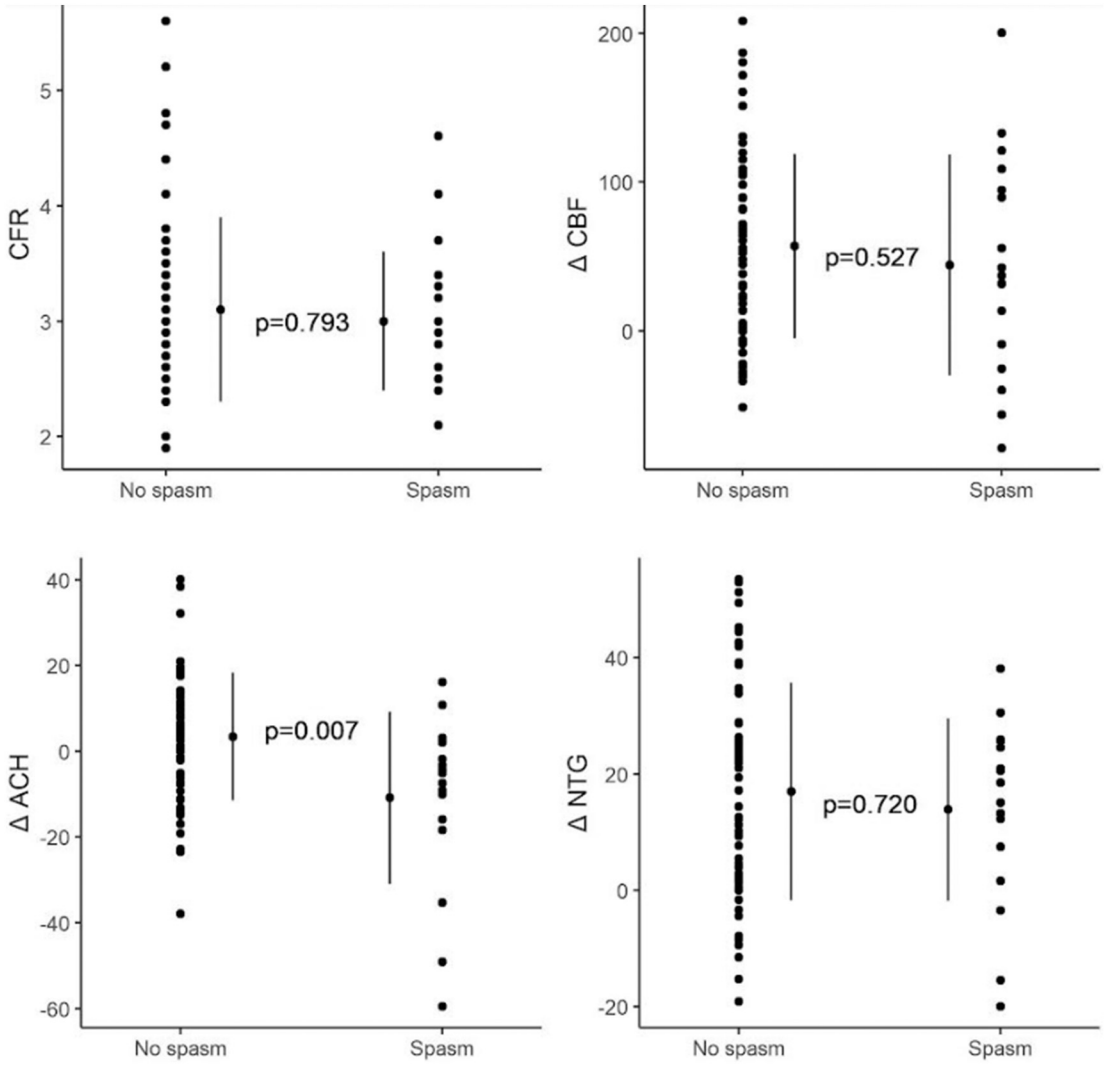

Fig. 3. Comparison of CFT measures in women with and without vasospasm.

and clinical history of myocardial infarction with no obstructive coronary disease, but no vasospasm by provocation testing. All five women with epicardial vasospasm and myocardial scar had a non-ischemic LGE pattern.

4. Discussion

In our study of 73 women with suspected INOCA, epicardial coronary vasospasm was present in nearly one quarter using sequential higher acetylcholine doses. The majority of provoked epicardial vasospasm occurred with the 108 μg ACh dose and without adverse events and most had concomitant coronary endothelial dysfunction. Clinically relevant findings among women with epicardial coronary spasm, include worse QoL measures, worse SAQ disease perception scores, and notably, a first report to our knowledge of poorer functional capacity, a potential correlate for worse outcomes in cardiovascular disease. Myocardial scarring on CMRI was observed infrequently in both those with and without vasospasm. Thus, inclusion of high dose intracoronary spasm ACh testing during CFT appears useful for identifying patients with epicardial vasospasm, a finding with clinically relevant implications.

Notably, women with epicardial vasospasm had more nocturnal angina and calcium channel blocker use, suggesting that these clinically ascertainable variables may be useful for diagnosis of vasospastic angina benefiting tailored therapy. The higher observed history of hormone therapy use is also notable as prior work has identified that vasomotor symptoms may be related to higher cardiovascular mortality and coronary endothelial dysfunction, and suggests a possible link with vasospasm [16].

These findings are similar and add to data from an independent group of investigators who showed that among women who underwent CFT, endothelial dysfunction was present in 94 % of patients who tested positively for vasospasm [17]. In our previous report from WISE studies, we described a similarly high prevalence of coronary endothelial dysfunction in women with suspected INOCA [18]. The current results suggest that single high dose ACh dose may be useful to simultaneously test for spasm and coronary endothelial dysfunction, given that a vast majority of subjects with vasospasm also tested positive for endothelial dysfunction. It is unclear if capturing spasm at the lower dose provides any additional diagnostic or prognostic information. Prior studies have demonstrated a favorable safety profile for the high dose ACh, suggesting it would be safe to omit the lower doses, though most studies to date have utilized sequential low-high doses [19]. More studies would be needed to discern the efficacy and safety of a single high dose of ACh.

The pathophysiologic basis of epicardial vasospasm remains incompletely understood. Proposed mechanisms include primary hyperreactivity of vascular smooth muscle cells, adventitial accumulation of mast cells, fibromuscular dysplasia, passive mechanical collapse and

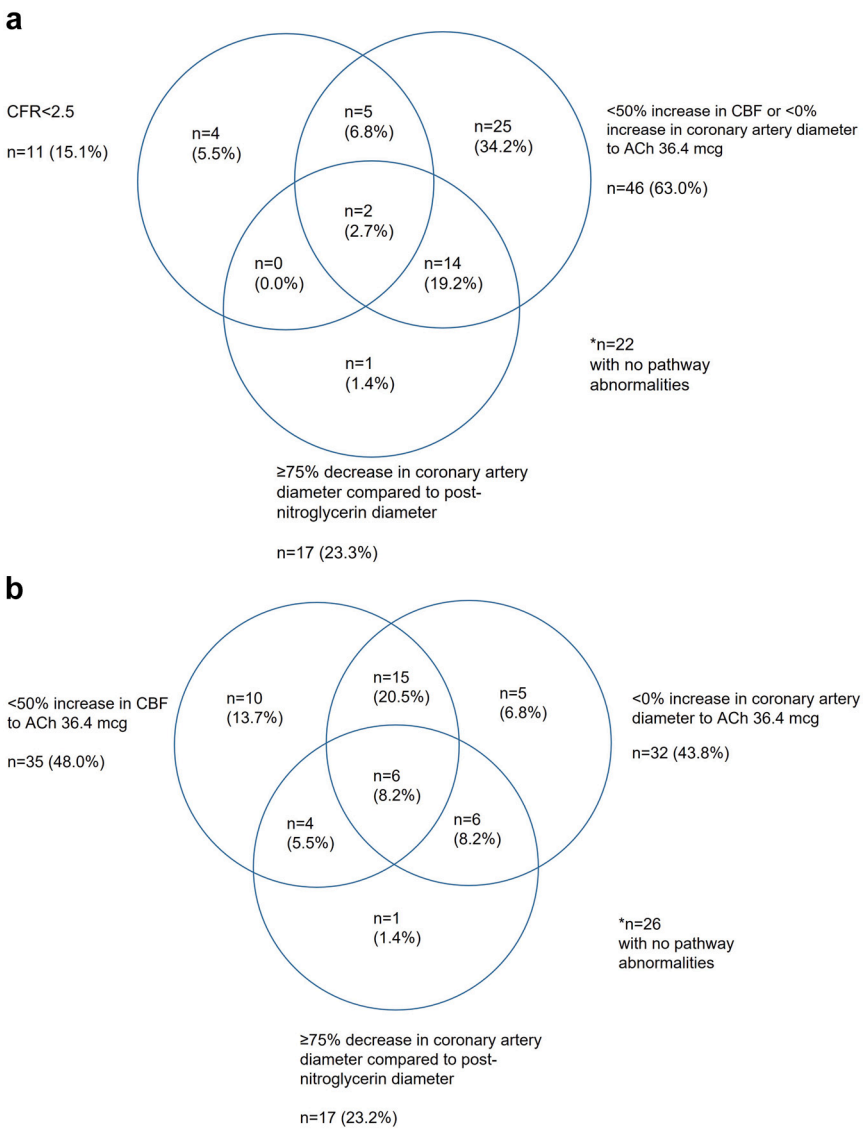

Fig. 4. Overlap of CMD and epicardial vasospasm.
a. Overlap of non-endothelial microvascular dysfunction, endothelial dysfunction and epicardial vasospasm.
b. Overlap of microvascular endothelial dysfunction, epicardial endothelial dysfunction and epicardial vasospasm.

stenosis in the presence of atherosclerotic disease or endothelial dysfunction [20,21]. The endothelium of arteries and arterioles act to regulate inflammation and protect vessels against toxic materials [22] and dysfunction is thought to be driven by reduced nitric oxide utilization leading to an inability to properly dilate arteries and arterioles, thereby leading to ischemia [23]. Here we report that women with epicardial coronary vasospasm had a higher rate of coronary endothelial dysfunction compared to non-endothelial dependent microvascular dysfunction. Together these findings suggest an overlap or continuum of dysfunction between epicardial vasospasm and coronary endothelial dysfunction, and a different pathway of dysregulation than that assessed by CFR measurement.

This study highlights the clinical utility of vasospasm testing as part of CFT. The observed associations between QoL measures including poor functional capacity and quality of life as assessed by DASI and SAQ-7 scores respectively demonstrate the significant morbidity associated with coronary vasospasm, supporting the need for diagnosis and targeted treatment. The randomized controlled CorMicA trial of stratified therapy for INOCA patients guided by invasive CFT findings showed improved angina and quality of life, compared to standard of care [24]. By properly identifying the underlying dysfunctional pathway using CFT, including acetylcholine testing, treatments can be appropriately tailored towards said pathway, with calcium channel blockers and nitrates favored for vasospasm and consideration of statin and, ACE or ARB for endothelial dysfunction [20,25]. Notably, women in this study with provoked vasospasm reported significantly more nocturnal angina, providing evidence supportive of a clinical symptom conventionally associated with vasospastic angina. Those with angina also had a higher history of treatment with calcium channel blockers and short acting nitrites, perhaps reflective of empiric treatment driven by symptomatic history. Optimal treatment for angina in women with suspected INOCA remains unclear and is being addressed by the ongoing Women's IschemiA TRial to Reduce Events In Non-ObstRuctive CAD (WARRIOR), a multicenter, prospective, randomized, blinded outcome evaluation (PROBE design) of a pragmatic strategy of IMT vs. usual care (UC) in symptomatic women with INOCA (NCT 03417388) at US sites.

We have previously demonstrated in an earlier WISE cohort with suspected INOCA but without vasospasm provocation testing that myocardial scar evidenced by LGE prevalence was 8 %, with 69 % having a documented history of myocardial infarction (MI) [15]. Similarly, in the present analysis, overall prevalence of LGE was 15 %, with reported history of MI in up to 25 % of women, with no significant

Table 1
Baseline characteristics and CFT results in women with and without epicardial coronary vasospasm ($n = 73$).

	Epicardial vasospasm $n = 17$ (23.3 %)	No epicardial vasospasm $n = 56$ (76.7 %)	*p*-Value
Age	57.1 (±10.0)	55.9 (±11.1)	0.784
Hypertension	6 (42.9 %)	14 (35.0 %)	0.749
Diabetes	1 (6.3 %)	3 (6.7 %)	1.000
Dyslipidemia	4 (28.6 %)	7 (18.9 %)	0.467
Current or former smoker	5 (31.3 %)	14 (31.1 %)	1.000
Family history of CAD	10 (62.5 %)	27 (65.9 %)	1.000
Ethnicity			0.821
Native American	1 (2.2 %)	0 (0.0 %)	
Asian/Pacific Islander	4 (8.9 %)	0 (0.0 %)	
African American	2 (4.4 %)	0 (0.0 %)	
Hispanic/Latino	2 (4.4 %)	1 (6.3 %)	
Caucasian	35 (77.8 %)	15 (93.8 %)	
Other	1 (2.2 %)	0 (0.0 %)	
History of MI	4 (25.0 %)	9 (20.5 %)	0.452
Myocardial bridge	5 (29.4 %)	7 (12.5 %)	0.135
Migraines	6 (37.5 %)	15 (33.3 %)	0.768
Raynaud's phenomenon	2 (12.5 %)	5 (11.6 %)	0.661
Thyroid medications	8 (50.0 %)	11 (24.4 %)	0.069
Angina nighttime awakening	11 (68.8 %)	17 (38.6 %)	0.047
ACE-I or ARB	4 (25 %)	19 (42.2 %)	0.250
Beta blocker	5 (31.3 %)	16 (35.6 %)	1.00
Calcium channel blocker	10 (62.5 %)	11 (24.4 %)	0.012
Nitrates (short-acting)	15 (93.8 %)	32 (71.1 %)	0.088
Ranolazine	4 (25 %)	8 (17.8 %)	0.456
Anxiolytics	2 (12.5 %)	8 (17.8 %)	1.000
History of hormone therapy	12 (85.7 %)	22 (50.0 %)	0.028
LGE	4 (25 %)	5 (11.1 %)	0.224
CFR[a]	3.0 (±0.6)	3.1 (±0.8)	0.793
ΔCBF	44.0 (±74.3)	56.9 (±61.9)	0.527
ΔACH	−10.9 (± 20.1)	3.4 (±14.9)	0.007
ΔNTG	13.9 (±15.7)	17.0 (±18.7)	0.720
Total coronary artery severity score	5.6 (±1.8)	5.1 (±0.4)	0.118
DASI-estimated METs[a]	4.8 (±3.9)	9.5 (±5.9)	0.006
SAQ-7 overall score	44.4 (±19.0)	56.1 (±20.2)	0.085
SAQ physical limitation	59.3 (±21.8)	63.6 (±20.8)	0.601
SAQ angina stability	48.4 (±23.2)	44.9 (±22.0)	0.609
SAQ angina frequency	41.3 (±25.3)	51.1 (±30.1)	0.223
SAQ treatment satisfaction	70.6 (±21.7)	74.0 (±17.2)	0.613
SAQ disease perception	34.9 (±15.9)	50.2 (±21.1)	0.014

Data are presented as mean (±SD) or n (%) for available data (missing data excluded).
ACE = Angiotensin-Converting Enzyme Inhibitor, ΔACH = change in coronary artery diameter in response to acetylcholine, ARB = Angiotensin Receptor Blocker, CAD = coronary artery disease, ΔCBF = change in coronary blood flow in response to acetylcholine, CFR = coronary flow reserve, DASI = Duke Activity Status Index, METs = Metabolic equivalents, MI = myocardial infarction, ΔNTG = change in coronary artery diameter in response to nitroglycerin, SAQ-7 = Seattle Angina Questionnaire-7.
[a] 10 women in the spasm group did not complete MRI, DASI-score missing in 13 individuals.

difference was observed between women with provoked vasospasm and those without. This discordance may be due to delays between clinical presentation and subsequent MRI, which tend to identify LGE more often when performed earlier in disease course [26]. Of note, the relatively small sample size of women with positive LGE limits our assessment of whether vasospasm led to myocardial scar, the converse, or if there may be a bi-directional relationship.

4.1. Study limitations

We did not study men by design although CMD, coronary vasospasm and endothelial dysfunction are increasingly recognized in men. We chose to utilize 108 μg as our maximum dose of ACh, though many centers have studied a 200 μg dose, with a recent study showing an increased incidence of spasm with a 200 μg dose compared to 100 μg in a cohort of 27 % women [27]. Of note, sex-specific differences in response to ACh have been reported, with men showing a dose-response relationship of constriction to ACh at doses up to 200 μg, and women exhibiting minimal change with doses above 50 μg [28]. It thus remains unclear whether spasm may be under-diagnosed in our present study, and if sex-differences are evident.

With regard to ACh administration, we adopted an infusion rate over the course of 3 min, though other centers have administered a bolus over 30 to 60 s. It is unclear if a faster rate of administration may elicit more vasospasm and studies are underway to evaluate this [29,30]. Doppler wire measurements did not allow for concomitant evaluation of index of myocardial resistance (IMR), an increasingly used parameter in INOCA patients, however CFT using doppler wire flow evaluation allows for signal inspection leading to accurate flow measurements unhampered by arterial wall artefacts, minimizing flow variability and allowing for accurate assessment of resistance, which itself is derived from flow measurements [31].

Our definition of epicardial vasospasm (≥75 % compared to post-nitroglycerin diameter) differs slightly from the proposed universal definition of >90 %, however we contend that our threshold with comparison to post-nitroglycerin diameter is likely of similar value and also highly standardized with core laboratory measurement of quantitative angiography within this study [6]. Overall, our study is limited by the relatively small sample size, particularly for patients undergoing follow-up CMR. Lastly, we assessed functional status through patient-reported outcome measures, which may be susceptible to reporting bias.

4.2. Implications

Women with suspected INOCA comprise a heterogeneous group and proper identification of patients with epicardial coronary vasospasm is of long-term prognostic value as these patients can be at risk of both non-fatal myocardial infarction and in severe cases, cardiac arrest [32]. Proper identification of underlying mechanisms of INOCA using CFT allows for tailored therapy, better symptom control, and improved quality of life [33]. Longer follow-up studies evaluating prognostic significance and clinical outcomes of provoked epicardial vasospasm and presence and patterns of LGE are necessary and are presently underway in this cohort, with additional studies needed for investigating mechanistic processes for treatment targets.

5. Conclusions

Among women with suspected INOCA, intracoronary spasm ACh testing is useful for detecting epicardial coronary vasospasm evident in one fourth of participants. Women with epicardial vasospasm most often also have endothelial dysfunction, report poorer QoL but not more frequent myocardial scar by CMRI.

Clinical perspectives (what's known, what's new, what's next)

What is known? Epicardial vasospasm is prevalent in women with suspected INOCA but is not commonly tested with provocative intracoronary acetylcholine (ACh) testing. The utility of higher dose ACh and relations to outcomes not well described.

What is new? Intracoronary ACh at sequentially higher doses is useful for diagnosis of epicardial coronary vasospasm. Almost all women with epicardial vasospasm also had coronary endothelial dysfunction, report poorer functional capacity and quality of life, but not more frequent myocardial scar.

What is next? Inclusion of high dose intracoronary spasm ACh testing during CFT appears useful for identifying patients with vasospasm, a group at higher risk of morbidity, including greater symptoms, poorer quality of life, which could impacting healthcare resource utilization, necessity of treatment intensification and potentially prognosis.

CRediT authorship contribution statement

Benita Tjoe: Writing – original draft. **Christine Pacheco:** Writing – original draft. **Nissi Suppogu:** Writing – review & editing. **Bruce Samuels:** Writing – review & editing. **Panteha Rezaeian:** Writing – review & editing. **Balaji Tamarappoo:** Writing – review & editing. **Daniel S. Berman:** Writing – review & editing. **Behzad Sharif:** Writing – review & editing. **Michael Nelson:** Writing – review & editing. **R. David Anderson:** Writing – review & editing. **John Petersen:** Writing – review & editing. **Carl J. Pepine:** Writing – review & editing. **Louise E. J. Thomson:** Writing – review & editing. **C. Noel Bairey Merz:** Writing – review & editing. **Janet Wei:** Writing – review & editing.

Ethical statement

The study was performed under an Institutional Review Board approved protocol in accordance with guidelines for human subjects in research. All patient subjects provided informed consent to participate in this study. All authors attest that this work is original and not under consideration for publication elsewhere.

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Declaration of competing interest

Dr. C. Noel Bairey Merz, serve as Board of Director for iRhythm, fees paid through CSMC from Abbott Diagnostics and SHL Telemedicine. Dr. Janet Wei served on an advisory board for Abbott Vascular. CJP serves as the Editor-in-Chief of AHJO.

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