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RESEARCH LETTER

Myocardial Scar Is Prevalent and Associated With Subclinical Myocardial Dysfunction in Women With Suspected Ischemia But No Obstructive Coronary Artery Disease

From the Women's Ischemia Syndrome Evaluation–Coronary Vascular Dysfunction Study

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Women with suspected ischemia and no obstructive coronary artery disease (INOCA) have a high prevalence of coronary microvascular dysfunction[1] and an elevated rate of major adverse cardiac events, including nonfatal myocardial infarction (MI).[2] Cardiac magnetic resonance (CMR) with late gadolinium enhancement (LGE) imaging accurately visualizes and characterizes myocardial scar, which predicts major adverse cardiac events.[3] The prevalence, incidence, and scar pattern in women with INOCA is not well characterized. We evaluated LGE in women with suspected INOCA in the WISE-CVD study (Women's Ischemia Syndrome Evaluation–Coronary Vascular Dysfunction; URL: http://www.clinicaltrials.gov. Unique identifier: NCT00832702).

Participants in the WISE-CVD study included women with suspected INOCA as previously described.[4] The study was approved by the site institutional review committees. All participants gave informed consent. Of the 369 total women enrolled, 341 underwent baseline CMR with LGE; 1 was excluded because of inadequate quality. A subset of 145 underwent invasive coronary reactivity testing.[5] The SAQ (Seattle Angina Questionnaire) was completed at baseline and 1-year follow-up. Retrospective review included clinical diagnosis of MI, electrocardiogram, and troponin levels. A subset of 200 participants underwent repeat CMR with LGE at 1-year follow-up; 179 were included with baseline CMR and follow-up within 1 year of study completion.

All scans were performed on a 1.5T scanner (Magnetom Avanto, Siemens Healthcare) and analyzed by the WISE-CMR core lab.[4] A total 0.2 mmol/kg gadolinium-based contrast (Optimark, gadoversetamide) in divided doses was used, and LGE images were acquired using a 2D inversion-recovery turbo FLASH (slice thickness 8 mm, skip 2 mm, TE 3 ms, TR 0.7 s, flip angle 25 degrees). Scans were read blinded to clinical information; the extent of LGE was quantified using the full width at half-maximum method. LGE type was defined as typical scar pattern when subendocardial or transmural and localized to a coronary artery distribution and atypical scar pattern when midmyocardial or epicardial. LGE quantification was performed by a single experienced operator using postprocessing software (QMass, Medis) by delineating regions of LGE across all the multislice short axis acquisitions. Fisher exact or 2-sample *t* tests were used to compare groups. Linear regression with log transformation of the troponin variable was used to assess the relationship between troponin level and scar size.

LGE was present at baseline in 26 (8%) women who were younger, had lower blood pressure, were more likely to be prescribed calcium channel blockers and clopidogrel, and had lower SAQ treatment satisfaction, compared with women without LGE (Table). Women with LGE also had lower left ventricular ejection fractions and higher end-diastolic and end-systolic volumes but no difference in myocardial perfusion reserve index. There were also no differences in the invasive variables in the coronary reactivity testing subset.

Key Words: chronic ischemic heart disease ■ magnetic resonance imaging ■ women

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Table. Clinical and Cardiac Magnetic Resonance Characteristics

Characteristics	Late Gadolinium Enhancement		*P* Value
	No (n=314)	Yes (n=26)	
Age, y	55±11	51±11	0.04
Body mass index, kg/m^2	29±8	31±9	0.55
Systolic blood pressure, mm Hg	131±20	120±18	0.004
Diastolic blood pressure, mm Hg	64±13	57±12	0.009
Hypertension	111 (39)	10 (40)	1.00
Diabetes mellitus	31 (10)	4 (15)	0.51
Dyslipidemia	45 (18)	3 (14)	0.78
History of smoking	114 (37)	9 (33)	0.94
Migraines	160 (51)	16 (59)	0.55
Postmenopausal	230 (73)	14 (56)	0.07
Medications			
Angiotensin converting-enzyme inhibitor	55 (18)	5 (20)	0.79
Angiotensin receptor blocker	20 (7)	2 (8)	0.67
Diuretic	42 (14)	4 (15)	0.78
Nitrate	93 (31)	8 (30)	1.00
β-Blocker	97 (32)	11 (42)	0.29
Calcium channel blocker	59 (20)	11 (41)	0.02
Ranolazine	22 (7)	2 (8)	1.00
Aspirin	183 (59)	19 (70)	0.31
Clopidogrel or other antiplatelet	5 (2)	3 (12)	0.02
Seattle Angina Questionnaire			
Physical Limitation Scale	68±24	75±24	0.18
Angina Stability Scale	49±26	48±28	0.90
Angina Frequency Scale	64±26	64±24	0.95
Treatment Satisfaction Scale	70±24	56±30	0.03
Disease Perception Scale	50±24	47±21	0.48
Cardiac magnetic resonance imaging			
Ejection fraction, %	68±7	63±9	0.004
End-diastolic volume, mL	122±24	136±25	0.01
End-systolic volume, mL	39±13	51±19	0.002
Left ventricular mass, g	93±17	96±19	0.42
Mass-to-volume ratio, g/mL	0.78±0.16	0.72±0.14	0.06
Myocardial perfusion reserve index	1.84±0.50	2.00±0.48	0.12
Scar size, g			
Typical scar pattern (n=18)		5.1±3.6	0.08
Atypical scar pattern (n=8)		8.9±7.0	0.08
Coronary reactivity testing (n=145)			
n	138	7	
Coronary flow reserve	2.75±0.65	2.36±0.45	0.07
Coronary blood flow response, %	77±95	64±64	0.62
Acetylcholine diameter response, %	1±13	4±19	0.69
Nitroglycerin diameter response, %	16±13	19±13	0.54

Values are mean±SD, or n (%).

Of the 26 participants with baseline LGE, 18 (69%) had a documented prior history of MI, with troponin available in 17 of 18 participants. Average peak troponin level was 25.5 ng/mL (median 4.3, min 0.1, max 250.0 ng/mL). There was no significant relationship between troponin level and scar size (*P*=0.18). In addition, 24 (92%) participants had electrocardiograms available for review, and 2 of these 24 (1 with typical scar, 1 with atypical scar) demonstrated pathological Q waves consistent with prior MI.

Most LGE cases (n=18/26) demonstrated a typical scar pattern, with vascular distributions in the left anterior descending artery (n=4), left circumflex artery (n=8), right coronary artery (n=4), left anterior descending and circumflex arteries (n=1), and left anterior descending and right coronary arteries (n=1). Atypical scar cases (n=8/26, 31%) were patchy epicardial (n=6), subepicardial right ventricular (n=1), or midmyocardial septal pattern (1). Compared with the typical scar pattern, the atypical scar pattern tended to be in younger (45±12 versus 53±9 years, *P*=0.068) participants with a larger scar size (8.9±7.0 versus 5.1±3.6 g, *P*=0.076).

Among the subset with 1-year CMR scans (n=179/340), new LGE was present in 1% (n=2/179), both were atypical scar pattern. Overall, 8% (n=14/179) had LGE in both baseline and 1-year CMR, of which 71% (n=10/14) demonstrated a typical scar pattern. There was no 1-year interval scar size change. Interval index events included 1 MI, 1 heart failure, and 19 angina hospitalizations in 21 women (12%). It is notable that both women with new LGE had interval angina hospitalizations but no interval clinical diagnosis of MI. The 1 subject with a clinically diagnosed interval MI did not have interval LGE change.

In summary, among women with suspected INOCA, LGE prevalence was 8%, with an annual 1% new LGE incidence. One-third of our women with LGE did not have prior diagnosis of MI, suggesting that women with suspected INOCA not uncommonly have a clinically underdiagnosed myocardial scar. Further phenotyping is needed to better understand women with a typical versus an atypical scar pattern because conditions such as myocarditis or coronary vasospasm may

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have a different clinical or prognostic impact. Longer follow-up is needed to determine whether CMR LGE predicts prognosis, changes clinical management, or results in improved patient outcomes. Our results raise the importance of diagnosis and improved mechanistic understanding of INOCA as well as clinical trials to develop evidence-based treatment guidelines.

ARTICLE INFORMATION

Data are available from the corresponding author on request.

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