

Vascular Stiffness in Women With Systemic Lupus Erythematosus

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Abstract—Large-vessel manifestations of systemic lupus erythematosus (SLE), a multisystem disease characterized by disturbances in the immune system, include higher than expected rates of hypertension and cardiovascular disease. Reductions in the elasticity of central arteries may act as a marker of early changes that predispose to the development of major vascular disease. This study evaluated risk factors associated with aortic stiffness measured by pulse wave velocity (PWV) in women with SLE. We expected SLE-specific factors, especially variables indicative of inflammation and active disease, to be associated with increasing PWV. The study population included 220 women currently enrolled in the Pittsburgh Lupus Registry. All risk factor data were collected on the day of the ultrasound examinations. PWV waveforms were collected from the right carotid and femoral arteries by Doppler probes. The mean age of the women was 45.5 ± 10.8 years, the median SLE disease duration approximated 9 years, and the mean PWV was 6.1 ± 1.7 m/s. Multiple regression models were stratified by menopausal status. Among postmenopausal women, PWV risk factors were primarily traditional factors and included age, systolic blood pressure, family history of vascular disease, carotid plaque, creatinine, obesity, glucose, white cell count, and cumulative SLE organ damage. Among premenopausal women, PWV risk factors consisted of a mix of SLE-related and traditional variables and included higher C3 levels, presence of ds-DNA antibodies, nonuse of hydroxychloroquine, lower leukocyte count, higher mean arterial pressure, and carotid plaque. SLE-specific variables appeared to be associated with increases in aortic PWV, indicating central artery stiffening. This was seen most clearly among premenopausal women. This finding may partially explain the higher rates of cardiovascular disease and hypertension observed in young women with SLE. (*Hypertension*. 2001;37:1075-1082.)

Key Words: aorta ■ lupus ■ women ■ immune system ■ cardiovascular disease

Systemic lupus erythematosus (SLE) is the prototypic autoimmune disease affecting young women. Large-vessel manifestations of SLE include high rates of hypertension,¹⁻³ myocardial infarction (MI),^{1,4} and stroke.⁴ Noninvasive ultrasound imaging techniques are used in epidemiological studies to evaluate cardiovascular health. One such technique, pulse wave velocity (PWV), measures vascular stiffness. It is important to measure vascular stiffness because reductions in the elasticity of these arteries may act as a marker of early changes that predispose to the development of major vascular disease. Previous research has found a strong association between hypertension and vascular stiffness.⁵⁻⁷ In SLE, the pathogenesis of vascular disease is unknown, although it is thought to be multifactorial and of atherosclerotic origin. Interactions between inflammation, corticosteroid use, augmented traditional risk factors, and kidney disease with resulting hypertension may initiate and promote changes to the vasculature, which ultimately lead to vascular stiffness and atherosclerosis.

Chronic vascular inflammation, a hallmark of SLE, may contribute to the development of vascular stiffness. Immune complexes may act as a source of arterial injury and can upregulate specific adhesion molecules involved in the atherogenic step of binding and recruiting monocytes/macrophages and T-lymphocytes.⁸ Immune complex deposition into the glomeruli can also result in nephritis and hypertension. The acute-phase response might increase the risk of vascular disease, and it has been suggested that prolonged exposure to low levels of acute-phase reactants may result in vascular injury.⁹ Recent studies found that higher levels of C-reactive protein predicted future MI and stroke.^{9,10} Antiphospholipid antibodies may also be involved in immune-mediated atherogenesis and have been associated with venous and arterial thrombotic events, stroke, and recurrent fetal loss in SLE.¹¹⁻¹³

In this study, vascular stiffness of the aorta was measured with PWV, and higher PWV values are indicative of stiffening. In 220 women with SLE, potential risk factors associated

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with increasing vascular stiffness were evaluated. We expected higher PWV values to be associated with SLE-specific factors, which probably reflect the immune and inflammatory process of this disease.

Methods

Study Population

The women recruited for this cardiovascular disease (CVD) study are currently enrolled in the Pittsburgh Lupus Registry. This registry includes patients examined by rheumatologists working at the University of Pittsburgh Medical Center and within the Pittsburgh metropolitan area. All registry women were required to fulfill the 1982 American College of Rheumatology revised criteria for the classification of SLE.¹⁴ All eligible women who were 18 years of age or older were invited to participate regardless of their history of cardiovascular events. Participation in this study consisted of an interview, a clinical examination, and laboratory and ultrasound tests, all of which took place on the same day. Each participant provided an authorization for release of medical information, and pertinent hospital and outpatient records were reviewed for any subject reporting a prior cardiovascular event. The University of Pittsburgh's Institutional Review Board approved this study, and all women provided written informed consent.

Traditional Cardiovascular Risk Factors

The clinic visit included anthropomorphic measurements (height, weight, and waist and hip circumferences), 2 consecutive blood pressure readings, heart rate, and a fasting blood draw. Blood samples were used to measure total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, insulin, and glucose with standardized laboratory procedures. Hypertension status was defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg or the use of antihypertensive agents. Pulse pressure was calculated by subtracting diastolic blood pressure from systolic blood pressure, and mean arterial pressure (MAP) was calculated by adding diastolic blood pressure to one-third pulse pressure. Information was also collected on age, race, education, smoking habits, family history of CVD (MI or stroke in a first-degree relative < 60 years of age), menopause status (follicle-stimulating hormone levels were obtained when menopausal status was uncertain), estrogen replacement, and diabetes.

SLE-Related Disease Factors

SLE-disease activity and cumulative organ damage were measured with the Systemic Lupus Activity Measure (SLAM)¹⁵ and the Systemic Lupus International Collaborating Clinics (SLICC) damage index.¹⁶ The SLICC assesses damage to 12 organ systems in patients with SLE.¹⁶ Information was obtained on corticosteroid treatment and hydroxychloroquine use. Kidney disease was defined by the SLICC renal variables, which require the presence of nephrotic-range proteinuria (≥ 3.5 g/24 hours) or renal insufficiency (glomerular filtration rate $< 50\%$) for ≥ 6 months. Laboratory studies included a lupus anticoagulant test (partial thromboplastin time or Russell's viper venom time with mix), C3, C4, and antibody tests for anticardiolipin (IgG > 15 GPL units, IgM > 10 MPL units; Incstar) and native DNA (*Crithidia luciliae*).

Inflammatory Markers

Serum albumin, C-reactive protein, and fibrinogen levels were measured. An ELISA was used to measure C-reactive protein, a dye-binding assay was incorporated to measure albumin, and a modified clot-rate assay was used for the measurement of fibrinogen.¹⁷

Pulse Wave Velocity

Each patient lay supine for 5 minutes before testing. During this time, ECG electrodes were attached. Simultaneous recordings of the arterial flow waves from the right common carotid artery and the

right femoral artery were made by nondirectional transcutaneous Doppler flow probes (model 810-a, 10 mHz, Parks Medical Electronics Inc). PWV measurements were derived from these waveforms. Visual flow waves were generated through ultrasound reflections off the moving column of blood. Three consecutive sets of waveforms were collected for each participant.

The aortic PWV was determined from the foot-to-foot flow wave velocity.¹⁸ At least 10 flow waves were averaged into one final waveform, with the peak of the R wave from the simultaneously recorded ECG used as a timing marker for both the carotid and femoral arteries. The foot of each averaged flow wave was identified visually as the point where systolic flow began, and the time from the R wave of the ECG to the foot of each flow wave was established. Transit time was the time delay between the feet of simultaneously recorded flow waves. After the waveform collection, distance measurements between the carotid and femoral sampling sites were taken with a standard tape measure. This required the following 3 measurements: (1) from the midpoint of the manubrium sterni to the lower edge of the umbilicus, (2) from the edge of the umbilicus to the femoral artery sampling site, and (3) from the midpoint of the manubrium sterni and the sampling site on the carotid. The third distance listed above was subtracted from the sum of the first two distances. PWV was calculated by dividing the time component by the distance component. The resulting unit of measure is meters per second.

The reproducibility of PWV readings was evaluated in 41 men and women ranging in age from 23 to 95 years of age. A single sonographer collected the waveforms, and 2 readers scored the data collection runs. The Pearson correlation coefficient was 0.98 ($P=0.001$), and high reader reproducibility was attained with an intraclass correlation equal to 0.97.

Carotid Atherosclerosis and Intima-Media Wall Thickness

A Toshiba SSA-270A scanner (Toshiba American Medical Systems) equipped with a 5-mHz linear array imaging probe was used to image the carotid arteries. Sonographers scanned the right and left common carotid arteries, carotid bulb, and the first 1.5 cm of the internal and external carotid arteries. Plaque was defined as a distinct area protruding into the vessel lumen, with $\geq 50\%$ greater thickness than that found in surrounding areas. For each segment, the degree of plaque was graded between 0 (no stenosis) and 3 ($> 50\%$ stenosis), and the grades from all 10 segments were summed to create the plaque index.¹⁹

Readers also measured the average intima-media wall thickness (IMT) across 1-cm segments of the near and far walls of the distal common carotid artery and the far wall of the carotid bulb and the internal carotid artery on both the right and left sides. Values from each location were then averaged to produce an overall measure of IMT.

Statistical Analysis

SAS-pc (SAS Institute) was used to perform all statistical procedures. Although age is a better predictor of CVD, the major analyses were stratified by menopause status because the development of vascular disease is confounded by hormonal status.²⁰ The distribution of the dependent variable, PWV, was skewed, and thus a log-transformation (natural log) was used to normalize its distribution. *t* tests were used to compare distributions of log PWV groups defined by dichotomous variables. The relations between categorical variables of > 2 levels and mean log PWV were assessed by 1-way ANOVA. Moving averages, a smoothing technique, and a graphical aid for each risk factor were evaluated and used to determine cut-points. Risk factors were either split into quartiles or were divided on natural cut-points. The antilog of the mean was calculated to transform the mean of log PWV to an approximate of the original scale. Linear comparisons involving ≥ 3 risk factor category means were evaluated by contrasts.

Differences in continuous variables between premenopausal and postmenopausal women were evaluated by either *t* tests or the

Wilcoxon rank-sum test. Categorical differences between premenopausal and postmenopausal women were evaluated with the χ^2 test; the Cochran-Mantel-Haenszel test for nonzero correlation was evaluated for ordering of groups of >2 levels.

Multiple linear regression evaluated predictors of log PWV. The models were built with stepwise regression. All potential 2-way interactions were tested, and appropriate regression diagnostics were examined for influential points. Regression models for both menopausal subgroups were also built to exclude women reporting a confirmed MI or stroke, and these models were not significantly different from the models including the event women. Thus, we present the models including all women.

Results

Participation

Of the 279 women who entered the study, 220 had ≥ 1 usable PWV data collection run. The 59 excluded women either had unclear waveforms or did not undergo the procedure because of refusal, equipment failure, or time constraint. The 220 participants were slightly older than the 59 women missing PWV data (45.5 ± 10.8 versus 43.5 ± 11.7 years), although the difference was not significant. Likewise, there were no differences between those with and those without PWV data with regard to SLE activity, SLE cumulative organ damage, SLE duration, menopause status, mean blood pressure, and carotid plaque. In comparison to women in the Pittsburgh Lupus Registry, the 220 study participants were younger (45.5 ± 10.8 versus 51.8 ± 14.7 years; $P < 0.01$), had a shorter mean SLE disease duration (10.9 ± 7.1 versus 14.8 ± 7.1 years; $P < 0.01$), and were less likely to be black (white 90.5% versus 84.4%; $P = 0.05$).

Demographic, SLE, and Cardiovascular Characteristics

Table 1 presents basic demographic, SLE-specific, and cardiovascular variables for the entire sample and compares distributions of these variables by menopausal status. The 220 women were predominantly white and well educated (completed 2 years of college). The mean age of the postmenopausal women was 53.7 years, and the mean age of the premenopausal women was 39.0 years ($P < 0.01$). The postmenopausal women were less educated, heavier, and had a larger waist circumference compared with the premenopausal women. In terms of SLE, the postmenopausal women had a longer median disease duration and a higher cumulative organ damage score, took prednisone for a longer duration, and were more likely to use prednisone. Approximately 20% of the 220 women were positive for antibodies to cardiolipin and to native DNA (anti-dsDNA), and a quarter of the group were positive for lupus anticoagulant. Last, mean C4 levels were significantly higher in the postmenopausal women, and there was no difference in mean C3 levels by menopause status.

Cardiovascular characteristics for the overall sample and by menopausal subgroup are also presented in Table 1. The sample mean PWV was 6.1 ± 1.7 m/s. PWV was significantly higher in the postmenopausal women compared with the premenopausal group (6.9 versus 5.4 m/s; $P < 0.01$). Seventy-three (33%) women had evidence of focal carotid plaque (plaque index ≥ 1). Although carotid atherosclerosis was more common in the postmenopausal women, 21 of the 124

(17%) premenopausal women had evidence of plaque. IMT was also significantly greater in the postmenopausal group (0.8 versus 0.66 mm; $P \leq 0.01$). The postmenopausal subgroup had significantly higher mean blood pressure (systolic and diastolic blood pressure), mean pulse, and arterial pressure compared with the premenopausal women. Approximately 50% of the postmenopausal women and a quarter of the premenopausal women were hypertensive, and a higher proportion of postmenopausal women reported current use of antihypertensive agents. The postmenopausal subgroup had significantly higher mean cholesterol (total and HDL cholesterol) and median triglyceride levels than did the premenopausal women. All inflammatory markers, with the exception of albumin, were higher in the postmenopausal women, whereas only C-reactive protein was significantly greater in the older women. Last, a previous vascular event was seen in 14 women (6 MI, 7 stroke, and 1 both), and these frequencies were similar to previously reported rates from other North American SLE cohorts.^{2,21}

With the use of ANOVA, the association between mean PWV values by risk factor categories was examined in the overall sample (Table 2). Controlling for age and MAP, risk factors positively associated with increasing mean PWV included C3, C4, immunosuppressive use, antihypertensive use, body mass index (BMI), insulin, family history of CVD, antidepressant use, prior MIs, and carotid plaque. A J-shaped relation, where the mean PWV value for the lowest and highest categories were significantly greater than the middle group's mean, existed between glucose and mean PWV.

PWV risk factor models were built and stratified by menopause status (Table 3). In the postmenopausal women, PWV was associated with increasing MAP, older age, carotid plaque, CVD family history, greater SLE cumulative organ damage, lower (<4.7 mmol/L) and higher (≥ 5.8 mmol/L) glucose categories, lower ($<5 \times 10^3/\text{mm}^3$) leukocyte count, higher creatinine, and obesity. Both glucose and leukocyte count exhibited a J-shaped relation with PWV, and the reference group was the middle category. Age accounted for almost half of the variation (partial $R^2 = 0.251$) in PWV explained by this model of postmenopausal women (adjusted $R^2 = 0.59$).

With adjustment for age, independent risk factors associated with increasing log PWV among the premenopausal women included higher MAP, increasing C3 levels, focal carotid plaque, nonuse of hydroxychloroquine, presence of antibodies to native DNA, and lower leukocyte count (Table 3). The complement protein C3 accounted for most of the variation explained by this model (partial $R^2 = 0.17$); the adjusted R^2 of the model was 0.30.

Discussion

This is the first study to investigate aortic stiffness in women with SLE. The results from this study indicate that SLE-specific variables appear to be independently associated with increases in aortic PWV, and this is seen most clearly among premenopausal women. Two patterns of aortic stiffness risk factors emerged from this study. Among the premenopausal subgroup, variables associated with SLE and inflammation are the most important factors associated with aortic stiffness,

TABLE 1. Demographic, SLE, and Cardiovascular Characteristics in the Entire SLE Sample and Stratified by Menopausal Subgroup

Variable	Overall (Mean ± SD) n=220	Premenopausal (Mean ± SD) n=124	Postmenopausal (Mean ± SD) n=96
Age‡	45.5 ± 10.8	39.0 ± 7.6	53.7 ± 8.3
Race, % white§	90.5	91.9	88.4
Smokers, %§	12.7	12.1	13.5
Education, y§	14	14	13
BMI, kg/m ² †	27.7 ± 6.6	26.9 ± 5.9	28.8 ± 7.3
Waist circumference, mm*	900 ± 174	880 ± 181	925 ± 162
Median SLE duration, y†	9.4	8.2	11.1
SLE cumulative organ damage‡	1.5 ± 1.8	1.2 ± 1.5	2.0 ± 2.0
SLE activity score	6.9 ± 3.7	7.1 ± 4.0	6.7 ± 3.5
Median steroid duration, y†	3.0	2.5	4.0
% Current medication			
Prednisone†§	40.5	34.7	47.9
Hydroxychloroquine§	45.0	46.8	42.7
Immunosuppressives§¶	11.4	15.3	8.3
Anti-dsDNA, %§	19.7	18.9	20.8
White blood cell count, 10 ⁹ /L	5.80 ± 2.2	5.99 ± 2.2	5.59 ± 2.2
Lupus anticoagulant, %§	24.3	23.8	25.0
Anticardiolipin antibodies, %§	17.5	16.5	18.8
C3, g/L	0.96 ± 0.24	0.94 ± 0.25	0.98 ± 0.23
C4, g/L‡	0.22 ± 0.07	0.21 ± 0.07	0.23 ± 0.08
PWV, m/s‡	6.1 ± 1.7	5.4 ± 1.2	6.9 ± 1.9
Carotid plaque, %‡§	33.6	16.9	55.2
IMT, mm‡	0.72 ± 0.16	0.66 ± 0.07	0.80 ± 0.19
Systolic blood pressure, mm Hg‡	122.7 ± 17.9	117.2 ± 14.1	129.2 ± 19.8
Diastolic blood pressure, mm Hg‡	75.2 ± 10.3	73.5 ± 10.3	77.3 ± 9.8
Pulse pressure, mm Hg‡	47.5 ± 14.1	43.7 ± 10.4	52.4 ± 16.6
MAP, mm Hg‡	91.0 ± 11.5	88.0 ± 10.6	94.8 ± 11.5
Hypertension, %‡§**	36.8	25.8	51.0
Antihypertensive medication, %‡§	28.2	17.7	41.7
Cholesterol, mmol/L‡	5.05 ± 1.08	4.83 ± 1.12	5.33 ± 0.96
LDL-cholesterol, mmol/L*	2.90 ± 0.87	2.82 ± 0.91	3.04 ± 0.81
HDL-cholesterol, mmol/L‡	1.47 ± 0.43	1.40 ± 0.37	1.57 ± 0.47
Median triglycerides, mmol/L‡	1.21	1.05	1.39
Glucose, mmol/L	5.57 ± 1.48	5.55 ± 1.82	5.61 ± 0.88
Insulin, pmol/L	129.2 ± 69.6	123.4 ± 58.8	136.3 ± 81.1
Median C-reactive protein, mg/mL‡	2.1	1.5	2.8
Median fibrinogen, g/L*	2.96	2.94	2.99
Albumin, g/L*	47.0 ± 4.0	47.0 ± 4.0	46.0 ± 4.0
MI, %††	3.2	1.6	5.2
Stroke, %††	3.6	3.2	4.2

*P ≤ 0.1, †P ≤ 0.05, ‡P ≤ 0.01.

§By χ^2 test.

||By Wilcoxon rank-sum test.

¶Immunosuppressives are cyclophosphamide, azathioprine, methotrexate, cyclosporine, or FK506.

**Women were considered hypertensive if they were taking antihypertensive medication or their sitting systolic blood pressure was ≥ 140 or their diastolic blood pressure ≥ 90 mm Hg.

††By Fisher's exact test.

TABLE 2. Mean PWV Adjusted for Age and MAP by Risk Factor Category in Overall Sample (n=220)

Variable	Mean PWV, m/s	P*†	Variable	Mean PWV, m/s	P*†
SLE organ damage score			Cholesterol, mmol/L		
0	5.647	0.111*	<4.34	5.858	0.966*
1	5.854		4.34–4.84	5.901	
2+	6.068	0.036†	4.85–5.72	5.804	0.686†
			≥5.73	5.783	
C3, g/L			Triglycerides, mmol/L		
<0.80	5.506	0.008*	<0.82	5.684	0.471*
0.80–0.95	5.669		0.82–1.20	5.736	
0.96–1.10	5.896	<0.001†	1.21–1.80	5.872	0.129†
≥1.11	6.288		≥1.81	6.052	
C4, g/L			Heart rate, bpm		
<0.16	5.392	0.063*	<70	5.672	0.274*
0.16–0.20	5.945		70–75	6.090	
0.21–0.26	5.933	0.036†	76–79	5.998	0.915†
≥0.27	5.965		≥80	5.742	
Steroid duration, y			Antihypertensive use		
≤12	5.831	0.269*	No	5.726	0.042*
>12	6.095		Yes	6.145	
Immunosuppressive use			Waist-hip ratio		
No	5.783	0.069*	<0.77	5.727	0.021*
Yes	6.273		0.77–0.82	5.990	
			0.83–0.89	5.506	0.450†
			≥0.90	6.176	
BMI, kg/m ²			Antidepressant use		
≤26	5.659	0.039*	No	5.766	0.068*
>26	6.009		Yes	6.160	
Insulin, pmol/L			Carotid plaque (index)		
<87.5	5.637	0.051*	0	5.621	0.002*
87.5–111.9	5.619		1	5.885	
112.0–151.4	5.901	0.008†	2	6.549	<0.001†
≥151.5	6.215		3+	6.733	
Glucose, mmol/L			Previous MI		
<4.50	6.421	<0.001*	No	5.798	0.005*
4.50–5.50	5.570		Yes	7.305	
≥5.51	6.255	0.731†			
Creatinine, μmol/L			C-reactive protein, mg/mL		
<70.7	5.500	0.160*	<0.9	5.558	0.148*
70.7–79.5	5.820		0.9–2.07	5.920	
79.6	5.860	0.034†	2.08–4.2	6.086	0.294†
>79.6	6.072		≥4.3	5.756	
Family history of CVD					
No	5.665	0.054			
Yes	5.991				

*From overall F test; †Evaluating linear trend.

whereas traditional cardiovascular risk factors appear to overshadow the potential impact of SLE-specific variables among the postmenopausal women.

Noninvasive evaluations of CVD, such as PWV, play important roles in studies evaluating health. It is thought that

increases in arterial stiffness may be a marker of early vascular changes that may lead to major vascular disease. Although the preponderance of PWV literature used a cross-sectional study design, one recent longitudinal study found that increased aortic stiffness predicted all-cause and coro-

TABLE 3. Predictors of Log PWV in Postmenopausal and Premenopausal SLE Women By Linear Regression

Variable	Postmenopausal Women (n=96)			Premenopausal Women (n=124)		
	Standardized Estimate	Partial R ²	P	Standardized Estimate	Partial R ²	P
MAP, mm Hg	0.244	0.129	<0.001	0.145	0.030	0.084
Age, y	0.327	0.251	<0.001	0.086	0.006	0.300
C3, g/L	0.470	0.170	<0.001
Focal carotid plaque*	0.143	0.016	0.068	0.206	0.067	0.011
CVD family history†	0.183	0.061	0.014
SLE cumulative organ damage score	0.235	0.061	0.002
Hydroxychloroquine use	-0.167	0.025	0.032
Fasting glucose categories‡						
<4.7 mmol/L	0.118	0.021	0.097
≥5.8 mmol/L	0.254	0.038	0.002
ds-DNA antibodies	0.160	0.017	0.066
White blood cell count, 10 ⁹ /L§	-0.145	0.022	0.069
<5×10 ⁹ /mm ³	0.147	0.016	0.049
≥8×10 ⁹ /mm ³	0.056	0.002	0.479
Creatinine, μmol/L	0.203	0.033	0.006
BMI>26, kg/m ²	0.115	0.012	0.093

*Focal carotid plaque was defined as follows: for postmenopausal women, 0=plaque index ≤1; 1=plaque index 2+; for premenopausal women, 0=no plaque; 1=plaque index ≥1.

†Family history of CVD was defined as MI, stroke, or sudden death before the age of 60 years in first-degree relative.

‡Fasting glucose reference group, 85 to 104 mg/dL.

§White blood cell count is continuous for premenopausal women and white cell reference group, 5 to 7.9 10⁹/L for postmenopausal women.

nary death in patients with end-stage kidney disease.²² Additionally, a study in hypertensives reported a 7-fold increased risk in cardiovascular death in individuals falling in the upper quartile of the PWV distribution.²³

SLE is characterized by chronic vascular inflammation. This inflammation may act as a contributing factor in the initiation or the progression of vascular stiffness. Research has focused on several factors associated with immune regulation and vascular function. Immune complexes, for example, may act as a source of arterial injury, which result in vascular changes. Although these complexes have not been linked to arteriosclerosis, they have been shown to upregulate specific adhesion molecules involved in the atherogenic step of binding and recruiting monocytes/macrophages and T-lymphocytes.⁸ Additionally, immune complex deposition into the glomeruli may result in nephritis and hypertension as well as an elevation in levels of coagulation factors, such as fibrinogen. The acute-phase response might increase the risk of vascular disease, and it has been suggested that prolonged exposure to low levels of acute-phase reactants may result in persistent vascular injury.⁹ Recent studies found that higher levels of C-reactive protein predicted future cardiovascular events.^{9,10}

SLE-related factors were associated with increasing aortic stiffness among both menopausal subgroups, although their impact is depicted most clearly among premenopausal women. Adjusting for age and MAP, this study found a strong linear association between elevated C3 and aortic stiffness among the premenopausal subgroup. Although com-

plement activation and thus lower C3 levels are associated with increasing activity of SLE, complement can act as an acute-phase reactant, resulting in increasing levels in inflammatory states.²⁴ Furthermore, additional analyses found strong positive associations between C3 and C-reactive protein and fibrinogen, other inflammatory markers. It has been suggested that complement might be involved in the development of arterial wall lesions, and proposed modes of action include damage to the membrane or increased endothelium permeability, which could lead to the influx of plasma proteins into the arterial wall.²⁵ The role of C3 in vascular stiffness and CVD in SLE remains unclear.

Additional SLE-related risk factors associated with higher PWV among the premenopausal women independent of age and MAP include lower leukocyte count, hydroxychloroquine nonuse, and presence of antibodies to native DNA. Low white cell count is a common manifestation of active SLE, and this association with increased PWV may be a reflection of the activity of the underlying disease. An inverse association was noted between current hydroxychloroquine use, a drug used to treat mild SLE symptoms, and PWV. Hydroxychloroquine is thought to elicit cardioprotective properties,²⁶ and its use may also be a marker of less severe SLE. Last, antibodies to native DNA were associated with aortic stiffness, and its mode of action is unclear. Because antibodies to native DNA are associated with active SLE and kidney disease, this antibody may act as a marker of more active disease, particularly renal manifestations.

Among the postmenopausal women, several SLE-related risk factors were also associated with increasing aortic

stiffness, adjusting for age and MAP. Women with more cumulative organ damage were more likely to have a stiffer aorta. The association between increased aortic stiffness and more cumulative organ damage could be a marker of a more severe course of disease. Higher creatinine levels, a signal of renal dysfunction and a common SLE condition, were also associated with PWV in the postmenopausal women. Kidney disease is tightly coupled with hypertension and lipid disturbances, which are also thought to be PWV risk factors.

Although the disease processes associated with SLE may play an important role in the development of vascular changes, several traditional cardiovascular risk factors associated with increased aortic stiffness should not be overlooked. This study found a positive association between arterial pressure and aortic stiffness, which is consistent with the literature.⁵⁻⁷ Potential stiffening mechanisms associated with increasing blood pressure includes medial layer thickening, smooth muscle cell hypertrophy and hyperplasia, expansion of the extracellular matrix, and shifts in the collagen-to-elastic ratio.^{27,28} As SLE-related variables are associated with aortic stiffness independent of MAP, it should be noted that the SLE variables might also induce similar cellular changes. Elevated blood pressure affects between 39% and 64% of SLE patients in the United States,^{1,2} which is much greater than the general population.³ The cause of increasing blood pressure includes corticosteroid use and its resulting weight gain, kidney disease, and potentially inflammation-induced vascular injury.

Additionally, stiffened vessels are vulnerable to atherosclerosis and susceptible to increased lipoprotein and leukocyte permeability.^{29,30} The resulting lipid deposition into carotid arteries can be detected with ultrasound. This study found an association between focal carotid plaque and reduced aortic elasticity in both menopausal subgroups independent of age and MAP. Because there appears to be a direct association between carotid atherosclerosis and coronary artery stenosis, the measure of focal carotid plaque can be used as a surrogate marker for systemic atherosclerosis.³¹ Thus, the systemic nature of atherosclerosis may explain the link between carotid plaque and aortic stiffness.

Last, obesity is considered to be a traditional cardiovascular risk factor, and weight change can be a manifestation of SLE treatment. This study found an association between higher BMI and aortic stiffness in the postmenopausal women, with adjustment for age and MAP. Weight gain is a common side effect of long-term corticosteroid use, and this obesity could be reflective of more severe SLE requiring higher doses of corticosteroids. Alternatively, obesity could be a marker of inactivity and thus an indication of poorer health, or it could represent insulin resistance. An inverse association between physical activity and PWV or BMI was not found. Insulin levels were significantly elevated in the older women with a high BMI.

As with all studies, limitations hinder the ability to draw conclusions. Although SLE appears to be more prevalent in blacks, this study included well-educated white women, which could have precluded the detection of other risk factors associated with aortic stiffness. Including women with prevalent CVD could have biased the study results by attracting

study participants with cardiovascular concerns, although the prevalence of vascular events in this sample was similar to what is expected in large SLE cohorts.^{1,2,21} Excluding the women with a documented vascular event (MI and stroke) did not change the variables associated with PWV in the regression models; thus, selection bias seems unlikely.

Additional limitations are attributed to the study design and the analysis stratification. This study used a cross-sectional study design and lacked a control group. Cross-sectional data tend to be problematic in that causality cannot be established. Future research in the area of vascular stiffness should include a longitudinal component coupled with control subjects. The potential for the reversibility of aortic stiffness with fluctuation in disease activity, particularly among the younger women, could be evaluated by a prospective study. Last, this study does not tease out the relation between menopause and age. Although age is a better predictor of CVD, the analyses were stratified on menopause status because the development of vascular disease is confounded by hormonal status. Current research has shown that estrogen positively influences the vasculature, cardiac physiology, metabolism, and clotting.²⁰

Summary

This study found that SLE-specific variables appear to be associated with increases in aortic stiffness independent of age and blood pressure. This finding is seen most clearly among premenopausal women. Older age and traditional cardiovascular risk factors appear to overshadow the impact of SLE-specific variables among the postmenopausal women. Although the elucidation of the mechanisms involved is unclear, it appears as though the underlying disease state, its activity, and its influence on traditional risk factors play a role in the initiation or the progression of vascular changes. The associations between SLE-related factors and increasing aortic stiffness may partially explain the higher rates of cardiovascular events and hypertension observed in young SLE women.

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