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Prior Myocardial Infarction is Associated with Coronary Endothelial Dysfunction in Women with Signs and Symptoms of Ischemia and No Obstructive Coronary Artery Disease

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Compared to men, women who present with signs and symptoms of myocardial ischemia are more likely to have no obstructive coronary artery disease (CAD) when they undergo coronary angiography (1). These symptomatic patients with evidence of ischemia often have coronary microvascular dysfunction (CMD) due to endothelial dependent and/or independent mechanisms, despite absence of visible obstructive CAD on routine angiography (2, 3). A definitive diagnosis of coronary endothelial dysfunction and abnormal flow reserve requires invasive coronary reactivity testing (CRT). We and others have demonstrated that coronary endothelial dysfunction detected by abnormal response to acetylcholine(4), as well as abnormal coronary flow reserve to adenosine(5) are associated with an adverse prognosis in women. The endothelium plays a key role in the regulation of vascular tone, growth, thrombogenicity, and inflammation (6); endothelial dysfunction has been implicated as an underlying mechanism in the pathogenesis of atheroma formation. Thus, endothelial dysfunction may be associated with increased occurrence of myocardial infarction (MI). We evaluated for an association between endothelial dysfunction and prior MI in women who underwent CRT for suspected CMD.

We studied 67 symptomatic women with signs and symptoms of ischemia and no obstructive CAD (<50% luminal obstruction in one or more epicardial coronary arteries on invasive angiography) enrolled in the "Coronary Microvascular Disease and Endothelial Function in Women" Study at Cedars-Sinai Medical Center between the years 2006 and 2008. Exclusion

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criteria: recent acute coronary syndrome, contraindications to angiography, no structural or valvular heart disease, unable to safely withhold nitrates, beta blockers, calcium channel blockers, angiotensin converting enzyme inhibitors (ACE) and angiotensin receptor blockers for 48 hours prior to testing, significant liver disease, renal disease (creatinine >1.5), psychiatric illness and pregnancy. Study was IRB approved and all participants gave written informed consent. Participants underwent clinically indicated CRT via a highly standardized protocol as previously published (7), with Doppler tipped guidewire (Flowire®, Volcano) placed in the left anterior descending coronary artery. Bolus injections of intracoronary adenosine (18 µg, 18 µg and 36 µg) were used to determine coronary flow reserve (CFR). A CFR ≥ 2.5 was considered normal. Intracoronary acetylcholine (ACH) (total of 36.4 µg) infusion over 3 minutes was used to assess endothelial function. Coronary artery dilation >5% in response to ACH was considered normal. Lastly, intracoronary nitroglycerin (200 µg) was injected to determine smooth muscle response. Normal nitroglycerin response was defined as a diameter increase $\geq 20\%$.

History of prior MI was obtained through supervised, self-reported questionnaires and confirmed with medical record evidence of elevated troponin when available. Retrospective chart review was performed when available to confirm evidence of MI. MI was diagnosed based on the 2012 third universal definition of MI criteria by European Society of Cardiology/American College of Cardiology Foundation/American Heart Federation/World Heart Federation (8). The independent t-test was used to determine statistical differences between the two groups.

Patient demographics are shown (Table 1). 10 of the 67 (15%) women had a history of previous MI, and 4/10 (40%) had medical records confirming MI. There was no difference in age, hypertension, dyslipidemia, body mass index, smoking history, family history of heart disease, and diabetes between the MI and no MI groups. Overall, 69% of women had an abnormal response to ACH, 34% had an abnormal coronary flow reserve to adenosine, and 61% had a suboptimal response to IC nitroglycerin. The change in coronary diameter in response to high dose ACH was significantly different between the two groups ($p = 0.013$) (Table 2). There was no coronary artery spasm noted to highest dose of ACH in this protocol (36.4 µg), with coronary artery spasm defined as >70% vasoconstriction (7).

These findings suggest an association between endothelial dysfunction and history of prior MI in women with signs and symptoms of ischemia with no obstructive CAD. In this cohort of women suspected of CMD who underwent CRT, a majority had endothelial dysfunction, and mean LVEDP was elevated despite having preserved ejection fraction and no previous history of cardiomyopathy, valvular disease or congestive heart failure.

Endothelial dysfunction has been shown to constitute an independent predictor of CV events providing valuable prognostic information in addition to that derived from conventional risk factor assessment (9). We have previously demonstrated that impaired response to ACH was independently linked to adverse CV outcomes regardless of CAD severity in the Women's Ischemia Syndrome Evaluation (WISE) study (4). Suwaidi et al studied patients with no obstructive CAD who underwent invasive CRT and intracoronary ultrasound. After an average of 28 month-follow up, patients with abnormal response to ACH demonstrated

increased risk of CV events including MI, percutaneous or surgical coronary revascularization and death (10).

Risk factor modification and pharmacologic therapy that targets endothelial function, such as statins, angiotensin inhibitors, and newer generation beta-blockers (nebivolol), may potentially improve prognosis in those with CMD, however randomized clinical trials are needed. Interventions such as cardiac rehabilitation and external counterpulsation therapy can also play a significant role in symptom improvement in women with endothelial dysfunction (11–13). Endothelial dysfunction is an attractive primary target in the effort to optimize individualized therapeutic strategies to reduce CV adverse events in those with CMD (9).

The association between coronary endothelial dysfunction and prior MI demonstrated in this pilot study should be confirmed in larger patient populations. While we demonstrate an association between coronary endothelial dysfunction and those with a history of prior MI, causality cannot be inferred based on this study. Secondly, prior history of MI was obtained through self-reported questionnaires. Therefore, recall bias might have influenced the results of the study. We tried to decrease this error by confirming elevated troponin levels of women in MI group from their medical records.

We report that a history of prior MI in women with signs and symptoms of ischemia and no obstructive CAD is associated with coronary endothelial dysfunction. Future studies should consider coronary endothelial dysfunction as a treatment target in women with a history of MI and no obstructive CAD.

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Table 1

Demographic Characteristics

	MI (n=10)	No MI (n=57)	p-value
Age (mean $\pm$ SD)	51 $\pm$ 12	55 $\pm$ 9	0.22
BMI (mean $\pm$ SD)	26.4 $\pm$ 6.1	26.1 $\pm$ 3.7	0.89
Hypertension (n, %)	2, 20%	23, 41%	0.21
Dyslipidemia (n, %)	5, 50%	25, 45%	0.80
Diabetes (n, %)	0, 0%	0, 0%	-
Current Smoker (n, %)	0, 0%	2, 4%	0.55
Family history of CAD (n, %)	8, 80%	37, 65%	0.36
Statins	6, 60%	34, 60%	1.00
ACE inhibitors	2, 20%	17, 30%	0.71
ARB	1, 10%	3, 5%	0.49
Beta Blockers	4, 40%	28, 42%	0.74
Calcium Channel blockers	2, 20%	21, 37%	0.47

ACE= angiotensin converting enzyme, ARB= angiotensin receptor blocker, BMI= body mass index, CAD= coronary artery disease, MI=myocardial infarction.

Table 2

Results of Coronary Reactivity Testing

	MI (n=10) (mean $\pm$ SD)	No MI (n=57) (mean $\pm$ SD)	p-value
RPP	9628 $\pm$ 2814	10073 $\pm$ 2700	0.636
CFR to Adenosine	2.46 $\pm$ 0.57	2.73 $\pm$ 0.68	0.242
Change in LAD diameter to Acetylcholine	-29.85 $\pm$ 29.52	-7.97 $\pm$ 24.34	0.013
Change in LAD diameter to Nitroglycerin	19.46 $\pm$ 20.41	17.04 $\pm$ 14.01	0.641
LVEDP	17.40 $\pm$ 3.89	15.47 $\pm$ 4.79	0.240

CFR=coronary flow reserve, LVEDP= left ventricular end-diastolic pressure, RPP= rate pressure product