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Blood Pressure and Vascular Dysfunction Underlie Elevated Cerebral Blood Flow in Systemic Lupus Erythematosus

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Abstract

Objective—In previous studies, cerebral blood flow (CBF) has been found to be altered in patients with systemic lupus erythematosus (SLE) compared to controls. In the present study, the relationships between CBF and clinical data from SLE subjects were explored with the aim of determining the pathologic factors underlying altered CBF in SLE.

Methods—42 SLE subjects and 19 age and gender matched normal control subjects were studied. Dynamic susceptibility contrast (DSC) magnetic resonance imaging (MRI) was used to measure CBF. Patients and controls underwent complete clinical and laboratory evaluations in close proximity with their MRI studies.

Results—A higher CBF was present in the SLE group and was independently associated in statistical models with higher systolic blood pressure (sBP) ($p < 0.01$). However, the intensity of the relationship (slope of curve) between CBF and mean arterial blood pressure (MAP), diastolic blood pressure (dBP), or blood levels of tissue plasminogen activator (tPA) in the SLE group were significantly blunted relative to the healthy control group.

Conclusion—These findings are consistent with an underlying cerebral hyperperfusion in SLE induced by elevated but non-hypertensive levels of systolic blood pressure. The factors underlying this relationship may be functional and/or structural (atherosclerotic, thrombotic, thromboembolic, or vasculitic) cerebrovascular disease.

Key Indexing Terms

lupus; brain; cerebral blood flow; magnetic resonance imaging

Introduction

Systemic lupus erythematosus (SLE) is an important autoimmune inflammatory disease affecting multiple organ systems, including the brain. Though the mechanisms of brain injury of SLE are complex and incompletely understood, numerous studies have reported

structural, functional, and biochemical brain abnormalities in SLE patients that underlie the clinical manifestations of neuropsychiatric SLE (NPSLE) (1). Periventricular or deep white matter abnormalities (WMA) including cerebral infarcts by magnetic resonance imaging (MRI) are present in over 50% of SLE cases (2) and histopathologic studies have shown evidence of widespread likely multifactorial vasculopathy both focal and diffuse brain injury (3). Furthermore, several studies have reported abnormalities in cerebral blood flow (CBF) in SLE (4–10). The vast majority of the latter studies measured relative CBF with single photon emission computed tomography (SPECT) and found that CBF was lower in focal or broad regions of the brain with respect to a region presumed to be normal within the SLE subjects (4–10). However, it has recently been demonstrated using dynamic susceptibility contrast MRI (DSC-MRI) that both CBF and cerebral blood volume (CBV) may be higher in normal appearing brain tissue in SLE patients than healthy controls (11). Elevated CBF has also been observed in other neurological disorders, including epilepsy (12), stroke (13), transient ischemic attack (14), fibromyalgia (15), metabolic brain disease (16), and migraine (17). However, the mechanisms underlying higher perfusion in these disorders are likely to be diverse and not necessarily identical to those underlying elevated CBF in SLE.

The purpose of the current study was to explore the relationships between CBF and clinical and laboratory data in SLE subjects and healthy controls with the goal of gaining insight into the mechanism or factors causing elevated CBF in SLE.

Materials and Methods

Subjects

This study was approved by the University of New Mexico institutional review board (IRB) and conformed with the ethical standards of the Declaration of Helsinki. All subjects signed an informed consent. The diagnosis of SLE was established in each subject using the American College of Rheumatology (ACR) 1997 revised criteria for SLE (Tan 1982, Hochberg 1997). A cohort of 42 SLE subjects (40 women, 37.3 ± 12.8 years old) and 19 age and gender matched normal healthy control subjects (17 women, 31.9 ± 10.1 years old) were studied. Twenty-six SLE subjects (62%) were positive for anti-phospholipid antibody, 10 (24%) were positive for anti-ribosomal P antibodies, and 26 (65%) were positive for anti-dsDNA antibodies. Eighteen SLE subjects (43%) were diagnosed with active NPSLE using the neurological SLE disease activity index (Neuro-SLEDAI) criteria (seizures (2 patients), psychosis (3 patients), organic brain syndrome (5 patients), visual disturbance (1 patient), cranial neuropathy (2 patients), lupus headache (7 patients), and stroke (4 patients)). Patients with past but not active NPSLE were excluded from the study. The two groups were similar in all demographic variables (Table 1). More extensive clinical data and findings on this cohort can be found in Table 2 and in a previous report (11).

Clinical and Laboratory evaluations

Patients and healthy control subjects underwent clinical and laboratory evaluations including specific parameters inflammation, coagulation, and fibrinolysis. Group differences in several of these tests are reported in Table 1. As part of the clinical evaluation, systolic (sBP) and diastolic (dBP) blood pressure measurements were obtained in the supine position from the brachial artery using an automatic sphygmomanometer. The mean arterial pressure (MAP) was derived as $= \frac{2}{3}dBP + \frac{1}{3}sBP$. Mean disease duration, activity, severity, therapy, and serology of the SLE patients, including antiphospholipid antibodies, are reported in Tables 1 and 2 and in our previous report (11).

MRI

Anatomical MRI, DSC MRI, and MR angiography to assess brain injury, cerebral perfusion, and cerebral atherosclerosis were performed on all subjects within 7 days of clinical assessment using a 1.5-T Siemens Sonata scanner with an 8-channel head coil. The total examination time of the MRI protocol was approximately 1 hour. Scout images were used to prescribe a series of whole-head T1-weighted, T2-weighted, and Fluid attenuated inversion recovery (FLAIR) images aligned with the interhemispheric midline and parallel to the anterior commissure-posterior commissure (AC-PC) line. T1-weighted images (3D fast low angle shot (FLASH) sequence, TR/TE = 12 ms/4.76 ms, flip angle=20°, field of view (FOV) = 256 mm × 256 mm, resolution = 1 mm × 1 mm, 128 slices, slice thickness = 1.5 mm) and T2-weighted images (Turbo spin echo sequence, TR/TE = 9040 ms/64 ms, turbo factor = 5, FOV = 220 mm × 220 mm, resolution = 1.1 mm × 1.1 mm, 128 slices, slice thickness = 1.5 mm) were acquired for anatomical segmentation of normal appearing gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). The FLAIR image (variable flip, TR/TE/TI = 6000 ms/358 ms/2100 ms, averages = 2, slice thickness = 1.5 mm, FOV = 220 mm × 220 mm, matrix size = 192 × 192) was used to manually segment lesions. The segmented gray matter, white matter, cerebrospinal fluid, and lesion maps were used to identify these regions in the processed perfusion maps. The DSC MRI images (Kikuchi 2001, Barber 2001) were acquired with a perfusion-weighted echo planar imaging (EPI) sequence (TR/TE = 1430 ms/46 ms, Flip= 90°, 20 slices, time course of 50 sequential acquisitions, FOV=200 mm × 200 mm, matrix size 128×128) Magnevist® contrast agent (gadopentetate dimeglumine) was injected into an antecubital vein at the standard dose as 0.1 ml per Kg body weight using a power-injector at 5 ml/sec, starting 15 sec after the start of scan acquisition, followed by 20 ml of saline at the same rate. Raw DSC MRI data were analyzed using the software package Penguin (NordicImagingLab, Bergen, Norway) and the CBF maps constructed with Penguin were co-registered to the T1-weighted images to identify distinct brain regions within gray and white matter as previously described (11). Briefly, pixel intensity changes due to contrast (gadopentetate) passage over the time series of images are converted into pixel-by-pixel tissue contrast concentration curves, C(t). With user supervision, the software selects candidate arterial pixels to construct an arterial input function, AIF(t), based on the higher intensities and narrow time courses of the concentration changes. In this work an attempt was made to locate and use pixels associated with the middle cerebral artery consistently for the construction of the AIF(t). A gamma variate function is fit to the raw C(t) and AIF(t) curves to capture just the first pass of the contrast bolus and used to represent C(t) and AIF(t) in further analyses. The calculation of CBF involves an equation relating C(t) to CBF and the convolution of AIF(t) and the residue function R(t), the fraction of contrast agent in the vasculature at any time: $C(t) = CBF \cdot [AIF(t) \otimes R(t)]$, where $\otimes$ denotes the convolution operation. CBF maps constructed with Penguin were co-registered to the T1-weighted images to identify distinct brain regions within gray and white matter. This procedure involved automatically segmenting the T1-weighted image into GM, WM, and CSF and co-registering the lesion map that was manually traced from the FLAIR image to the T1-weighted image. T1-weighted image was warped into a standard brain template for identifying the major cortical and subcortical brain regions. Mean gray and white matter CBF values for 4 cerebral regions (occipital, parietal, temporal, and frontal) and 4 subcortical regions (caudate, putamen, thalamus, and globus pallidus) for each hemisphere were determined. In order to resolve CBF in normal appearing tissue from CBF in lesions, the mean regional cerebral or subcortical values of CBF were calculated without the lesion pixels included. This permitted comparison of normal appearing tissue between groups (those with lesions and those without lesions) without the confound of the lower lesion CBF values reducing the overall mean values for the region.

Statistical Analysis

The primary goal of the statistical analysis was to gain insight into those factors most associated with the presence of elevated CBF in SLE patients. Since a large number of clinical and laboratory variables were considered, the statistical strategy incorporated three levels of analysis with progressively increasing complexity and focus. At the first level, group differences in the various variables obtained for both healthy control and SLE subjects were examined with the Student's t-test and correlations between regional CBF and these measures were explored with univariate Pearson correlation analyses. In order for a clinical or laboratory variable to be a candidate for further analysis, the Pearson correlation with CBF was required to be significant ($p < 0.05$) in at least one of the 16 gray or white matter brain regions in which CBF was measured. Furthermore, to discount significant correlations that may have depended on outliers, a Spearman correlation analysis was also performed. Hence, both Pearson and Spearman correlations needed to be significant in order for a variable to be considered in further analyses. Using these criteria, 6 out of 36 variables collected from both SLE and healthy control subjects qualified for further analyses. A list of these variables is shown in Table 3. The mean values and significance of group differences in the variables can be found in Table 1.

In the second stage of analysis, each of these candidate factors was added as a covariate in a repeated measures Repeated Measures (RM) analysis of covariance (ANCOVA) model. The use of RM ANCOVA follows the approach taken in our initial report on differences in CBF and CBV only and is motivated by the fact that CBF varies substantially from region to region in the brain (11). This regional variability would obscure small group differences in CBF in conventional t-tests. In the current RM ANCOVA model, 8 brain regions were entered as a repeated factor (combined normal appearing gray and white matter CBF in occipital, parietal, temporal, frontal, caudate, putamen, thalamus, and globus pallidus regions), the two groups (SLE, controls) as a grouping factor, and the presence of lesions as a covariate. The brain regions used in the computation of CBF excluded the lesions, but the presence of lesions still was included in the model as an important confounder. If the effect of group (SLE v.s. control) were rendered non-significant by the addition of the covariate, then the factor would be considered a potential mediator between CBF and group. A common interpretation of such an effect is that the covariate "explains" ("intervenes" between) the group effect on the dependent variable. In each analysis, if the group-by-covariate interaction term were significant, then an interaction plot of CBF versus the covariate by group was examined to determine how the relationship between CBF and covariate differed in SLE and control groups. In the interaction plot for our model, we used the least-square means of the CBF values for each group while controlling for the lesion variable.

In the final stage of analysis, both univariate and stepwise multivariate regression models (forward/backward selection with p -value < 0.05 for variables to enter and to stay in the model) were used to explore directly the relationships between explanatory covariates identified in the various RM ANCOVA models and various physiologic measures in the study.

Results

Group differences in combined gray and white matter CBF in the eight brain regions examined in this study are illustrated in Figure 1. These plots demonstrate an anterior-to-posterior increase in CBF and overall higher CBF in SLE patients relative to healthy subjects, as reported previously (11). Initial univariate correlation analyses revealed both significant Pearson and Spearman correlations between regional CBF estimates and 6 clinical variables: BMI, MAP, sBP, dBP, platelet count, and tPA levels. Three of the variables demonstrated significant group differences in Student's t-tests ($p < 0.05$) (Table 1).

The means of MAP, sBP, and dBp were, respectively, 5%, 5%, and 4% higher in the SLE group, though the sBP difference was not significant. The platelet count was significantly higher in the control group.

Each of the 6 variables that correlated with CBF was entered as a covariate in a RM ANCOVA model with brain region as the repeated measure, group (SLE and control) and the presence of focal brain lesions (present or not present) as main effects, and a group-by-covariate interaction term. If the interaction effect was not significant ($p > 0.05$), the analysis was repeated with the interaction term absent from the model. Table 3 summarizes the results from this analysis. With no covariate in the model, the main effects of group and lesion presence are both significant independent predictors of CBF, in agreement with our previous report in which gray and white matter CBF were examined separately (11). CBF is elevated in the SLE group with respect to the control group and the group with lesions (23 of the 42 SLE subjects and 3 of the 19 control subjects) had lower CBF than the group without lesions. Post hoc tests with only SLE subjects demonstrated that SLE subjects without lesions significantly predicted higher CBF. However, active NPSLE had no significant impact on CBF, based on entering the Neuro-SLEDAI score as a covariate in the ANCOVA model. When the other clinical variables are added to the RM ANCOVA model as covariates, 5 demonstrate significant effects as independent predictors of CBF. Three variables, MAP, dBp, and tPA, show a significant group-by-covariate interaction, indicating that the relationships between CBF and these variables within each group differ significantly. As can be appreciated in the interaction plots of Figure 2, these relationships appear to be blunted in the SLE group relative to the control group. Only one of the 6 variables, sBP, has an effect that is strong enough when entered as a covariate to render the group effect non-significant. Hence, though causality cannot be proven from correlation analyses, these results suggest 1) that the relationship between CBF and factors related to blood pressure and tPA differ significantly between SLE and healthy subjects, and 2) that differences in sBP, in particular, may underlie the group differences in CBF observed in this study.

Since covarying with sBP uniquely rendered the group effect non-significant in the ANCOVA analyses, univariate correlation and stepwise multivariate regression models were used to explore the relationship between sBP and any of the clinical and laboratory variables obtained from subjects in the study. The aim of this analysis was to gain insight into what underlying factors might be driving the sBP differences in groups that, in turn, might explain the higher CBF in SLE subjects. Initial univariate analyses, uncorrected for multiple comparisons, revealed only 8 factors that correlated significantly with sBP that were not other measures of blood pressure. These factors are listed in Table 4. No significant correlation was discovered between corticosteroid (prednisone) dose and either CBF or any measure of blood pressure.

As expected, both body weight and BMI correlated strongly with sBP. However, neither mean weight nor BMI were significantly different between groups. Furthermore, mean white blood cell count was lower in the SLE group (though not significantly). Hence, though moderately correlated with sBP within or across groups, these factors are unlikely to account for the higher mean sBP in SLE subjects or underlie the effect of sBP as a covariate on the group CBF differences in the ANCOVA analysis. Of the remaining 5 factors, one, IgA anti-phospholipid antibody (aPI-IgA), was measured only in SLE subjects. Since aPI-IgA demonstrates a negative correlation with sBP and, moreover, since aPI-IgA levels are expected to be absent or lower in healthy controls, this factor is also unlikely to account for the relationship between sBP and CBF group differences revealed in the ANCOVA analysis. The remaining 4 factors that correlated with sBP were blood urea nitrogen (BUN), tPA, plasminogen activator inhibitor 1 (PAI 1), and triglyceride levels. These factors were

entered as independent variables in a stepwise multivariate regression model with sBP as the dependent variable. Group membership (SLE or control) was included as a binary independent variable to examine the contribution of group in predicting sBP. The best model selected by this analysis was one with group ($p=0.291$), BUN ($p=0.026$), and tPA ($p=0.010$) as independent variables and an adjusted r^2 of 0.20.

Discussion

The results of this study reveal two major findings: 1) increased CBF in the normal appearing brain tissue of the SLE patients examined is statistically most strongly associated with sBP, and 2) the relationship between CBF and blood pressure in SLE patients differs from the relationship in healthy controls, with SLE patients demonstrating a weaker correlation between CBF and either MAP or dBP. Since MAP is weighted much more by dBP (2/3) than by sBP (1/3), the similarity in the statistical relationship between MAP or dBP with CBF is not unexpected. However, only sBP was found to account statistically for the group affect on CBF, suggesting that the higher CBF observed in SLE patients may be directly related to higher sBP in that group. Though the SLE subjects in this study were not clinically hypertensive as defined by the American Heart Association (18), as a group they had higher blood pressure than the control group, with sBP demonstrating a difference at the greatest confidence level ($p<0.01$). In post hoc correlation analyses, sBP was found to correlate with parameters of SLE disease activity and/or severity such as renal dysfunction, thrombogenesis, and dyslipidemia.

Normal resting CBF is regulated against changes in cerebral perfusion pressure (MAP minus intracranial pressure) by changes in cerebrovascular resistance to blood flow via vasoconstriction or vasodilatation (19, 20). Vasomotor control is effected by vascular smooth muscle cells (the vascular myocytes of arteries and arterioles) or capillary pericytes which, depending on the local state of neural activation, respond to various factors in a complex and exquisitely coordinated system which is far from being fully understood (21). These factors could include the depolarizing effects of intravascular pressure on cell membranes, shear stress on endothelial cells, intramural vascular signalling, direct neuronal activation of myocytes and pericytes, or the response of vascular cells to various metabolic by-products (e.g., hydrogen ions, free radicals, lactate, adenosine, CO_2), neurotransmission factors (e.g., K^+ , Ca^{++} , acetylcholine, dopamine, GABA, noradrenalin), or other vasoactive agents derived from local neurons, astrocytes, or endothelium (e.g., NO, prostacyclin, substance P, endothelin, prostaglandins). A diminished vasomotor response to changes in blood pressure, therefore, could indicate a dysfunction in one or more of these systems.

In the present study, a stronger relationship between CBF and either MAP or dBP was found within the healthy subject group relative to the SLE group. While these findings might seem to run counter to the expectation that CBF would be better regulated against systemic blood pressure changes in healthy subjects, it is important to bear in mind that the cross-sectional data of this study do not reflect the dynamic responses of CBF to local neural activation nor to challenges to CBF by changes in blood pressure in individual subjects. Rather, they reflect the relationships between regional resting state CBF in combined gray and white matter and various clinical and laboratory variables taken few days before the CBF measurement. As such, caution must be exercised when interpreting the blunted relationship of CBF to MAP, dBP, or tPA observed in the SLE group with respect to any particular mechanism involved in CBF autoregulation. These data simply demonstrate that a portion of the group variance in CBF across healthy individuals can be explained by the variance in MAP, dBP, or tPA. In light of this, what appears abnormal in the SLE group is a weakening of these relationships: variations in resting CBF across the brain are not as strongly related to MAP, dBP, or tPA across the SLE group. Hence, though not directly probing the

vasomotor response in subjects, these data are nonetheless consistent with an abnormal vascular condition (vasculopathy or vasoregulatory abnormality) in SLE group, which may have a multifactorial origin.

One factor that might underlie this abnormality is increased arterial stiffness (reduced compliance) due to increased vascular tone resulting in vasoconstriction, atherothrombosis, thromboemboli, vasculitis, or atherosclerosis (22). Arterial stiffness limits CBF increases by reducing distensibility and, at the same time, leads to increased sBP (23). In the present study, sBP correlated with a subset of markers of SLE disease activity and/or severity, such as renal dysfunction (BUN), thrombogenesis (platelets, tPA, and PAI-1) and dyslipidemia (triglycerides). While, none of these markers were significantly higher in the SLE group, they are commonly of clinical significance in SLE patients and can be associated with arterial stiffness and hypertension (24). In a study on patients with kidney disease and elevated blood pressure, including one patient with SLE, Kuwubara et al. observed higher CBF in patients relative to healthy control subjects and also found a significant correlation between CBF and MAP (25).

Another possible origin of an abnormal vasomotor function is the vascular endothelium. The endothelium is a central player in both the regulation of vascular tone and the production of tPA (26) and endothelial dysfunction has been reported in SLE (27–31). Endothelial dysfunction is also associated with and can be an initiating factor of atherosclerosis (32, 33). However, in the present study, the mean blood level of endothelium derived microparticles (CD144) in SLE patients (157 ± 247 particles/ μ L plasma) was not significantly higher than in control subjects (153 ± 125 particles/ μ L plasma), nor did levels of endothelium derived microparticles correlate with CBF. Hence, there is no direct evidence that endothelial dysfunction underlies differences in CBF observed in this study.

Finally, we cannot exclude the possibility that transient factors not measured in this study contributed to elevated CBF or dBp in the SLE group at the time MRI scanning, for example, physiological factors related to sudden changes in symptoms. However, the fraction of subjects experiencing such an event, and its effect size, would have had to be substantial to account for the group differences observed. Similarly, due to the sample size and the heterogeneity of medications the subjects in the SLE group were taking during the study, which included corticosteroids, antihypertensive drugs, anti-platelet drugs, and anti-malarials, it is not possible to evaluate with sufficient statistical power the effect of any one drug on CBF or blood pressure, other than pregnisone, which did not show a significant correlation with either measurement. Nonetheless, even though these medications would not be expected to increase CBF, we cannot exclude the possibility of a medication effect.

In summary, the higher CBF found in the SLE group relative to the control group of this study could be statistically accounted for by the higher sBP in the SLE group. The weaker relationship between CBF and either MAP, dBp, or tPA within the SLE group is consistent with vascular dysfunction (systemic vasculopathy) in the SLE group. Group differences and correlations with other physiologic measures, as well as findings by other groups, suggest that the higher sBP and blunted relationship of CBF with MAP, dBp, or tPA may derive from, atherothrombosis, vasculitis, atherosclerosis or a combination of these conditions. Although having on average a higher blood pressure than control subjects, the SLE patients were not hypertensive, suggesting that the observed cerebrovasomotor changes are pathologic dysregulation of CBF at normotensive or pre-hypertensive levels. The exploration of CBF autoregulation in SLE to test these hypotheses will be a productive focus for future research.

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Figure 1.

Plots of mean CBF values for each brain region (Fr = frontal, Pr = parietal, Tm = temporal, Oc = occipital, Gl = globus pallidus, Ca = caudate, Pu = putamen, Th = thalamus) in controls (circles) and SLE subjects (diamonds).

Figure 2. ANCOVA group-by-covariate interaction plots for MAP (top left), dBP (top right), sBP (bottom left), and tPA (bottom right).

Table 1

Group statistics of selected clinical and laboratory test results.

	SLE (n=42)	Control (n=19)	p
Demographic			
Age (yr)	37.3±12.8	31.9±10.1	0.11
Female percentage	95	89	0.58
Body Composition			
Weight (kg)	72.0±12.7	72.1±12.8	0.96
BMI (kg/m ²)	26.9±4.8	26.8±6.0	0.97
Blood Pressure			
MAP (mm Hg)	91.9 ±10.1	87.1±5.7	0.02
sBP (mm Hg)	123.8±13.9	116.0±8.0	<0.01
dBp (mm Hg)	76.0±10.2	72.7±6.5	0.13
Blood composition			
Hematocrit (%)	38±4	40±3	0.07
White Blood cell count (k/mL)	5.8±2.4	6.5±1.8	0.25
Red blood cell count (k/mL)	4.3±0.5	4.6±0.3	<0.01
Blood urea nitrogen (mg/dL)	15.2±4.9	12.3±3.4	0.02
Creatine (mg/dL)	0.82±0.30	0.71±0.10	0.04
Triglyceride (mg/dL)	139.9±59.3	144.6±87.5	0.83
Cholesterol (mg/dL)	177.4±40.1	179.8±42.2	0.85
Hemoglobin (g/dL)	13.1±1.6	13.8±1.34	0.10
Inflammation Factors			
C5a (pg/mL)	30.2±11.4	29.8±10.1	0.91
C3a (pg/mL)	2118±3253	1932±2121	0.82
Monocyte CD14 microparticles (μL ⁻¹)	436±700	476±509	0.82
Thrombogenesis			
Platelets (k/mL)	239±86	275±43	0.04
tPA (units/mL)	9.1±4.1	7.4±4.4	0.15
Plasminogen activator inhibitor 1 (units/mL)	11.0±13.3	18.4±37.8	0.40
Tissue factor positive microparticles (μL ⁻¹)	204±323	236±230	0.70
Platelet CD41 microparticles (μL ⁻¹)	639±763	542±617	0.63
Annexin positive microparticles (μL ⁻¹)	651±755	559±561	0.64
Other Microparticles			
Total Microparticles (uL)	2716±1691	2661±1125	0.90
Endothelium CD144 Microparticles (μL ⁻¹)	157±247	153±125	0.94

Table 2

Selected clinical and laboratory test results obtained for SLE subjects only.

	<u>SLE (n=42)</u>
Disease duration (yr)	9.1±7.3
Age of onset (yr)	28.5±13.5
Pregnisone (mg/d)	7.7±12.8
DNA titer (dilutions)	41.3±58.3
Anti-nuclear antibody titer (dilutions)	394±465
C3 (pg/mL)	96.7±30.8
C4 (pg/mL)	20.5±26.6
C-reactive protein	1.1±1.6
Erythro sedimentation rate (mm/hr)	26.7±27.1
Anti-phospholipid antibody IgG (IU)	14.3±17.2
Anti-phospholipid antibody IgM (IU)	11.2±15.5
Anti-phospholipid antibody IgA (IU)	7.4±12.2

Table 3

RM ANCOVA model significant effects.

Covariate	p values			
	Group	Lesion	Covariate	Group × Covariate
None	0.02	< 0.001	NA	NA
Blood Pressure				
MAP	0.002	< 0.001	NS	0.003
sBP	0.75	< 0.001	< 0.001	NS
dBp	< 0.001	< 0.001	< 0.001	< 0.001
Thrombogenesis				
platelets	< 0.001	0.006	< 0.001	NS
tPA	< 0.001	< 0.001	0.02	< 0.001
Other				
BMI	0.03	< 0.001	< 0.001	NS

Table 4

Correlation coefficients (r) and p values for measures that correlated significantly with sBP (p=0.05) in either Pearson or Spearman correlation analyses in one or both groups.

	SLE						Controls						Combined Groups					
	Pearson			Spearman			Pearson			Spearman			Pearson			Spearman		
	r	p		r	p		r	p		r	p		r	p		r	p	
Weight	0.389	0.01		0.439	0.003		0.583	0.008		0.635	0.003		0.397	0.001		0.482	<0.001	
BMI	0.5	<0.001		0.573	<0.001		0.523	0.02		0.567	0.01		0.461	<0.001		0.528	<0.001	
aPL IgA	-0.44	0.003																
WBC	0.373	0.02		0.477	0.002											0.326	0.01	
BUN													0.331	0.01				
Triglyceride	0.315	0.04		0.356	0.02											0.338	0.008	
tPA							0.731	<0.001		0.709	<0.001		0.351	0.006		0.426	<0.001	
PAI-1				0.324	0.04					0.493						0.403	0.001	