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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

Janet Wei, MD[1], **May Bakir, MD**[1], **Navid Darounian, MD**[1], **Quanlin Li, MS**[2], **Sofy Landes, MD**[1], **Puja K. Mehta, MD**[3], **Chrisandra L. Shufelt, MD**[1], **Eileen M. Handberg, PhD**[4], **Sheryl F. Kelsey, MD**[5], **George Sopko, MD**[6], **Carl J. Pepine, MD**[4], **John W. Petersen, MD**[4], **Daniel S. Berman, MD**[1], **Louise E. J. Thomson, MBChB**[1], and **C. Noel Bairey Merz, MD**[1]

[1]Barbra Streisand Women's Heart Center, Cedars-Sinai Heart Institute, Los Angeles, CA

[2]Biostatistics and Bioinformatics Research Center, Cedars-Sinai Medical Center, Los Angeles, CA

[3]Emory University School of Medicine, Atlanta, GA

[4]University of Florida, Gainesville, FL

[5]University of Pittsburgh, Pittsburgh, PA

[6]National Heart, Lung, and Blood Institute, Bethesda, MD

Women with suspected ischemia and no obstructive coronary artery disease (INOCA) have a high prevalence of coronary microvascular dysfunction (CMD)[1] and an elevated major adverse cardiac event (MACE) rate, including nonfatal myocardial infarction (MI)[2]. Cardiac magnetic resonance (CMR) with late gadolinium enhancement (LGE) imaging accurately visualizes and characterizes myocardial scar which predicts MACE[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 Women's Ischemia Syndrome Evaluation – Coronary Vascular Dysfunction (WISE-CVD) study. (Clinical Trial Registration: URL: http://www.clinicaltrials.gov. Unique Identifier: NCT00832702.)

WISE-CVD participants were women with suspected INOCA, as previously described[4]. The study was approved by the site institutional review committees; all participants gave informed consent. Data are available from the corresponding author upon request. Of the 369 total women enrolled, 341/369 underwent baseline CMR with LGE; 1 was excluded due to inadequate quality. A subset of 145/340 underwent invasive coronary reactivity testing

Correspondence: C. Noel Bairey Merz MD, Barbra Streisand Women's Heart Center, Cedars-Sinai Heart Institute, 127 S San Vicente Blvd, #A3906, Los Angeles, CA 90048. Telephone: (310)423-9680, Fax: (310)423-9681, merz@cshs.org.

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(CRT)[5]. The Seattle Angina Questionnaire (SAQ) was completed at baseline and one 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 one year follow-up; 179 were included with baseline CMR and follow-up within one 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; 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 mid-myocardial or epicardial. LGE quantification was performed by a single experience operator using post-processing software (QMass, Medis), by delineating regions of LGE across all the multi-slice short axis acquisitions. Fisher’s exact or two 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, more likely to be prescribed calcium channel blockers and clopidogrel, and had lower SAQ treatment satisfaction, compared to 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 CRT subset.

Of the 26 participants with baseline LGE, 18 (69%) had a documented prior history of MI, with troponin available in 17/18 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, 24/26 (92%) participants had electrocardiograms available for review, and 2/24 (1 with typical scar, 1 with atypical scar) demonstrated pathologic Q waves consistent with prior MI.

Most LGE cases (18/26) demonstrated a typical scar pattern, with vascular distributions in the LAD (4), LCX (8), RCA (4), LAD and LCX (1), LAD and RCA (1). Atypical scar cases (8/26, 31%) were patchy epicardial (6), subepicardial right ventricular (1), or mid-myocardial septal pattern (1). Compared to typical scar pattern, atypical scar pattern tended to be in younger (45±12 vs 53±9 years, p=0.068) participants with larger scar size (8.9±7.0 vs 5.1±3.6 grams, 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 one-year CMR, of which 71% (n=10/14) demonstrated a typical scar pattern; there was no one-year interval scar size change. Interval index events included 1 MI, 1 heart failure and 19 angina hospitalizations in 21 women (12%). Notably, both women with new

LGE had interval angina hospitalizations but no interval clinical diagnosis of MI. The one 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 clinically under-diagnosed myocardial scar. Further phenotyping is needed to better understand women with typical vs atypical scar pattern, as conditions such as myocarditis or coronary vasospasm may have different clinical or prognostic impact. Longer follow-up is needed to determine whether CMR LGE predicts prognosis, changes clinical management and/or results in improved patient outcomes. Our results raise the importance of diagnosis and improved mechanistic understanding of INOCA, as well clinical trials to develop evidence-based treatment guidelines.

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Table

Clinical and CMR Characteristics

Mean ± SD, or n (%)	**No LGE (n=314)**	**LGE (n=26)**	**P value**
Age (years)	55 ± 11	51 ± 11	**0.04**
Body Mass Index (kg/m^2)	29 ± 8	31 ± 9	0.55
Systolic Blood Pressure (mmHg)	131 ± 20	120 ± 18	**0.004**
Diastolic Blood Pressure (mmHg)	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			
ACE 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
Beta 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 MRI (n=340)			
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 (gm)	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) Atypical Scar Pattern (n=8)		5.1 ± 3.6 8.9 ± 7.0	0.08
Coronary Reactivity Testing (n=145)	**(n=138)**	**(n=7)**	

Mean ± SD, or n (%)	No LGE (n=314)	LGE (n=26)	P value
Coronary Flow Reserve	2.75 ± 0.65	2.36 ± 0.45	0.07
Coronary Blood Flow Response (%)	77 ± 95	64 ± 64	0.62
ACH Diameter Response (%)	1 ± 13	4 ± 19	0.69
NTG Diameter Response (%)	16 ± 13	19 ± 13	0.54

ACE, angiotensin converting-enzyme; ACH, acetylcholine; NTG, nitroglycerin