# Brachial Endothelial Function Is Impaired in Patients with Systemic Lupus Erythematosus

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***ABSTRACT.*** ***Objective.*** To verify if endothelial function is impaired in pre-menopausal women with systemic lupus erythematosus (SLE) and whether endothelial dysfunction is related to disease duration, cumulative prednisone dose, antimalarial use, anticardiolipin antibody (aCL), hypertension, Raynaud's phenomenon, disease activity score, and vasculitis.

***Methods.*** Using high-resolution ultrasound, we measured the diameter of brachial artery at rest, during reactive hyperemia, and after glyceryl trinitrate (GTN). We compared 69 pre-menopausal female patients with SLE (mean age 29 ± 8 years) with 35 age and sex-matched controls (mean age 29 ± 6 years). The mean disease duration was 72 months.

***Results.*** There was no significant difference in baseline brachial artery diameter. The flow-mediated dilation (endothelial dependent dilation) was significantly impaired in SLE patients when compared to controls (5.0 ± 5.0% vs 12.0 ± 6.0%, $p < 0.001$), even in the subgroup of patients without coronary artery disease risk factor (4.5 ± 4.0% vs 12.0 ± 6.0%, $p < 0.001$). The GTN induced dilation (endothelial independent dilation) was significantly lower in the aCL positive SLE patients when compared to the controls (11.9 ± 4.0% vs 16.3 ± 6.0%, $p < 0.05$). The endothelium-dependent dilation was not related to disease duration, cumulative prednisone dose, antimalarial use, anticardiolipin antibody, hypertension history, Raynaud's phenomenon, SLE disease activity score or vasculitis.

***Conclusion.*** This is the first study using brachial artery ultrasound imaging to evaluate endothelium function in SLE. Patients with SLE presented lower flow mediated dilation (endothelium dependent dilation) than sex and age-matched controls, even in patients without traditional cardiovascular risk factors and this may represent an early atherosclerotic process. (J Rheumatol 2002;29:292–7)

*Key Indexing Terms:*
SYSTEMIC LUPUS ERYTHEMATOSUS
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Atherosclerosis is a multifactorial disease and its pathogenesis is not completely known. The risk factors associated with coronary arterial disease (CAD) may be divided into modifiable factors, such as dyslipidemia, smoking, arterial hypertension, obesity, sedentarism and diabetes mellitus, and non-modifiable ones, such as age, male sex and family history of premature CAD[1].

In 1976, Urowitz *et al*, showed a bimodal mortality pattern in systemic lupus erythematosus (SLE), with early death mainly due to active disease and infection and later death due to cardiovascular disease[2]. More recent studies show that women with SLE have a high prevalence of CAD[3] and that young SLE patients have an incidence of myocardial infarction up to 52-fold higher than age-matched women without SLE[4].

Several mechanisms may be implicated in CAD pathogenesis in SLE patients. Chronic steroid use may be one of the most important of them[5-8]. Other possible mechanisms include vasculitis[9,10], spasm of coronary artery, and acute obstruction due to thrombosis[11,12].

There is strong evidence that the endothelial dysfunction *in vivo* occurs in the peripheral and coronary arteries, affecting the resistance and conduit vessels at different atherosclerotic stages[13]. This evidence suggests that endothelial dysfunction in atherosclerosis is a systemic process, and is not restricted to the vessels that show clinical manifestations of atherosclerosis[14].

In 1992, Celermajer *et al* described a non-invasive method using high-resolution ultrasound image of the brachial artery to study endothelial function. The dilation of brachial artery in response to increased flow is dependent on intact endothelial function, whereas glycerol trinitrate (GTN) is a direct smooth-muscle dilator that acts independently of the status of the endothelium[15].

The prognosis for SLE patients has improved over the last decades. However, CAD primary risk factors such as

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smoking, obesity, sedentary lifestyle, family history, arterial hypertension and dyslipidemia, as well as SLE-related factors such as the use of high doses of steroids and nephritis have been often overlooked in patient followup. Therefore, it seems relevant to evaluate the endothelial function in this group of patients, considering that endothelial dysfunction may be the earliest demonstrable step of atherosclerosis in humans.

Our aim was to evaluate the endothelial function through brachial artery ultrasound imaging in pre-menopausal women with SLE and to determine if there is any association between endothelial dysfunction and disease duration, steroid dose, antimalarial use, previous arterial hypertension, Raynaud's phenomenon, anticardiolipin antibody (aCL), disease activity score, and vasculitis.

## MATERIALS AND METHODS

*Patients*. SLE patients followed at the Rheumatology Division of Universidade Federal de São Paulo (UNIFESP) from February 1997 to March 1999 were enrolled in this study according to the following inclusion criteria: presence of 4 or more American College of Rheumatology criteria for SLE classification[16], female sex, regular menses, and agreement to participate in the study. Age-matched pre-menopausal healthy women (physicians and hospital employees) constituted the control group.

Patients and controls were excluded if they had any of the following criteria: typical angina, myocardial infarction, diabetes mellitus (fasting glucose > 110 mg/day), renal failure (creatinine > 1.4 mg/dl), hypertension (arterial pressure > 140 × 90 mmHg), family history of CAD, total cholesterol > 240 mg/dl, triglycerides > 200 mg/dl, active infectious diseases, smoking (in the last 6 months) or use of antihypertensive, oral hypoglycemic or lipid lowering drugs (in the last 3 months).

Although the use of oral contraceptive was not an exclusion criterion, no patients with SLE and only 2 controls were using oral contraceptive pills at the time of study.

All patients and controls answered a questionnaire concerning demographic data and history of risk factors for CAD. Hospital charts were reviewed to collect data on arterial hypertension, Raynaud's phenomenon, venous and arterial thrombosis, coronary artery disease, vasculitis, cerebrovascular disease, aCL, and medications used in the past.

All patients underwent a physical examination and blood sampling for the following laboratory tests: blood cell count, urinalysis, anti-dsDNA antibodies, aCL, serum complement, creatinine, cholesterol (total and fractions), triglycerides, and fasting glucose. The disease activity was evaluated using SLEDAI score (Systemic Lupus Erythematosus Disease Activity Index)[17]. The body mass index (BMI) was used to classify patients and controls as obese (BMI ≥ 27.3) or not (BMI < 27.3) according to criteria of the National Institutes of Health[18].

Obesity and lipid profile abnormalities according to proposal of the National Cholesterol Education Program (total cholesterol > 200 mg/dl, HDL-cholesterol < 35 mg/dl, LDL-cholesterol > 130 mg/dl and Castelli's index > 4.5)[19] were considered as a CAD risk factor.

The ethics and research committee of Universidade Federal de São Paulo approved the study and all participants signed the informed consent.

*Brachial endothelial study design*. The brachial endothelial study was designed in the flow laboratory of the Vascular Surgery Division of UNIFESP according to the method described by Celermajer *et al* in 1992[15]. All examinations were performed by the same individual and all patients and controls were non-fasting and had not used alcohol on the morning of their examination. No restriction was made concerning caffeine intake and all menstrual cycles were spontaneous with the exception of the 3 women taking oral contraceptives. High-resolution ultrasound (*Advanced Technology Laboratories ultramark-9)* with a 7.0 MHz linear array transducer was used to image the brachial artery longitudinally 7 cm above the elbow, after at least 10 minutes of rest in the supine position. Depth and gain setting were optimized to identify the vessel wall/lumen interface and a baseline scan was recorded. When we found a satisfactory transducer position, the skin was marked and the arm kept in the same position throughout the study. Hyperemia was induced by inflation of a pneumatic cuff placed around the forearm (below the scanned part of the artery) and inflated to 250 mm Hg for 5 minutes producing distal limb ischemia. After release of the cuff, reactive hyperemia occurs, that is, flow in the brachial artery increases to accommodate the dilated resistance vessels in the forearm. The artery was scanned before cuff inflation (baseline measures) and 30 seconds before until 60 seconds after cuff deflation, to measure the endothelium-dependent dilation. After 15 minutes' rest, a single 400 $\mu$g dose of GTN spray was then administered sublingually and the artery was scanned 3-4 minutes later, to evaluate the endothelium independent dilation.

We recorded a Doppler-derived flow measurement using a pulsed Doppler signal at a 60° angle to the vessel wall in the center of the artery. All scans were recorded on super-VHS tapes and saved in a computer program (IMS Professional 2.0). Two independent observers blinded to the scan sequence and to the subject group (patient or control) measured the arterial diameters. The diameters of the artery were measured from the anterior to the posterior interface between media and adventitia (the m-line) The mean diameter was calculated from 3 cardiac cycles coincident with the R-wave on the electrocardiogram. Diameter changes were derived as percent change relative to the first (baseline) scan. Thus, flow-mediated dilation equaled

$$[(\text{diameter after cuff deflation} - \text{resting diameter})/\text{resting diameter}] \times 100\%.$$

Baseline blood flow was estimated by multiplying angle-corrected, pulsed Doppler recording of the flow-velocity integral by $\pi$ and the square of the radius of the artery. Flow change (reactive hyperemia) was calculated as

$$[(\text{flow after cuff deflation} - \text{resting flow})/\text{resting flow}] \times 100\%.$$

*Statistical analysis*. Descriptive data are presented as mean value ± SD. The comparisons of variables with interval or ordinal level between pairs of independent groups were done through the Mann-Whitney test. Two way analysis of covariance (ANCOVA) was used to compare patients and controls to evaluate flow and GTN-induced dilation considering the baseline diameter as co-variable. The comparisons of categorical variables between the pairs of groups were done through the chi-square or Fisher test. The correlations between variables were determined using the Spearman correlation coefficient[20]. Statistical significance was set at $p < 0.05$.

The inter-observer variability calculated after measurement by 2 observers in 104 examinations was 0.04 ± 0.15 mm and the intra-class correlation coefficient was good (R = 0.89). The intra-observer variability calculated after 2 measurements by the same observer in 30 examinations was 0.08 ± 0.16 mm and the intra-class correlation coefficient was also good (R = 0.81).

## RESULTS

Sixty-nine women with SLE and 35 healthy women participated in our study. There were no statistically significant differences between SLE patients and controls in relation to variables such as age, weight and diastolic arterial pressure, showing that they are comparable. The mean BMI (24 ± 3 vs 22 ± 2) and systolic arterial pressure (117 ± 10 vs 113 ± 9 mmHg) were higher in SLE patients than controls. The mean height was greater in the control group than in SLE patients (163 ± 6 vs 160 ± 6 cm, $p < 0.05$).

Lipid profile abnormalities were more frequent in patients than in the control group (42 vs 8.5%, $p < 0.01$). The presence of risk factors for CAD (mild dyslipidemia and/or obesity) was found in 48% of patients and 11% of controls ($p < 0.001$).

All patients had used steroid at some time during the disease evolution. At the moment of study, 61 (88%) patients were using prednisone regularly, with a mean dose of 18 mg/day and a mean cumulative dose of 35 ± 29 grams.

Fifty-one patients (74%) had used hydroxychloroquine or chloroquine diphosphate in the past. However, at the time of the study, only 32 (46.4%) were taking that medication. Eight (12%) patients had taken and 11 (16%) were taking cyclophosphamide, azathioprine or methotrexate during the study.

The ultrasonographic study of the brachial artery at rest and during reactive hyperemia was performed in all patients and controls. Fifty-two patients and 28 controls also underwent a GTN-induced dilation test. All patients and controls withstood the examination well. There was no significant difference in the baseline flow or in the flow change after hyperemia between patients and controls. The baseline diameter of patients had a tendency to be larger than in the control group, but the difference was not statistically significant ($p = 0.06$).

The flow-mediated dilation of the brachial artery (endothelium dependent response) was significantly lower in patients than in the control group (5.0% ± 5.0 vs 12% ± 6.0, $p < 0.001$). The ANCOVA test showed that the result was independent of baseline diameter. In contrast, the GTN-induced dilation (endothelium independent dilation) did not differ between the groups (16.0 ± 6.0 in controls vs 14.0 ± 6.0 in patients, $p > 0.05$). Table 1 shows some characteristics and the vascular study results of patients and controls, and Figure 1 shows the flow-mediated and GTN-induced vasodilator response in both groups.

We observed a weak positive association between the SLEDAI score and baseline diameter, $r_s = 0.26$, $p < 0.05$. We also found a positive association between flow-mediated dilation and GTN-induced dilation ($r_s = 0.42$, $p < 0.05$). There was no association between the disease activity index and flow-mediated dilation ($r_s = –0.05$, $p = 0.69$) or between disease activity index and GTN-induced dilation ($r_s = –0.09$, $p = 0.51$).

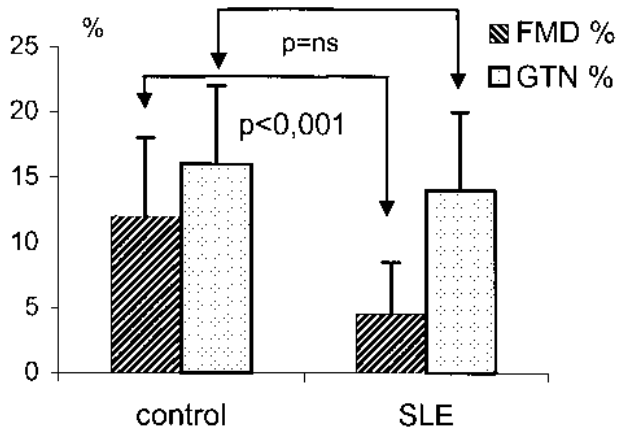


*Figure 1.* Flow-mediated dilation (FMD) and GTN-induced dilation in patients with SLE and controls. Flow-mediated dilation: 69 SLE patients; 35 controls. GTN-mediated dilation: 52 SLE patients; 28 controls.

In the 36 patients and 31 controls with no CAD associated risk factors, it was also observed that flow-mediated dilation was lower in patients than in the control group (4.5 ± 4.0 vs 12 ± 6, $p < 0.001$). GTN-induced dilation was similar in both groups (14 ± 6.0 vs 16 ± 6.0) (Figure 2).

We did not find a significant difference between flow-mediated or GTN-induced dilation when we compared 21 aCL positive and 48 aCL negative SLE patients. When we analyzed the aCL positive and negative patients and control group together, using the Kruskal Wallis test, we did not find a significant difference, but when we compared only the 21 aCL positive SLE patients and 35 controls the GTN-induced dilation was significantly

*Table 1.* Baseline characteristics and vascular study results.

| | Controls | Patients | p |
|---|---|---|---|
| Age (years) | 29 ± 6 | 29 ± 8 | NS |
| Total cholesterol (mg/dl) | 167 ± 19 | 166 ± 32 | NS |
| LDL cholesterol (mg/dl) | 101 ± 17 | 102 ± 30 | NS |
| HDL cholesterol (mg/dl) | 45 ± 7 | 42 ± 13 | < 0.05 |
| Dyslipidemia (%) | 8 | 42 | < 0.01 |
| CAD-RF (%) | 11 | 48 | < 0.001 |
| Baseline flow (ml/min) | 41 ± 20 | 45 ± 30 | NS |
| Hyperemia (% increase in flow) | 727 ± 428 | 650 ± 466 | NS |
| Baseline artery diameter (mm) | 3.37 ± 0.2 | 3.52 ± 0.3 | 0.06 |
| Flow-mediated dilation (%) | 12 ± 6 | 5 ± 5 | < 0.001 |
| GTN-induced dilation (%) | 16 ± 6 | 14 ± 6 | NS |

Data presented are mean value ± SD or number (%). GTN: glyceryl trinitrate; HDL: high density lipoprotein; LDL: low density lipoprotein; CAD-RF: coronary artery disease risk factors; NS = not significant.

reduced in patients than in controls (11.9% ± 4.0 vs 16.0% ± 6.0, $p < 0.05$) (Figure 3).

No significant influence of past arterial hypertension, Raynaud's phenomenon or vasculitis on the flow-mediated dilation or GTN-induced dilation was observed. When we compared patients who had received antimalarials with those who had not, we did not find a significant difference concerning the baseline diameter, for either the flow-mediated or the GTN-induced dilation. The mean disease duration did not influence the vascular reactivity study. There was no association between the current prednisone dose and the flow-mediated dilation ($r_s = 0.12$, $p = 0.33$), or between the cumulative prednisone dose and the flow-mediated dilation ($r_s = –0.13$, $p = 0.29$).

The Spearman correlation coefficient showed that there was no association between flow-mediated dilation and the total cholesterol level ($r_s = –0.16$, $p = 0.19$), the LDL cholesterol level ($r_s = –0.16$, $p = 0.19$), the HDL cholesterol level ($r_s = –0.08$, $p = 0.51$) or Castelli's index ($r_s = 0.01$, $p = 0.19$).

## DISCUSSION

Cardiovascular and cerebrovascular diseases are acknowledged as an important cause of morbidity[21] and mortality in SLE[2]. Endothelial function studies with brachial artery ultrasound in patients with coronary disease[22] and in subjects with CAD risk factors like diabetes mellitus[23], smoking, hypercholesterolemia and hypertension[24] have shown that the subjects with CAD risk factors had decreased flow-mediated dilation when compared with normal controls.

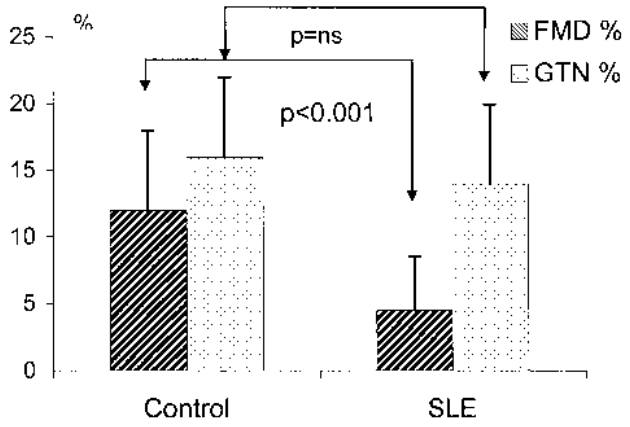


*Figure 2*. Flow-mediated dilation (FMD) and GTN-induced dilation in SLE patients and controls without CAD risk factors. Flow-mediated dilation: 36 SLE patients; 36 controls. GTN-mediated dilation: 18 SLE patients; 28 controls.

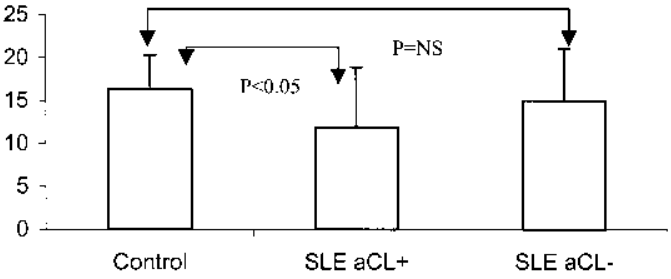


*Figure 3*. GTN-induced dilation in aCL positive and negative SLE patients and controls.

Several studies in women have emphasized the serum lipid profile abnormalities as an important risk factor for CAD. There is consensus that the increase of total cholesterol, LDL cholesterol[19] and triglyceride serum levels[25] and the Castelli's index[26] are risk factors for CAD, while the high levels of HDL cholesterol are protective[19].

Abnormal lipid profile is one of the most frequent risk factors for CAD in SLE patients and has been reported in 46 to 56% of SLE patients[3,27]. Furthermore, the majority of SLE patients show 3 or more CAD risk factors, such as hypertension, hypercholesterolemia, obesity, smoking, diabetes mellitus, CAD family history and sedentary lifestyle[3,27].

In our study, even excluding patients with serum triglyceride levels > 200 mg/dL and/or total cholesterol > 240 mg/dL, minor abnormality in lipid profile was found in 42% of patients. Nineteen percent of patients showed total cholesterol > 200 mg/dL, 19% LDL cholesterol > 130 mg/dL, 38% Castelli's index > 4.5, and 29% had HDL cholesterol < 35 mg/dL.

Obesity was found in only 13% of the sample. The low prevalence of obesity in our study was probably due to exclusion of patients with other risk factors that are generally associated with obesity[28-30].

The baseline brachial artery diameter showed a tendency to be larger in patients than controls. In a pilot study of 40 SLE patients and 20 controls, we found the baseline diameter in patients with CAD risk factor significantly larger than in controls[31]. Belmont, *et al*, 1997[32] reported that SLE patients had a higher nitric oxide production than normal subjects, and this increase was associated with disease activity. Considering these data, we evaluated the association between brachial artery baseline diameter and disease activity but found that the association was weak. Another possible cause of larger brachial artery baseline diameter in SLE patients could be atherosclerosis, as found by Celermajer, *et al*[15].

When we evaluated the influence of baseline diameter in the flow-induced dilation, the ANCOVA test showed that the result was independent of baseline artery diameter.

Several studies showed that the reduced endothelium-dependent vasodilation is not always followed by diminished GTN-induced vasodilation[33-35]. However, in a study with a high number of patients, it was also observed that there was reduced GTN-induced vasodilation in patients with CAD risk factors[36]. The authors suggested that in the beginning of the atherosclerotic process, changes in the arterial wall are not limited to the endothelium and that the

decreased vasodilation in response to nitric oxide and GTN can be partially due to change in the vascular smooth muscle cell.

In the present study, although GTN-induced vasodilation was similar in SLE patients and controls, the aCL antibody-positive subgroup of SLE patients had lower GTN-induced dilation than the control group. It is possible that in aCL positive SLE patients, the smooth muscle cell lesion takes place earlier than in the SLE group without these antibodies.

It has been demonstrated in middle aged men that aCL antibodies in high titers are an independent risk factor for myocardial infarction[37] and that aCL and anti-oxidized LDL antibodies may cross react[38]. In SLE patients, CAD has been correlated with aCL and anti-oxidized LDL antibodies[39]. These findings along with the evidence of increased lipid peroxidation in aCL positive SLE patients[40] suggest that the presence of these antibodies can be associated with premature atherosclerosis in SLE.

Although 42% of our patients had mild abnormalities in lipid profile, significant correlation between the total cholesterol levels, LDL and HDL cholesterol, and flow-mediated dilation was not observed. Possibly this is due to exclusion of patients with more serious dyslipidemia. Vasculitis, past hypertension, Raynaud's phenomenon, aCL antibody, cumulative dose of prednisone, use of antimalarial drug, and mean disease duration did not show significant influence on the flow-mediated dilation. The lack of significant difference may be due to the small number of patients with each studied variable.

The loss of endothelial function in SLE patients probably is multifactorial and includes the traditional CAD risk factors, some of which might be secondary to lupus and/or to its treatment, such as hypertension, dyslipidemia, diabetes mellitus, sedentary lifestyle, hyperhomocysteinemia, and CAD family history. The inflammatory process due to SLE, as well as vascular thrombosis induced by anti-phospholipid antibodies are other factors that may contribute to endothelial dysfunction in these patients.

The technique introduced by Celermajer[15] allows non-invasive study of vasodilator response of the arteries. It is a simple technique and can be performed with low risk and discomfort, and it has good accuracy and reproducibility. It can be repeated many times and has been used to study the effect of therapeutic intervention in subjects with reversible CAD risk factors.

The inconveniences of this method include the difficulty of obtaining good artery images, and the variation in the transducer position during the various examination steps.

It is also important to remember that the variation of endothelium-dependent dilation is very high in healthy individuals[41]. The test cannot be used in clinical practice to identify or quantify atherosclerosis severity in one subject, but it can be used to evaluate endothelial function in a group of patients with CAD risk factors.

This is the first study using brachial artery ultrasound imaging to evaluate endothelium function in SLE patients. We showed that SLE patients have decreased flow-mediated dilation when compared to sex and age-matched controls, even in the absence of CAD risk factors and this may represent an early atherosclerotic process. It will be necessary to evaluate if intervention can modify the impaired endothelial function in SLE patients.

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