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A controlled comparison of brachial artery flow mediated dilation (FMD) and digital pulse amplitude tonometry (PAT) in the assessment of endothelial function in systemic lupus erythematosus

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Abstract

The utility of flow mediated dilation (FMD) a measure of endothelial function is limited by operator dependence. Pulse amplitude tonometry (PAT) is a novel, less operator-dependent technique to assess endothelial function. This study compares PAT to FMD in SLE and controls. Thirty women with SLE and 31 controls were enrolled. Medications, cardiovascular disease and risk factors, SLE activity (SLAM-R) and damage (SLICC-DI) were recorded. FMD and PAT were performed simultaneously. Endothelium-independent function was assessed with nitroglycerin. Average age was 48.3 ± 10.1 years, SLE duration 16.2 years, SLAM-R 8.3 and SLICC-DI 1.0. Framingham Risk Scores were $\leq 2\%$ in most subjects. There were no differences between SLE cases and controls in FMD, PAT or response to nitroglycerin. This study found no association between FMD and PAT in SLE or controls. In the 17 SLE cases with a history of Raynaud's, correlation between FMD and PAT was 0.50 ($P = 0.04$). There was no difference in endothelial function assessed by FMD or PAT in SLE cases versus controls. FMD did not correlate with PAT except in SLE cases with a history of Raynaud's. Correlation between FMD and PAT may be stronger in populations with greater variation in endothelial function and more cardiovascular risk factors.

Keywords

atherosclerosis; brachial artery (ultrasonography); endothelium; vascular (ultrasonography); humans; systemic lupus erythematosus; vasodilation

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Introduction

Systemic lupus erythematosus (SLE) is associated with an increased risk of accelerated atherosclerosis and resultant cardiovascular events.^{1,2} Traditional cardiovascular risk factors alone explain only a part of the cardiovascular risk in SLE^{3,4}; SLE and/or its treatment appears to be the most important independent risk factor for cardiovascular disease.

A validated biosurrogate for atherosclerosis risk and progression of atherosclerotic disease would be a major contribution to assessing risk and monitoring. Endothelial dysfunction, manifested as loss of normal vasoreactivity, is an early event in atherogenesis and predicts cardiovascular events in various populations.⁵ Flow mediated dilation (FMD), a technique to assess bioavailable nitric oxide, is considered a measure of endothelial function⁵ and is abnormal in individuals with SLE,^{6–9} but its clinical utility is limited by its operator dependence.

Pulse amplitude tonometry (PAT) is a novel technique to assess nitric oxide bioavailability and is less dependent on the operator making it a potentially convenient measure of endothelial function.¹⁰ In contrast to measuring FMD, which requires a trained ultrasonographer to obtain accurate and reliable serial images of the brachial artery, PAT measurement simply requires insertion of two fingers into thimble-like peripheral arterial tonometers. Pressure changes associated with changes in pulse amplitude are detected by the tonometers and transmitted to a computer for recording and analysis.

As with FMD, PAT is reduced in the presence of cardiovascular risk factors in a dose-dependent fashion, as well as with atherosclerosis.¹¹ In an ambulatory clinic setting, PAT values have been found to be lower in individuals with more than two cardiac risk factors, as well as in individuals with coronary artery disease.¹² The presence of coronary endothelial dysfunction is associated with lower PAT values in patients without obstructive coronary artery disease.¹³ A linear relationship has been found between PAT and brachial artery FMD measurements in a population of patients with a range of traditional cardiovascular risk factors.¹¹

This new technique to assess endothelial function has not been evaluated in SLE. Although Raynaud's phenomenon is relatively common in patients with SLE, there had been no evidence that a history of Raynaud's affected FMD or PAT. Given the great potential utility of a simple tool for cardiovascular assessment of patients with SLE, we compared PAT to FMD in SLE and control subjects.

Patients and methods

Study population

Female patients age 18–64 fulfilling the updated revised 1982 American College of Rheumatology criteria for the Classification of SLE^{14,15} who had visited a rheumatologist at Brigham and Women's Hospital in the prior 2 years and lived within 30 miles of the hospital were identified from the Brigham and Women's Hospital SLE Registry. After obtaining permission from their physician, potential subjects were mailed letters introducing them to the study. Those expressing interest were called and invited to participate. A subset who had not responded to the mailing were also called and invited to participate. This subset was selected to ensure comparability of the ages in the two groups. Exclusion criteria included factors confounding the vascular measurements, diabetes mellitus, current pregnancy or lactation, tobacco use in the prior 30 days or change in vasoactive medication in the prior 30 days.¹⁶ Subjects were not excluded on the basis of renal disease. Control subjects without evidence of a connective tissue disease as determined by a negative Connective Tissue Disease Screening Questionnaire (CSQ)¹⁷ were recruited in a similar manner from a primary care practice

affiliated with Brigham and Women's Hospital. All subjects gave written informed consent which was approved by the Institutional Review Board and the General Clinical Research Center of Brigham and Women's Hospital.

Clinical and laboratory assessment

All subjects had a directed history and physical exam. Demographic data, height, weight, blood pressure, current medications, date of last menses, cardiovascular disease and risk factors and history of Raynaud's phenomenon or previous thrombosis were recorded. In subjects with SLE, disease activity and cumulative damage were assessed by the SLE Activity Measure (SLAM-R)¹⁸ and the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC-DI),¹⁹ respectively.

All subjects' outpatient medical records were reviewed for cardiovascular disease and risk factors, Raynaud's phenomenon and previous thrombosis. In addition, medical records of subjects with SLE were reviewed for evidence of SLE-related damage relevant for the SLICC-DI.

Blood was drawn from all subjects for measurement of plasma glucose, lipid profile, and high sensitivity C-reactive protein (CRP) (Roche COBAS Integra 400, Roche Diagnostics, Indianapolis, Indiana, detection range 0.01–19 mg/dL). In subjects with SLE, additional blood was drawn for measurement of complete blood count and differential Westergren erythrocyte sedimentation rate and serum creatinine, and urine was collected for evaluation of the urine sediment for completion of the SLAM-R. We calculated Framingham Risk Scores for all participants from the following clinical variables: sex, age, total cholesterol, smoking status, high-density lipoprotein (HDL), systolic blood pressure and use of anti-hypertensive medication.²⁰

Assessment of flow mediated dilation

Vascular studies were performed on the same day as the clinical and laboratory assessment. Flow mediated dilation (FMD) was assessed according to published protocol by a trained ultrasonographer.²¹ Subjects were studied in a controlled environment in the supine position after a minimum 4 h fast. After a 10 min equilibration period, baseline two-dimensional images of the brachial artery were obtained approximately 2 cm above the antecubital fossa. A blood pressure cuff placed proximal to the imaging transducer on the upper arm was inflated to suprasystolic pressure for exactly 5 min. The vessel was imaged continuously for 1 min after release of occlusion. Longitudinal brachial artery images from end-diastole were recorded on super-VHS videotape with a high-resolution (7.5 MHz) linear-array vascular ultrasound scanning transducer (Toshiba Powervision 8000).

Reactive hyperaemia was confirmed by measuring arterial blood flow using pulse-wave Doppler scanning interrogation. After a 10 min period of re-equilibration, baseline measurements were repeated. Subjects in whom nitroglycerin was not contraindicated and who consented to its use were administered 0.4 mg nitroglycerin sublingually and the brachial artery was imaged continuously for 5 min as described above.

Blinded measurement of vessel diameter was performed using customised image analysis software (Medical Imaging Applications, Iowa City, Iowa). For each condition, the results from three images were averaged. FMD was defined as the brachial artery diameter 1 min after cuff deflation compared with the baseline vessel diameter. Nitroglycerin mediated dilation (NMD) was defined as the brachial artery diameter 5 min after administration of nitroglycerin compared with the baseline vessel diameter.

To be considered interpretable, a study had to have distinct visualisation of the proximal and distal intima-media arterial layers perpendicular to the ultrasound beam with less than 5% diameter variation across the field of measurement. In our laboratory, the intraobserver variability in measuring brachial diameters was 2.9% and the variability of the hyperaemic response was 1.4%.²²

Assessment of PAT

PAT measurement was performed simultaneous with FMD measurement. PAT was assessed in the distal phalanx of the third finger by a peripheral arterial tonometer (Itamar-Medical, Caesarea, Israel).^{10,11} Pressure changes within the probe accompanying pulsatile volume changes in the finger were fed to a personal computer where the signal was band pass filtered (0.3–30 Hz), amplified, displayed and stored. The pulse amplitude was analysed by a computer algorithm (Itamar Medical Ltd, Caesarea, Israel) (1) under baseline conditions, (2) following the release of a 5 min occlusion of the upper arm by a blood pressure cuff inflated to supersystolic pressures (hyperaemia), (3) during a second baseline period before nitroglycerin administration and (4) after nitroglycerin administration.

The PAT reactive hyperaemia index (PAT-RH index) is the ratio of average pulse amplitude during hyperaemia over a 1-min time interval starting 1 min after cuff deflation divided by the average baseline pulse amplitude obtained over a 1-min interval immediately preceding cuff inflation, adjusted for any fluctuations in the magnitude of the signal in the contralateral finger. The PAT nitroglycerin response (PAT-Nitro) is the ratio of the average pulse wave amplitude during a 1-min period beginning exactly 5 min after administration of sublingual nitroglycerin compared with the average pulse amplitude during the second baseline period. All FMD and PAT studies were read by a single-blinded cardiologist with expertise in these techniques (Marie D. Gerhard-Herman). PAT measurements were analysed with a computerised, automated algorithm (Itamar Medical Ltd, Caesarea, Israel). Reproducibility of PAT has been evaluated previously.²³

Statistical analysis

Sample size was estimated to be approximately 64 subjects (32 SLE and 32 controls) for 80% power to detect a 3.6% difference in FMD between the groups with a 5% type 1 error rate for a two-sided test assuming a common standard deviation of 5%.

Categorical variables are presented as frequency and percent and compared with the chi-squared test. Normally distributed continuous variables are presented as mean $\pm$ standard deviation and compared using independent sample *t*-tests. Continuous variables that were not normally distributed are presented as median and range, and the groups are compared using Wilcoxon rank-sum tests. Correlations between variables were determined using the Spearman correlation coefficient. Linear regression analysis was performed to adjust for potential confounding by baseline vessel diameter.

Two-sided significance level of 0.05 was used for all analyses. Analyses were performed using SAS statistical software (version 9.1 SAS Institute Inc, Cary, North Carolina, USA).

Results

Study population

Thirty SLE participants and 31 control participants were studied. Twenty-eight of the SLE subjects' and 31 of the control subjects' imaging studies were adequate for analysis. Their characteristics are shown in Table 1. Subjects' mean age was 48.8 ± 8.8 years in the SLE group and 47.7 ± 11.3 years in the control group. Menstrual status and menstrual phase were not

significantly different between the groups. Among SLE subjects, the mean disease duration was 16.2 ± 10.2 years, mean disease activity (SLAM-R) was 8.3 ± 4.0 and median (range) SLICC damage index was 1.0 (0–7). Elevated CRP was more common in SLE subjects ($P = 0.01$). History of Raynaud's was more common in SLE subjects (61%, $n = 17$) compared with controls (6%, $n = 2$). In all, 18% ($n = 5$) of the SLE subjects had a history of vasculitis. There were more SLE subjects with a history of deep vein thrombosis, pulmonary embolus or other thrombosis. There was no significant difference in history of coronary artery disease or cerebrovascular accident between the groups, with low frequency in both groups. More than 98% of all subjects had 10-year Framingham Risk Scores of $\leq 2\%$. In all, 25% ($n = 7$) of SLE subjects reported use of calcium channel blockers, compared with none in the control group. There was no significant difference in the reported use of other anti-hypertensive medications, cholesterol lowering medications, hormone therapy, non-steroidal anti-inflammatory drugs (NSAIDs), cox 2 inhibitors or aspirin between the groups. Corticosteroids were being used by 39% ($n = 11$) of SLE subjects and none of the controls. Anti-malarial medications were used by 57% ($n = 16$), mycophenylate mofetil by 14% ($n = 4$) and azathioprine by 11% ($n = 3$) of the SLE subjects. No subjects reported using any other immunomodulators in the prior 30 days. There was no significant difference in body mass index, blood pressure, glucose, total or HDL cholesterol between the groups.

Measurements of FMD and PAT in SLE cases and controls

The brachial artery ultrasound and PAT data are shown in Table 2. Flow increased by a minimum of 100% following release of the ischemic stimulus, with a mean increase of 447%. There was a difference of 0.2 mm between the mean baseline diameters in the two groups. Although this magnitude of a difference is not considered clinically meaningful, it did achieve statistical significance. However, there were no statistically significant differences between SLE cases and controls in FMD, considered as absolute dilation ($P = 0.30$) or as percent dilation ($P = 0.99$), and adjustment for baseline diameter did not change these results. There were no statistically significant differences between SLE cases and controls in PAT ($P = 0.64$). There were no statistically significant differences between SLE cases and controls in response to nitroglycerin at the brachial artery ($P = 0.32$) or at the fingertip ($P = 0.68$).

Relationship between PAT and FMD

Evaluation of the relationship between PAT and FMD is presented in Table 3 and graphically in Figure 1. There was no significant association between PAT and FMD in subjects with SLE, nor was there any significant association between PAT and FMD in controls or in the entire population.

In the 17 SLE cases with a history of Raynaud's phenomenon, PAT was moderately correlated with FMD, with a correlation coefficient of 0.50 ($P = 0.04$). No clinically apparent digital ischemia was noted during testing. This correlation did not appear to be driven by calcium channel blocker use as the correlation of PAT with FMD in SLE cases using calcium channel blockers was negative ($r = -0.36$, $P = 0.43$). Excluding subjects using calcium channel blockers or reporting a history of vasculitis improved the correlation in the SLE subjects but did not achieve statistical significance ($r = 0.43$, $P = 0.07$). No correlation was found between FMD and PAT in the 23 SLE subjects without thromboembolic disease ($r = 0.34$, $P = 0.11$).

Relationship between FMD and PAT and measures of inflammation

Neither FMD nor PAT was correlated with disease activity (SLAM-R) in the subjects with SLE. Neither FMD nor PAT was correlated with CRP levels in subjects with SLE or controls.

Discussion

This controlled study shows normal endothelial function as assessed by FMD in a population of patients with SLE. This finding is in striking contrast to prior studies which have reported blunted FMD in SLE.^{6–9} Wright, *et al.*²⁴ have recently reported a reduction in diastolic shear stress in response to a forearm arterial occlusion-release stimulus in SLE cases compared with controls. As this type of forearm stimulus was used in the prior studies of FMD in SLE, it is possible that the weakness of the stimulus, and not necessarily any actual endothelial dysfunction, was responsible for the blunted FMD reported in prior studies of FMD in SLE.

Wright, *et al.*²⁵ have subsequently published a study reporting increases in FMD in patients with SLE taking omega-3 fatty acids. The treatment group was noted to have an increase in diastolic shear stress in the brachial artery after reactive hyperaemia that could account for the increase in FMD. This finding is consistent with the concept that in SLE, FMD may be sensitive to the strength, or weakness, of the shear stress stimulus.

The more proximal arterial occlusion-release stimulus used in this study is known to produce a stronger shear stress stimulus which may be related to recruitment of more resistance vessels²¹ leading to the production of significantly greater hyperaemic and vasodilatory responses.²⁶ Cuff placement proximal to the elbow results in a significant increase in the peak hyperaemic flow with a proportional increase in FMD compared with distal cuff placement.²⁷ The strong correlation between hyperaemic flow and FMD suggests that the more extensive increase in brachial artery flow with proximal cuff placement is the predominant cause for the increase in FMD in this setting. Although proximal cuff placement is technically more difficult, the signal-to-noise ratio is reduced with the cuff in this proximal location.²⁷ The proximal cuff is used routinely in our vascular laboratory for these test characteristics, where the technicians are proficient in its use. The more proximal cuff placement in this study may account for the difference in the results found in this study.

Alternatively, or in addition, the normal FMD and lack of correlation between PAT and FMD observed in our SLE subjects may indicate that they had little or no atherosclerosis despite 16 years of disease and moderate disease activity (mean SLAM-R 8.3), on average. The variation in PAT and FMD we observed is in the normal range of determinations. It may be that for a correlation between PAT and FMD to be evident, a wider distribution of values are required. In the study by Kuvin, *et al.*,¹¹ the correlation between PAT and FMD in patients presenting for evaluation for chest pain appeared driven by the more extreme values that were not observed in this study. The generalisability of this study may be limited given the relatively few cardiovascular risk factors and low prevalence of clinical atherosclerosis in the population evaluated.

The correlation between PAT and FMD in those SLE subjects with Raynaud's may reflect a more diverse spectrum of values for PAT and FMD in this population. It is possible that ischemia occurred during the studies and that this produced a correlation. However, we observed no digital pallor or cyanosis during the studies. It is possible that vascular structure and/or function are altered in patients with a history of Raynaud's. Although brachial artery FMD may be relatively insensitive to these changes, measurement of PAT at the fingertip may be more susceptible. Although the study conditions have been designed to reduce changes in sympathetic stimuli or cool room temperatures that might provoke ischemia, subclinical changes may have been present in at least a subset of participants with Raynaud's.

Calcium channel blocker use did not appear to account for the correlation between PAT and FMD in SLE subjects with Raynaud's; indeed, there was a non-significant but negative correlation between PAT and FMD in those subjects using calcium channel blockers. Interestingly, exclusion of subjects reporting calcium channel use or a history of vasculitis

resulted in an improvement in the correlation between FMD and PAT, although this did not reach significance. It is possible that calcium channel blockers and these cases of vasculitis affected the relevant vascular beds differently, uncoupling the correlation of brachial FMD and fingertip PAT. Perhaps a significant correlation between FMD and PAT might be found with enrolment of additional subjects not taking calcium channel blockers and without a history of vasculitis.

Validation of FMD as a measure of endothelial function and predictor of future cardiovascular events in SLE is lacking despite data suggesting its predictive usefulness in other populations including patients with coronary artery disease, patients with hypertension, patients undergoing vascular surgery and patients with normal coronary angiograms.⁵ It is possible that the physiology differs in patients with SLE due to chronic inflammation, its treatment or other factors. Future studies evaluating the biology of brachial arterial responsivity in SLE are warranted as are studies evaluating the correlation of FMD with clinical outcomes.

In conclusion, in this study, we found no difference in FMD or PAT in SLE cases compared with controls. Our use of a proximal cuff may explain some differences from prior studies of FMD in SLE. Despite long disease duration and moderate disease activity, the SLE population studied had low cardiovascular risk and apparently relatively normal endothelial function. Although in this population PAT did not correlate with FMD in SLE subjects or in controls, correlation between FMD and PAT may be stronger in populations with greater variation in endothelial function and more cardiovascular risk factors.

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Figure 1. Correlation between FMD and PAT. (A) All subjects. (B) Control subjects. (C) SLE cases. (D) SLE cases with history of Raynaud's. FMD, flow mediated dilation; PAT, pulse amplitude tonometry; SLE, systemic lupus erythematosus.

Table 1

Characteristics of subjects

Characteristic	SLE (n = 28)	Control (n = 31)	P value
Age	48.8 ± 8.8	47.7 ± 11.3	0.68
Postmenopausal	13 (46)	12 (39)	0.82
Premenopausal with irregular menses	6 (21)	7 (23)	
Days since menstrual period with regular menses	11.1 ± 11.2	10.3 ± 9.8	0.85
Medications			
Ace inhibitor	4 (14)	2 (6)	0.41
Beta blocker	4 (14)	3 (10)	0.70
Calcium channel blocker	7 (25)	0	<0.01
Other anti-hypertensive	3 (11)	5 (16)	0.71
Statin	5 (18)	4 (13)	0.72
Hormone replacement	4 (14)	2 (6)	0.41
Aspirin	10 (36)	6 (19)	0.16
NSAIDs/Cox 2 inhibitor	9 (32)	16 (52)	0.13
Medical history			
Coronary artery disease	2 (7)	0	0.22
Cerebrovascular accident	1 (4)	2 (6)	0.99
Deep vein thrombosis, pulmonary embolism, clot	5 (18)	0	0.02
Vasculitis	5 (18)	0	0.02
Antiphospholipid antibodies	9 (32)	0	<0.01
Raynaud's	17 (61)	2 (6)	<0.01
Framingham Risk Score (points)	0 (0–8)	0 (0–2)	0.71
Body Mass Index (BMI) (kg/m ²)	26.4 ± 6.5	25.0 ± 5.2	0.39
Systolic blood pressure (mm Hg)	118.6 ± 15.0	114.9 ± 15.1	0.36
Diastolic blood pressure (mm Hg)	66.5 ± 7.4	67.8 ± 9.3	0.56
Glucose (mg/dL)	84.7 ± 9.7	89.9 ± 10.4	0.06
Total cholesterol (mg/dL)	182.5 ± 41.0	183.2 ± 31.5	0.94
HDL cholesterol (mg/dL)	62.5 ± 15.0	64.2 ± 17.0	0.70
CRP (mg/dL)	0.37 (0–4.5)	0.13 (0.01–1.77)	0.01

Abbreviations: SLE, systemic lupus erythematosus; NSAIDs, non-steroidal anti-inflammatory drugs; HDL, high-density lipoprotein; CRP, C-reactive protein.

For continuous, normally distributed variables mean ± standard deviation presented, with *P* values from *t*-tests, for continuous non-normally distributed variables median (range) presented with *P* values from Wilcoxon rank-sum tests, for categorical variables frequency (%) presented with *P* values from chi-square analyses and Fisher's exact test when appropriate. *P* values < 0.05 are represented in bold.

Table 2

Vascular findings

Measure	SLE	Control	<i>P</i> value [*]
Baseline diameter (mm)	3.0 ± 0.4	3.2 ± 0.4	0.04
Flow-induced dilation, absolute FMD (mm)	0.36 ± 0.12	0.40 ± 0.15	0.30
Flow-induced dilation, percent FMD (%)	12.5 ± 5.1	12.5 ± 4.5	0.99
Flow-induced PAT	2.7 (1.3–8.0)	2.6 (0.7–11.8)	0.64
Nitroglycerin-induced dilation, absolute NMD (mm)	0.60 ± 0.21	0.79 ± 0.34	0.13
Nitroglycerin-induced dilation, percent NMD (%)	20.2 ± 7.6	25.0 ± 13.3	0.32
Nitroglycerin-induced PAT	2.1 (1.2–5.7)	1.7 (0.6–5.3)	0.68

Abbreviations: SLE, systemic lupus erythematosus; FMD, flow mediated dilation; PAT, pulse amplitude tonometry; NMD, nitroglycerin mediated dilation.

^{*} *P* values for flow-induced PAT and Nitroglycerin-induced PAT are from Wilcoxon rank-sum tests. All other *P* values are from independent sample *t*-tests.

Table 3

Correlation between FMD and PAT

Sample	<i>N</i>	Correlation [*]	<i>P</i> value
Entire population	58	0.05	0.73
Controls	30	−0.05	0.81
SLE	28	0.22	0.26
SLE subgroups			
SLE without Raynaud's	11	0.03	0.93
SLE with Raynaud's	17	0.50	0.04
SLE without vasculitis	23	0.34	0.11
SLE with vasculitis	5	−0.70	0.19

Abbreviations: FMD, flow mediated dilation; PAT, pulse amplitude tonometry; SLE, systemic lupus erythematosus.

^{*} Spearman correlation coefficient. *P* values < 0.05 are represented in bold.