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Myocardial Ischemia in the Absence of Obstructive Coronary Artery Disease in Systemic Lupus Erythematosus

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OBJECTIVES The purpose of this study was to evaluate the presence of myocardial ischemia measured by adenosine stress cardiac magnetic resonance (CMR) using visual myocardial perfusion and a quantitative myocardial perfusion reserve index (MPRI) in the absence of obstructive coronary artery disease (CAD) in women with systemic lupus erythematosus (SLE) with anginal chest pain (CP).

BACKGROUND Ischemic heart disease is a leading cause of morbidity and mortality in SLE. Previous studies demonstrated the presence of perfusion defects using adenosine stress CMR in patients with CP and no obstructive CAD, consistent with microvascular coronary dysfunction in patients without SLE.

METHOD Twenty female SLE patients with typical and atypical anginal CP were prospectively enrolled. Patients with established cardiovascular disease were excluded. CMR was performed with 0.05 mmol/kg gadolinium adenosine stress first-pass perfusion in SLE patients and in 10 asymptomatic reference control women. SLE patients also underwent 64-slice coronary computed tomography angiography. CMR was scored visually and quantitatively (MPRI).

RESULTS Among 18 patients with complete data, no patient had obstructive CAD; however, 8 of 18 (44%) displayed visual perfusion defects on stress CMR compared with 0 in 10 control subjects ($p = 0.014$). The mean MPRI in patients versus controls was 2.0 ± 0.4 versus 2.4 ± 0.4 ($p = 0.031$) in the subepicardium and 1.8 ± 0.3 versus 2.1 ± 0.4 ($p = 0.24$) in the subendocardium. Multivariate linear regression revealed that SLE was the only predictor of subepicardial ($p < 0.0025$; $\beta = -1.059$) and subendocardial ($p < 0.05$; $\beta = -0.529$) MPRIs.

CONCLUSIONS We observed a 44% prevalence of abnormal stress myocardial perfusion by CMR in the absence of obstructive CAD in SLE patients with anginal CP. Compared with controls, reduced MPRI was observed in SLE patients, and SLE presence was a significant predictor of an abnormal MPRI. These findings are consistent with the hypothesis that anginal CP in SLE patients without obstructive CAD is due to myocardial ischemia potentially caused by microvascular coronary dysfunction. Further research in a larger SLE population is warranted. (J Am Coll Cardiol Img 2011;4:27–33) © 2011 by the American College of Cardiology Foundation

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Ischemic heart disease in systemic lupus erythematosus (SLE) patients, a leading cause of morbidity and mortality, has a complex pathogenesis that is incompletely understood. Because SLE occurs primarily in women, it is reasonable to explore whether certain features of ischemic heart disease seen in women may play an important role in SLE patients. Of women with acute ST-segment elevation myocardial infarction, 10% to 25% do not have obstructive coronary artery disease (CAD) on coronary angiography (1). Microvascular coronary dysfunction is prevalent in women with evidence of ischemia but without obstructive CAD (2). Although these women were originally described as having cardiac syndrome X, believed to be a benign condition, contemporary reports document that the presence of microvascular coronary dysfunction and myocardial ischemia has an adverse prognosis (1–4).

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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CMR = cardiac magnetic resonance

CP = chest pain

CTA = computed tomography angiography

MPRI = myocardial perfusion reserve index

SLE = systemic lupus erythematosus

Adenosine cardiac magnetic resonance (CMR) can detect stress-induced abnormal hypoperfusion in women with signs and symptoms of ischemia with no obstructive CAD (5,6). We initiated a pilot study to evaluate myocardial ischemia using visual myocardial perfusion and a myocardial perfusion reserve index (MPRI) in a prospective sample of women with SLE with anginal chest pain (CP) and in a reference control population to test the hypothesis that CP in SLE patients without obstructive CAD is due to myocardial ischemia potentially caused by microvascular coronary dysfunction.

MATERIALS AND METHODS

This study was approved by the institutional review board at Cedars-Sinai Medical Center, and all participants gave informed consent before study participation.

Patients. Consecutive female patients presenting to an SLE specialty practice who were 18 years of age and older and meeting revised American College of Rheumatology criteria for SLE were invited to participate if they reported typical and atypical anginal CP within the previous 6 months (7). Patients with established cardiovascular disease were excluded including a history of myocardial infarction, coronary artery stenting or bypass surgery, angiographically documented CAD (≥70% stenosis), as well as current pregnancy, allergy to radiocontrast, baseline glomerular filtration rate <60 ml/min, or the inability to tolerate undergoing CMR or coronary computed tomography angiography (CTA). Finally, participants with known atrial fibrillation, atrial flutter, and tachyarrhythmias were excluded because arrhythmia can interfere with accurate imaging of the coronary vasculature with coronary CTA.

Clinical data collection. Study patients completed a questionnaire to collect information regarding age, duration of SLE, SLE medication use during the past year, and traditional risk factors for CAD. On screening physical examination, the patient's body mass index and systolic and diastolic blood pressures were recorded. The 10-year Framingham risk score was calculated for all SLE patients. Patients were evaluated for CP with a brief, standardized symptom questionnaire asking whether they had had pain or discomfort above the waist within the past 12 months, although patients were enrolled only if the CP occurred in the past 6 months (8). The questionnaire also asked questions to assess the presence of substernal pain, precipitating factors of exertion or emotional stress, and/or relief within 10 min by rest or nitroglycerin to characterize the CP as typical or atypical angina. Laboratory values collected included antinuclear antibody titer, other autoantibody titers, complement levels, fasting lipid panel, fasting glucose level, and estimated glomerular filtration rate. A urine sample was obtained to rule out pregnancy. The SLE Disease Activity Index (SLEDAI) was calculated for all SLE pa-

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tients based on history, examination results, and laboratory data (9).

CMR. Adenosine stress/rest CMR and 64-slice coronary CTA were performed at Cedars-Sinai Medical Center. CMR at 1.5-T (Siemens Sonata, Erlangen, Germany) using electrocardiographic gating and a phased-array coil was performed using a standardized protocol with 0.05 mmol/kg gadolinium first-pass perfusion 3-slice stress (adenosine 140 $\mu g/kg^{-1}/min^{-1}$) followed by rest imaging, function, and delayed enhancement imaging. In 2 patients with a remote history of asthma, regadenoson, an equivalent stress agent, was substituted for adenosine. CMR was analyzed using visual 5-point /16- (perfusion) or 17- (wall motion and scar) segment scoring system: 0, normal; 1, mildly reduced/equivocal; 2, moderately reduced; 3, severely reduced; 4, absent perfusion. Perfusion scores were used to calculate an estimated percentage of abnormal myocardium by taking the sum of the severity scores divided by 64, which is the product of the number of segments analyzed (16 segments), and the worst uptake score of 4 (10,11). Any stress perfusion defect size ≥5% was considered significant.

First-pass perfusion images were separately analyzed using CAAS MRV CMR analysis software, Version 3.3 (Pie Medical Imaging B.V, Maastricht, the Netherlands). Epicardial and endocardial contours of the left ventricular myocardium were applied to the 3 slices in short-axis (basal, mid-, and apical) and intensity-over-time curves generated for rest and stress perfusion. Intensity-over-time curves were used to calculate the relative upslope defined as the ratio between the maximum upslope of the selected curve divided by the maximum upslope of the left ventricular cavity curve. Subendocardial and subepicardial MPRIs were calculated as the ratio of the relative upslope at stress/relative upslope at rest. The subendocardial region was established as the inner 50% of the volume between the epicardial and endocardial contours. Internal assessment has shown high intraobserver and interobserver reproducibility of the MPRI in our group, with the highest correlation in mid-myocardial segments. The interobserver reproducibility resulted in an intraclass correlation coefficient ranging from 0.72 to 0.85 in individual segments, and for intraobserver reproducibility, it ranged from 0.89 to 0.92.

Coronary CTA protocol and interpretation. Coronary CTA was performed using a 64-slice dual-source scanner (Definition, Siemens Medical Systems, Forchheim, Germany). To optimize imaging, participants without contraindication received β-blockade with oral and/or intravenous metoprolol to slow the heart rate to between 60 and 70 beats/min. An optimized dose modulation approach using helical acquisition and reduced voltage was used to decrease radiation exposure (12). Individuals with compromised renal function on screening laboratory testing had 48-h interval between CMR and coronary CTA. Coronary CTA was read by consensus of 2 imaging cardiologists who reported the following: 1) the coronary artery calcium score; and 2) the type (calcified, noncalcified, mixed) and location of each coronary plaque as well as the degree of coronary luminal narrowing using a 5-point scale (<25%, 25% to 49%, 50% to 69%, 70% to 89%, and ≥90%) (13). For dichotomous classification, coronary CTA was considered to reveal abnormal findings if there was any visualized coronary plaque (calcified, mixed, or noncalcified), regardless of the degree of coronary narrowing.

Control sample. An asymptomatic reference control group of 10 women without evidence of CAD by history, risk factor assessment, and exercise treadmill stress testing was identified for comparison analysis. Reference control subjects were recruited using the medical center's e-mail broadcast exchange and self-identified as not having SLE or heart disease risk factors such as hypertension, hyperlipidemia, and diabetes. All reference control women underwent a standard Bruce exercise treadmill test without signs or symptoms of ischemia before completing CMR.

Statistical analyses. For comparison of the MPRI between SLE patients and controls, Wilcoxon rank-sum test was applied. Correlations were measured by Spearman rank correlation coefficients. Univariate and multivariate linear regression analyses were performed with the MPRI and the presence of SLE and other potential risk variables. A p value <0.05 was considered statistically significant. All statistical analyses were performed using SAS 9.1 (SAS Institute Inc., Cary, North Carolina).

RESULTS

A total of 20 female SLE patients with CP were enrolled. All patients underwent coronary CTA, and 19 of 20 patients underwent stress CMR. The CMR data were unsuitable for analysis in 1 patient, leaving 18 of 20 patients for analysis of the MPRI.

Patient characteristics. The baseline clinical and laboratory characteristics of all 20 study patients are shown in Table 1, including serologic results. The mean age of SLE patients was 40.6 ± 11 years with an

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Table 1. Baseline Clinical and Laboratory Characteristics

Characteristic	
Age, yrs	40.6
Female sex, n (%)	20 (100)
Duration of SLE, yrs (range)	12.8 (1–37)
Average SLE criteria (range)	4.85 (4–6)
Average body mass index, kg/m^2	25.8
Corticosteroid use within past year, n (%)	16 (80)
Medication	
Azathioprine	2 (10)
Hydroxychloroquine	12 (60)
Methotrexate	2 (10)
Nonsteroidal anti-inflammatory drugs	6 (30)
Mycophenolate mofetil	3 (15)
β-blocker	1 (5)
Angiotensin receptor blocker	1 (5)
Baseline laboratory values	
Positive antinuclear antibody, n (%)	20 (100)
Positive double-stranded DNA antibody, n (%)	11 (55)
Positive anti-Ro antibody, n (%)	5 (25)
Positive anti-La antibody, n (%)	2 (10)
Positive anti-Smith antibody, n (%)	4 (20)
Positive anticardiolipin IgG or IgM antibody, n (%)	1 (5)
Creatinine, mg/dl	0.7 ± 0.14

Values are n, n (%), or n (range).
DNA = deoxyribonucleic acid; SLE = systemic lupus erythematosus.

average disease duration of 12.8 years and average body mass index of 25.8 kg/m^2. All SLE patients were antinuclear antibody positive, and 55% had a positive double-stranded deoxyribonucleic acid antibody. Risk factors for CAD are shown in Table 2. The 10-year Framingham risk score was 2% per year in 1 subject and ≤1% per year in the remaining study subjects (Table 3) (14). The reference control population consisted of 10 asymptomatic women who had no history of SLE, smoking, diabetes mellitus, hypertension, or hyperlipidemia and who completed a negative high workload Bruce protocol exercise tolerance test. The mean age of controls was 53.2 ± 5 years, which was significantly different from the study subjects with SLE ($p = 0.001$).

Coronary CTA results. Eighteen female SLE patients with anginal CP had complete data and were used for analysis. In this group, the SLEDAI score was 0 in 3 patients, 1 to 5 (mild) in 10 patients, and 6 to 10 (moderate) in 5 patients. Two SLE patients had mild coronary atherosclerosis (isolated noncalcified plaque with 25% to 49% stenosis in the left anterior descending coronary artery in 1 patient and a coronary artery calcium score of 5.9 in another patient, consistent with minimal calcification), but no patient had obstructive CAD by coronary CTA (Table 3).

CMR results. All patients and controls had normal cardiac structure and left ventricular systolic function on CMR. There were 2 SLE patients who had a history of asthma who received regadenoson instead of adenosine. There was no patient or control with delayed enhancement to suggest the presence of myocardial scarring. On CMR, stress-induced hypoperfusion was seen by semiquantitative visual analysis in 8 of 18 (44%; 95% confidence interval: 21.5% to 67.4%) SLE patients compared with 0 of 10 of the reference control group (Fisher exact test p value = 0.014). In all 8 patients with visual perfusion abnormalities, the pattern seen was one of circumferential subendocardial hypoperfusion (Fig. 1), predominantly in the mid-left ventricular slice. Both subjects with any coronary CTA abnormality demonstrated circumferential subendocardial myocardial perfusion defects on CMR (28% in the patient with noncalcified plaque and 9% in the patient with coronary calcium), not corresponding to a coronary vascular territory. The mean MPRI in patients versus controls was 2.0 ± 0.4 versus 2.3 ± 0.4 ($p = 0.16$); 2.0 ± 0.4 versus 2.4 ± 0.4 in the subepicardium ($p = 0.031$) and 1.8 ± 0.3 versus 2.1 ± 0.4 in the subendocardium ($p = 0.24$). Repeating the visual and quantitative CMR analyses after exclusion of the 1 subject with an intermediate stenosis did not change the results

There was no correlation between the MPRI and SLEDAI or SLE duration. Multivariate linear regression revealed that the presence of SLE was the only predictor of subepicardial ($p < 0.0025$, $\beta = -1.059$) and subendocardial ($p < 0.05$, $\beta = -0.529$) MPRI.

Table 2. Coronary Artery Disease Risk Factors

Risk Factor	
Systolic blood pressure, mm Hg	115 ± 11.5
Diastolic blood pressure, mm Hg	76 ± 10
Smoking ever, n (%)	7 (35)
Smoking current, n (%)	1 (5)
Fasting plasma glucose, mg/dl	70.0 ± 18.3
Total cholesterol, mg/dl	202.0 ± 45.3
Triglycerides, mg/dl	111.0 ± 67.6
High-density lipoprotein, mg/dl	66.0 ± 16.8
Low-density lipoprotein, mg/dl	114.0 ± 41.9
Use of a cholesterol-lowering agent	1 (5)
History of blood clot	3 (15)
Family history of stroke	3 (15)
Family history of premature coronary artery disease	4 (20)
Post-menopause	6 (30)
Hormone replacement therapy	6 (30)
History of arrhythmia	6 (30)

Values are mean ± SD or n (%).

Table 3. Subjects With Reversible Perfusion Defects on CMR

Subject	Age (yrs)	Framingham Risk Score (%)*	Severity of Perfusion Defect (%)	Coronary CTA Findings	LVEF (%)
2	59	1	Moderate (9)	Calcium score 5.9	63
3	39	<1	Severe (14)	Normal	69
8	52	1	Severe (28)	LAD ulcerated plaque	49
9	52	1	Severe (16)	Normal	66
10	54	1	Severe (14)	Normal	60
11	47	2	Severe (38)	Normal	70
13	43	<1	Severe (21)	Normal	64
19	35	<1	Severe (16)	Normal	64

*10-year risk of acute myocardial infarction or death.
CMR = cardiac magnetic resonance; CTA = computed tomography angiography; LAD = left anterior descending coronary artery; LVEF = left ventricular ejection fraction.

DISCUSSION

In this initial study of 18 female SLE patients with CP and low-to-moderate SLE disease activity, 44% of study patients had visually abnormal adenosine CMR despite a low prevalence of coronary atherosclerosis, no obstructive CAD, and preservation of myocardial structure and function. The pattern of visual perfusion defect was circumferential and subendocardial in all the patients with abnormal results. Unlike adenosine-induced perfusion defects seen in CAD, which correspond to the territory supplied by stenosed coronary arteries, this circumferential subendocardial distribution of hypoperfusion does not correspond to a vascular territory. Only 1 SLE patient had a 25% to 49% stenosis noted on coronary CTA and abnormal CMR findings. This degree of stenosis is rarely associated with ischemia, and, importantly, the circumferential subendocardial distribution of the abnormality in this patient is not consistent with left descending anterior coronary artery ischemia (15). The circumferential hypoperfusion pattern that we observed visually appears to be the same as that described in cardiac syndrome X and attributed to microvascular dysfunction (6,16). Because our findings show that the abnormal CMR perfusion pattern is circumferential and not associated with coronary atherosclerosis or obstructive CAD, the findings may be due to microvascular disease, as previously described in cardiac syndrome X.

Ischemic heart disease morbidity and mortality among SLE patients are prevalent, severe, accelerated, and a leading health care issue for this population. A bimodal mortality distribution has been described among SLE patients: those patients who die soon after diagnosis usually die of infections or complications of the disease itself; later in the course of the disease, 48% die of ischemic heart disease (17). The overall mortality of SLE has recently improved, yet ischemic heart disease remains a major factor influencing the pattern of morbidity and mortality (18,19). SLE patients with CP often present a diagnostic dilemma; they are frequently told that they have myofascial pain, chest wall pain, pericardial pain, or, in some cases, psychosomatic pain when standard cardiac evaluation testing does not identify obstructive CAD. The current study suggests that SLE patients without obstructive CAD have a high prevalence of CMR abnormal findings consistent with myocardial ischemia, potentially due to microvascular coronary dys-

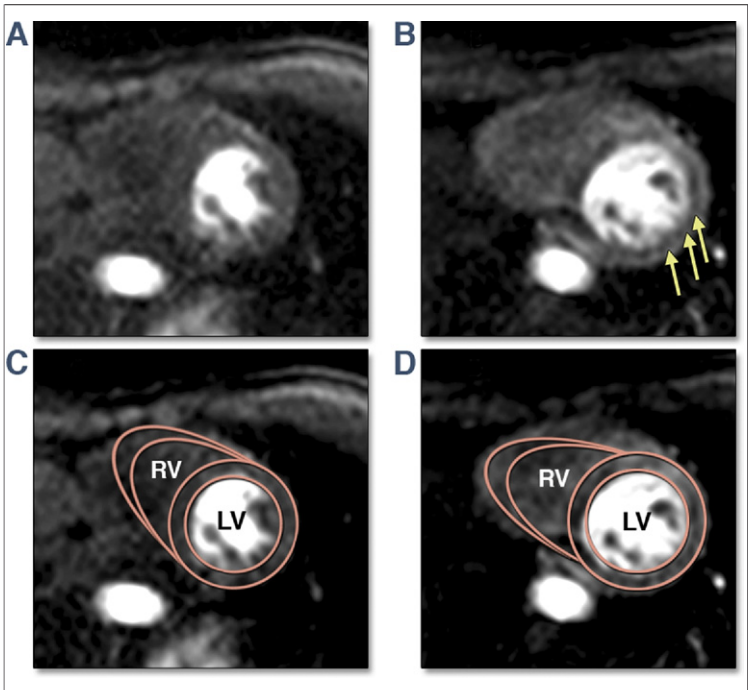

Figure 1. Rest and Stress Perfusion Images on Cardiac Magnetic Resonance

Illustrations of first-pass, rest **(left)** and stress **(right)** perfusion images through short-axis 2-chamber views demonstrating normal myocardial enhancement at rest **(A)** and circumferential area of subendocardial hypoperfusion **(arrows)** during stress **(B)**. **C and D** outline the anatomy of right ventricle (RV) and left ventricle (LV).

function (2,20,21). Notably, our SLE patients were a low-risk population when assessed for traditional CAD risk factors, such as cholesterol levels, blood pressure, and smoking status, and had low Framingham risk scores.

The Framingham risk score has been validated in predicting cardiovascular risk among the general population, but it has been shown to underestimate the prevalence of cardiovascular risk in SLE patients (14,22). It has been observed that assessment of coronary artery calcification by computed tomography may be more effective than the Framingham risk score in SLE patients (22). The absence of atherosclerosis and obstructive CAD by coronary CTA in almost all our study patients combined with a high prevalence of stress-induced myocardial perfusion defects by CMR supports our hypothesis that anginal CP in SLE patients without obstructive CAD is due to myocardial ischemia potentially caused by microvascular coronary dysfunction.

Coronary CTA and adenosine CMR were used in our study. Coronary CTA is capable of assessing plaque volume and composition as well as the presence of positive remodeling within the arterial wall; it is validated compared with both invasive coronary angiography and histological coronary disease on autopsy (23). Adenosine CMR is a validated noninvasive method for the detection of occlusive CAD and for the demonstration of abnormal coronary flow reserve in a variety of reported settings (24). Previous work demonstrated that CMR findings are abnormal in the population of patients with persistent CP, with evidence of ischemia but no obstructive CAD (6). In patients with clinically worrisome cardiac symptoms (angina, syncope, arrhythmias), negative CMR findings have been reported to have a negative predictive value of 99.1% for major adverse cardiac events in 1 year (25). Because coronary CTA and CMR evaluate differing aspects of ischemic heart disease (e.g., atherosclerosis and obstructive CAD vs. myocardial blood flow and myocardial perfusion, respectively), we used these methods to help delineate better the presumed complex, multifactorial pathogenesis of CAD in SLE patients. In addition to semiquantitative visual analysis in our study, we also used a quantitative analysis similar to that reported by Panting et al. (6). In our study, the SLE patients also had a significantly reduced mean subepicardial quantitative MPRI compared with a reference control group, and only SLE predicted an abnormal MPRI. Unlike the study of Panting et al. (6), our study did not show an abnormal subendocardial MPRI. The cause of this difference from previous results is unclear and may be related to the small sample size of our study.

Study limitations. Interpretation of these initial findings is limited by aspects of study design and generalizability of our results. We used a convenience reference control sample of patients without SLE that was not age matched. Our SLE patient group had very low traditional cardiac risk factors, similar to the control sample. Further, our visual readings of CMR and coronary CTA in our SLE population were not performed in a blinded manner, although the visual reading of the reference controls and quantitative CMR analyses in both populations were. Although our sample size is small, the presence of stress-induced hypoperfusion in almost half of the study subjects is of great interest because it may indicate a high prevalence of myocardial ischemia potentially due to microvascular coronary dysfunction in SLE patients with CP not caused by obstructive CAD. The segmental scoring system for perfusion used a range of 0 to 4, which may exceed the detectable grades of hypoperfusion. This may have resulted in an overestimation of the magnitude of the perfusion defects. Although we did not have age-matched reference controls, the older age among our control subjects would be expected to reduce our likelihood of finding the group differences that we describe, suggesting that our results are true differences.

Future work could include a separate reference control population with CAD risk factors similar to those of the SLE subjects but without SLE to further support our findings. CMR results have been correlated with coronary angiography results in patients without SLE, but not yet in SLE patients (26). In addition to further validation testing with masked readings in SLE patients, CMR techniques will need additional standardization procedures for reproducibility.

CONCLUSIONS

In summary, among SLE patients with anginal CP but no obstructive CAD, we observed a 44% prevalence of abnormal stress myocardial perfusion by CMR and a reduced MPRI compared with reference control subjects; SLE presence was a significant predictor of an abnormal MPRI. These findings are consistent with the hypothesis that anginal CP in SLE patients without obstructive CAD is due to myocardial ischemia potentially caused by microvascular coronary dysfunction. Further study is warranted to validate these initial findings by

correlation with invasive measures of microvascular coronary dysfunction and to investigate the pathophysiological pathways and prognostic significance in SLE patients.

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Key Words: cardiac magnetic resonance ■ chest pain ■ microvascular coronary dysfunction ■ myocardial ischemia ■ systemic lupus erythematosus.