Single Photon Emission Computed Tomography Dual Isotope Myocardial Perfusion Imaging in Women with Systemic Lupus Erythematosus. II. Predictive Factors for Perfusion Abnormalities

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ABSTRACT. ***Objective.*** We have reported that 40% of patients with systemic lupus erythematosus (SLE) had abnormal myocardial perfusion studies. Here we investigated risk factors for abnormal myocardial perfusion in a cohort of women with SLE without history of coronary artery disease.

Methods. Consecutive women with SLE followed at a large lupus clinic underwent single photon emission computed tomography dual isotope myocardial perfusion imaging (DIMPI) following pharmacological stress using dipyridamole. At the time of study each patient had a clinical and laboratory assessment performed by a standard protocol. We compared traditional risk factors as well as disease and therapy related factors in those with and without perfusion abnormalities.

Results. A total of 129 patients were studied. The mean ± SD age was 44.8 ± 10.9 yrs, and mean SLE Disease Activity Index was 4.2 ± 5.1. Forty-nine (38%) patients had an abnormality of myocardial perfusion. Factors associated with an abnormal DIMPI included current hypertension (OR 2.11, $p = 0.05$), elevated cholesterol ever (OR 2.51, $p < 0.05$), and total cholesterol:high density lipoprotein-cholesterol ratio (OR 1.96 for each increase of 1.0, $p < 0.008$).

Conclusion. Myocardial perfusion abnormalities are common in women with SLE without known coronary artery disease (CAD), suggesting a high burden of subclinical CAD. Several metabolic and therapy related factors appear to be associated with the process of atherogenesis in SLE. These results suggest that SLE should be considered a predisposing factor for atherosclerosis. (J Rheumatol 2003;30:288–91)

Key Indexing Terms:
LUPUS PREDICTIVE FACTORS MYOCARDIAL PERFUSION IMAGING

We have shown that mortality in systemic lupus erythematosus (SLE) follows a bimodal pattern, with deaths late in the disease frequently associated with premature atherosclerosis, especially coronary artery disease (CAD)[1]. Clinical CAD has been reported in 6–10% of patients with SLE in longterm observational cohort studies[2-4]. Subclinical CAD in women with SLE has been described using several different modalities in up to 30–50% of patients[5-8]. We recently described the results of single photon emission computed tomography (SPECT) dual isotope myocardial perfusion imaging (DIMPI) in patients with SLE including the type of diffusion defects and their reversiblity[8]. The aim of this study was to identify factors associated with myocardial perfusion abnormalities in women with SLE but without a known history of CAD. In particular we studied the association with demographic factors, clinical and serological features, therapy, and conventional CAD risk factors.

MATERIALS AND METHODS

Patients were recruited from the University of Toronto Lupus Clinic. At this clinic each patient undergoes a clinical and laboratory assessment according to a standard protocol. This includes assessment of disease activity using the SLE Disease Activity Index (SLEDAI)[9]. The protocol also includes details of past or current CAD related events, namely angina pectoris and myocardial infarction (MI). For this study we included consecutive patients who attended the clinic between September 1, 1996, and December 1998 who agreed to participate. Patients with a history of CAD were excluded. We did not exclude patients with cerebrovascular disease or peripheral vascular disease who did not have a CAD event. Informed consent was obtained prior to study and the University of Toronto Research Ethics Committee approved the study. Pregnant and lactating patients were excluded.

Dual isotope myocardial perfusion imaging. Patients underwent myocardial imaging as described[8]. Briefly, patients received 3.0 mCi of ^{201}TI (as thallous chloride) as an intravenous bolus at rest. Fifteen minutes after ^{201}TI adminis-

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tration, patients were positioned supine within a dual-head, fixed 90° angle SPECT acquisition system for rest ^{201}TI image acquisition. Data were acquired as 60 frames, 25 s per frame, according to the current conventional clinical protocol. Patients then proceeded immediately to pharmacologic cardiac stress using either dipyridamole (0.14 mg/kg/min IV for 4 min) or dobutamine (for patients with asthma or receiving methy-xanthine compounds, graded infusion of 5, 10, 20, 30, and then 40 µg/kg/min, 3 min per infusion rate). An injection of ^{99m}Tc sestamibi (22–25 mCi), and repeat imaging 30 min later using the same detector system for a total of 10 min, with electrocardiogram (ECG) gating, was performed according to the conventional clinical protocol. During and after pharmacologic stress, heart rate, blood pressure, and the 12-lead ECG was monitored each minute (until these returned to baseline). Constant 3-lead ECG ST segment and rhythm monitoring was performed. A physician was in attendance to supervise pharmacologic stress, which was terminated prematurely according to conventional clinical criteria.

Data processing. Rest ^{201}TI and ECG-gated stress ^{99m}Tc-sestamibi myocardial perfusion images were reconstructed using filtered back projection as per routine clinical protocols[10-12].

Statistical analysis. Patients with abnormal DIMPI were compared to those with a normal perfusion scan in terms of demographics, clinical and serological features of SLE, therapy, and conventional CAD risk factors. The latter included total cholesterol > 5.2 mmol/l, fasting LDL > 3.4 mmol/l, total cholesterol:high density lipoprotein (HDL) ratio, smoking, body mass index, and menopause (absence of menses for at least 12 consecutive months).

Chi-square or Fisher's exact tests were used for dichotomous variables and t tests were used for continuous variables. Univariate logistic regression was used to obtain odds ratios (OR) and confidence intervals (CI). Multivariate logistic regression was done to determine the significance of the risk factors when all variables are included in the model.

RESULTS

In total, 129 patients with SLE underwent DIMPI studies. The mean (SD) age and disease duration at study were 44.8 (10.9) and 13.8 (9.2) years, respectively. The mean (SD) SLEDAI at study was 4.2 (5.1). Forty-nine patients (38%) had perfusion defects. Of the 49 patients with abnormal DIMPI, 38 (77.6%) had one vessel, 7 (14.3%) had 2 vessels, and 4 (8.2%) had 3 vessels involved. Forty-four patients (89.8%) had reversible defects, 10 (20.4%) had fixed defects, and 5 (10.2%) had both fixed and reversible defects. Among the 129 patients who underwent DIMPI studies, 105 (84.0%) had ejection fraction > 50%, 20 (16.0%) had ejection fraction ≤ 50%, and 3 (2.4%) had ejection fraction ≤ 40%. Four patients had cerebrovascular events and 3 had documented peripheral vascular disease. Even if we exclude these 7 patients the prevalence of DIMPI abnormalities remains the same. Four of these 7 patients had DIMPI abnormalities and 3 had normal DIMPI results.

Patients who underwent DIMPI were slightly older (3.4 yrs) and had a longer disease duration (3.3 yrs) and a slightly lower SLEDAI (1.7) at the time of study but were otherwise similar to those who were seen during the same period of time but did not participate in the study (Table 1). The differences noted are not considered clinically important.

A comparison of the demographic features between DIMPI positive (n = 49) and DIMPI negative (n = 80) patients showed that DIMPI positive patients were 3 years older, but otherwise were similar to DIMPI negative patients in age of diagnosis, disease duration, race, SLEDAI at study, and SLEDAI > 20 (ever) (Table 2).

Major clinical organ involvement including cardiac, thromboembolic, vasculitis, renal, and central nervous system involvement was similar in both groups (Table 3).

There were no differences in serologic abnormalities observed at the time of the imaging studies between the 2 groups (Table 4). As well there was no difference in steroid usage or total dose between the 2 groups (Table 4).

A comparison of conventional CAD risk factors between the 2 groups revealed that DIMPI positive patients were more often postmenopausal, but the difference did not reach statistical significance. DIMPI positive SLE patients were more likely to be hypertensive, especially at the time of the study (OR 2.11, CI 0.99, 4.48; p = 0.05). Elevated cholesterol ever was more likely to have been detected among patients with abnormal DIMPI results (OR 2.51, CI 0.98, 6.40; p < 0.05). The total cholesterol to high density lipoprotein (HDL) ratio was significantly higher among women with abnormal DIMPI studies (OR 1.96, CI 1.09, 3.52; p = 0.008) (Table 5). A multivariate analysis revealed that only the total cholesterol to

Table 1. Comparison of women who agreed to those who refused to participate in perfusion imaging study with respect to demographics and cardiac risk profile. In nonparticipants, each variable was taken at the first visit to the clinic after September 1, 1996. All women did not have history of coronary artery disease.

	Participants, n = 129	Nonparticipants, n = 263	p
Age at study, mean (SD) yrs	44.8 (10.9)	41.4 (14.2)	0.0096
Disease duration, mean (SD) yrs	13.8 (9.2)	10.5 (9.2)	0.0010
Ethnicity, % Caucasian	101 (78.3)	192 (73.6)	0.257
SLEDAI at presentation, mean (SD)	9.2 (8.2)	9.3 (7.3)	0.927
SLEDAI at study, mean (SD)	4.2 (5.1)	5.9 (6.0)	0.0031
Current hypertension > 140/90 (%)	47 (36.4)	75 (28.5)	0.1117
Total cholesterol > 5.2 mmol/l (%)	39 (32.5)	88 (35.3)	0.591
Current smoking, n (%)	19 (14.8)	42 (16.0)	0.762
Diabetes mellitus, n (%)	6 (4.7)	13 (5.0)	0.893
Postmenopause, n (%)	47 (36.4)	76 (28.9)	0.131

Table 2. Characteristics of SLE patients with normal and abnormal DIMPI.

	DIMPI +, n = 49	DIMPI –, n = 80	p
Age at study, mean (SD) yrs	46.9 ± 11.1	43.5 ± 10.7	0.0878
Age at diagnosis, mean (SD) yrs	32.4 ± 13.1	30.1 ± 9.5	0.2948
Disease duration, mean (SD) yrs	14.5 ± 10.0	13.3 ± 8.7	0.5089
Caucasian, n (%)	42 (85.7)	59 (73.8)	0.1096
SLEDAI at study, mean (SD)	4.73 ± 5.96	3.83 ± 4.51	0.3606
SLEDAI > 20 ever (%)	12 (24.5)	18 (22.5)	0.7951

Table 3. Clinical features in patients with normal and abnormal DIMPI.

	DIMPI +, n = 49	DIMPI – , n = 80	p
Cardiac (%)	9 (18.4)	19 (23.8)	0.4717
Thromboembolic (%)	3 (6.1)	4 (5.0)	1.00
Vasculitis (%)	16 (32.7)	21 (26.3)	0.4351
Renal (%)	33 (67.4)	63 (78.8)	0.1497
Central nervous system (%)	27 (55.1)	33 (41.3)	0.1258

HDL ratio remained significant when all variables were included in the model.

DISCUSSION

We found a high prevalence (38%) of perfusion abnormalities among 129 women with SLE attending a single center. This confirms and extends our previous results in 130 patients (which included patients with known CAD)[8], revealing that myocardial perfusion abnormalities are common in women with SLE, suggesting a high burden of subclinical CAD.

Table 4. Comparison of serological tests in patients with normal and abnormal DIMPI.

	DIMPI +	DIMI –	p
Anti-DNA antibody*, (%)	36.7	30.0	0.4282
Low complement*, (%)	28.6	26.3	0.7735
aPL*, (%)	27.9	16.9	0.1539
Steroids ever, %	75.5	85.0	0.1789
Previous steroids SE, %	89.2	80.9	0.2696
Steroids cumulative dose	42.7 ± 33.5	36.6 ± 42.5	0.4567
Antimalarials ever, %	81.6	72.5	0.2387

*Tests performed at the time of imaging studies. aPL: antiphospholipid antibody.

Studies have shown that demographic features, hormonal status, drug therapy, Framingham classic risk factors, and other lipid abnormalities contribute to the accelerated atherosclerosis noted in patients with SLE[2-4]. Although SLE patients with a cardiac event had fewer traditional risk factors than non-SLE patients with premature CAD[13], persistent hypercholesterolemia in the first 3 years of SLE was associated with the development of CAD[14]. The presence of hypertension was also associated with subsequent development of CAD in patients with SLE[15]. Thus both hypercholesterolemia and hypertension were associated with clinical CAD. This study suggests that these features are also associated with subclinical evidence for CAD, as documented by abnormalities detected on DIMPI scans.

Bruce, *et al*[16,17] recently compared women with SLE without clinical evidence for CAD to an aged matched control group visiting a family physician for their yearly checkup. They found that patients with SLE had earlier onset of menopause, a more sedentary lifestyle, a more frequent at-risk body habitus, and higher very low density lipoprotein (VLDL), triglyceride, and homocysteine levels than their controls.

Table 5. Conventional CAD risk factors in patients with normal and abnormal DIMPI.

	DIMPI +	DIMPI –	p	OR (CI)
Total cholesterol > 5.2, %				
At study	35.4	30.6	0.5775	1.25 (0.57, 2.71)
Ever	85.7	70.5	0.0496	2.51 (0.98, 6.40)
LDL > 3.4, %				
At study	42.9	36.1	0.6590	1.33 (0.38, 4.67)
Ever	63.6	65.0	0.9145	0.94 (0.32, 2.79)
Total cholesterol/HDL	4.7 ± 1.6	3.7 ± 1.1	0.0082	1.96 (1.09, 3.52)
Hypertension, %				
At study	42.9	26.3	0.0507	2.11 (0.99, 4.48)
Ever	71.4	56.3	0.0847	1.94 (0.91, 4.16)
Smoking, %				
At study	14.3	15.2	0.8888	0.93 (0.34, 2.55)
Ever	24.5	21.5	0.6963	1.18 (0.51, 2.75)
Body mass index	26.0 ± 5.5	24.4 ± 5.8	0.1206	1.05 (0.99, 1.12)
Menopause, %	42.9	32.5	0.2355	1.56 (0.75, 3.25)
HRT if postmenopausal (%)	9/21 (42.9)	15/26 (57.7)	0.3118	0.55 (0.17, 1.76)

HRT: hormone replacement therapy.

We reported that antimalarials may lower cholesterol and VLDL levels in patients with SLE[18,19]. The current study suggests that antimalarials may be insufficient to significantly influence CAD related morbidity, and that these metabolic abnormalities require specific attention.

Our investigation revealed that among SLE patients without a history of CAD who underwent myocardial perfusion studies, patients with perfusion abnormalities had higher frequency of hypertension at time of study and had a higher total cholesterol:HDL ratio. However, in multivariate analysis the lipid abnormalities were the only factor that remained significant. Thus the increase of these abnormalities in comparison to the control population may be associated with the development of premature CAD in patients with SLE. While these metabolic factors should be treated in all patients with SLE, it is important to identify patients with existing subclinical disease and intensify therapy in order to prevent clinical CAD.

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