Aortic Stiffness Is Associated With Left Ventricular Diastolic Dysfunction in Systemic Lupus Erythematosus: A Controlled Transesophageal Echocardiographic Study

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ABSTRACT

Background: Aortic stiffness and left ventricular (LV) diastolic dysfunction are common and associated with increased morbidity and mortality in systemic lupus erythematosus (SLE).

Hypothesis: In SLE, aortic stiffness and LV diastolic dysfunction may be associated.

Methods: This 6-year-duration, cross-sectional, and controlled study was conducted in 76 SLE patients (69 women; mean age, 37 ± 12 years) and 26 age- and sex-matched healthy controls. All subjects underwent clinical and laboratory evaluations and transesophageal echocardiography (TEE) to assess LV diastolic function and stiffness of the descending thoracic aorta using the pressure-strain elastic modulus (PSEM). To validate results using PSEM, aortic strain, stiffness, and distensibility were assessed.

Results: Patients as compared with controls had higher PSEM (8.14 ± 4.25 vs 5.97 ± 2.31 U, $P < 0.001$) and had lower mitral inflow E/A and septal and lateral mitral annulus tissue Doppler E′/A′ velocity ratios, longer isovolumic relaxation time, lower septal and lateral mitral annulus E′ velocities, and higher mitral E/septal E′ and mitral E/lateral E′ velocity ratios (all $P \leq 0.03$), all indicative of LV diastolic dysfunction. In patients, PSEM was correlated with parameters of LV diastolic dysfunction (all $P < 0.05$), was independently negatively associated with E/A and E′/A′ ratios and E′ velocities, and was positively associated with E/E′ ratios ($P \leq 0.02$ for each parameter and $P < 0.001$ for all parameters as a profile). Aortic strain, stiffness, and distensibility were also worse in patients than in controls (all $P < 0.05$) and were correlated with parameters of LV diastolic dysfunction (all $P \leq 0.03$).

Conclusions: Aortic stiffness is independently associated with LV diastolic dysfunction in young adult patients with SLE.

Carlos A. Roldan, MD, designed and conducted the study, performed and interpreted transesophageal echocardiograms and measured left ventricular end-diastolic diameters and aortic wall intima-media thicknesses, analyzed and interpreted the data, and wrote the manuscript. Ihab B. Alomari, MD, participated in the conduction of the study, performed measurements of left ventricular diastolic function, participated in the analysis and interpretation of the data, and reviewed and edited the manuscript. Khaled Awad, MD, participated in the conduction of the study, performed measurements of left ventricular diastolic function, participated in the analysis and interpretation of the data, and reviewed and edited the manuscript. Nathan M. Boyer, MD, participated in the conduction of the study, performed measurements of aortic diameters, participated in the analysis and interpretation of the data, and reviewed and edited the manuscript. Clifford R. Qualls, PhD, participated in the design of the study, managed the databases, performed all statistical analyses, and critically reviewed and edited the manuscript. Ernest R. Greene, PhD, participated in the design and conduction of the study, participated in the analysis and interpretation of the data, and critically reviewed and edited the manuscript. Wilmer L. Sibbitt Jr, MD, participated in the design and conduction of the study, recruited and evaluated SLE patients, participated in the analysis and interpretation of the data, and critically reviewed and edited the manuscript.

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Introduction

Aortic stiffness and left ventricular (LV) diastolic dysfunction are common and associated with increased morbidity and mortality in systemic lupus erythematosus (SLE).[1–7] Aortic stiffness may cause earlier return of the pulse wave reflection to the heart and lead to increased aortic systolic but decreased diastolic pressure, increased LV afterload and LV mass, decreased coronary perfusion, and consequently to LV diastolic dysfunction.[8] To our knowledge, an association of aortic stiffness with LV diastolic dysfunction in autoimmune inflammatory diseases including SLE has not been reported, but may be etiologically and clinically important. Therefore, this study was designed to determine whether aortic stiffness and LV diastolic dysfunction simultaneously assessed by transesophageal echocardiography (TEE) are independently associated.

Methods

Study Populations

This 6-year (December 2006–December 2012) cross-sectional and controlled study is part of a protocol approved by the National Institutes of Health and our institutional review board for the study of cardiovascular disease using TEE and cerebrovascular disease in SLE. The study was conducted according to the Declaration of Helsinki and all participants provided signed informed consent.

Seventy-six consecutive patients with SLE (69 women; mean age, 37 ± 12 years [range, 18–60 years]) participated in the study. Patients were recruited from 266 well-characterized patients actively followed at the Rheumatology Clinics of the University of New Mexico Health Sciences Center. Patients were excluded due to age <18 or >60 years, pregnancy, atrial fibrillation or flutter, cardiomyopathy, drug abuse, renal dysfunction, difficult venous access, self-withdrawal or noncompliance with study protocol, or contraindications to TEE or magnetic resonance imaging.

To provide a normal reference and validate blinded interpretation and diagnostic accuracy of tests, 26 age- and sex-matched healthy controls (22 women; mean age, 34 ± 11 years [range, 18–57 years]) were studied.

Clinical and Laboratory Evaluations

Patients and controls underwent clinical and laboratory evaluations including parameters of inflammation, platelet activity, coagulation, and fibrinolysis (Supplemental Table 1). Patients were also characterized with regard to SLE duration, activity, injury, therapy, and standard serologies, including antiphospholipid antibodies (Supplemental Table 2).

Transesophageal Echocardiography

All subjects underwent multiplane TEE with the I-E33 imaging system (Philips; Andover, MA) using a 7-MHz transducer. Studies of patients and controls were codified, digitally stored, and randomly intermixed for blinded analysis.

Aortic Diameters and Intima-Media Thickness: At a low depth (3–4 cm) and using a narrow sector scan to improve image resolution, 2-dimensional guided M-mode images were used to assess systolic and diastolic diameters of proximal aorta (25–30 cm from incisors), mid aorta (30–35 cm), and distal descending thoracic aorta (35–40 cm[3]; Supplemental Figure 1). At each location, 3 end-systolic and end-diastolic aortic diameters were measured from short- or long-axis views. At each aortic location, 3 measurements of aortic intima-media thickness (IMT) were performed at end-diastole using M-mode imaging.[9] To assess intraobserver variability, 26 randomly selected studies had repeat aortic measurements. The mean percent coefficient of variation in systolic and diastolic diameters of the proximal, mid, and distal aorta were 1.51% and 1.55%, 0.69% and 0.70%, and 1.21% and 1.76%, respectively.

Blood Pressures: During assessment of the aorta, 3 to 6 automatic brachial blood pressures were obtained and matched in time with measurement of aortic diameters.

Aortic Stiffness: Stiffness of the proximal, mid, and distal thoracic aorta was assessed with the pressure-strain elastic modulus (PSEM), a well-validated parameter of static arterial stiffness, $as = [k(sBP - dBP)/(sD - dD/dD)]/10\,000$, where $k = 133.3$ is the conversion factor from mm Hg to Nm^{-2} (Pascal units), sBP is brachial systolic blood pressure, dBP is brachial diastolic blood pressure, sD is systolic diameter, and dD is diastolic diameter.[3,10] To validate the results derived from using PSEM, we also measured (1) strain (%) $= (sD - dD)/dD$, which assesses percent change of vessel deformation independent of blood pressure; (2) stiffness (units) $= (sBP/dBP)/(sD - dD/dD)$, which, as PSEM, assesses the amount of pressure required to distend a vessel; and (3) distensibility (units) $= (dD/IMT)/(sBP/dBP)/(sD - dD/dD)$, which assesses changes in vessel diameter as a function of blood pressure and wall thickness.[10]

Left Ventricular Structure and Function and Left Atrial Volume: Left ventricular end-diastolic diameter and inferior and anterior end-diastolic wall thicknesses were measured at the papillary muscles level from transgastric TEE short- or long-axis views using 2-dimensional guided M-mode images. Left ventricular mass was calculated using the following formula: 0.80×1.05 [(inferior wall thickness + anterior wall thickness + LV internal diameter)^3 − (LV internal diameter)^3].[11] Left ventricular wall motion and systolic function were visually assessed. Because TEE visualization of the entire left atrium (LA) is uncommon, LA volumes were measured from transthoracic echocardiography (TTE) obtained immediately after TEE.

Left Ventricular Diastolic Function: From basal 4-chamber TEE view and using pulsed-wave Doppler, LV diastolic function was assessed according to American Society of Echocardiography guidelines[12]: (1) mitral inflow early filling (E wave) and atrial contraction (A wave) peak velocities at the leaflets tip; (2) E-wave deceleration time; (3) early (E′) and late (A′) peak velocities of septal and lateral mitral annulus; (4) isovolumic relaxation time (IVRT) using septal mitral annulus tissue Doppler recordings; and (5) left or right upper pulmonary vein systolic and diastolic peak velocities (Supplemental Figure 1). Measurements of LV

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diastolic function were performed using electronic calipers and averaged over 3 cardiac cycles. To assess intraobserver variability, 14 randomly selected TEE studies had repeat measurements. The mean percent coefficient of variation of mitral E and A, septal E′ and A′, IVRT, and pulmonary vein systolic and diastolic velocities were 2.67% and 2.88%, 2.59% and 1.74%, 4.44%, and 3.06% and 4.21%, respectively.

To avoid interpretation bias, one observer measured aortic diameters, a second observer measured parameters of LV diastolic function, a third observer measured LV size and wall thickness and aortic IMT, and a fourth observer measured LA volumes.

Statistical Analysis

The Student *t* test or Wilcoxon rank-sum test (for non-normally distributed data) and Fisher exact test were used for comparison of continuous and categorical variables among groups, respectively. Pressure-strain elastic modulus, strain, stiffness, and distensibility at each aortic location and across 3 locations were compared between patients and controls. To adjust for confounding effects of heart rate, and especially of blood pressure, on the association of PSEM and LV diastolic dysfunction with disease state (SLE vs controls), we standardized these outcomes for each individual to the same pooled (patients and controls) mean heart rate (73.7 beats per minute) and mean arterial blood pressure (MAP; 85.6 mm Hg) using multiple linear regression. Also, PSEM in patients who were normotensive during TEE, normotensive on no vasodilators, ambulatory normotensive (blood pressure during enrollment clinical evaluation), and normotensive without prehypertension (blood pressure ≤135/85 mm Hg) and without aortic atherosclerosis was compared with that of controls. Pressure-strain elastic modulus, strain, stiffness, and distensibility were correlated with LV mass, LA volume, and LV diastolic dysfunction using Pearson correlations. Because a single, specific definition of LV diastolic dysfunction applicable to young women is not feasible based on current guidelines, the 5 most accepted parameters of LV diastolic dysfunction were analyzed as a profile by repeated measures analysis of variance (rANOVA). Because the profile of LV diastolic dysfunction differed between patients and controls, we analyzed each variable separately as post hoc tests to our overall analysis. These analyses determined the independent effect of PSEM (after adjusting for blood pressure and left ventricular mass index [LVMI]) and clinical, laboratory, and therapy variables (described in Supplemental Tables 1 and 2) on these 5 parameters of LV diastolic dysfunction. The effect sizes of predictor variables are reported as standardized β (number of SD change in the outcome for a 1-SD change in the predictor variable). A 2-tailed *P* value <0.05 was considered significant.

Results

Clinical and Laboratory Characteristics

Patients and controls were similar in age, sex, body mass index, and atherogenic risk factors. Patients as compared with controls had higher nonhypertensive systolic and diastolic blood pressures (122.5 ± 15.02 mm Hg and 76.18 ± 10.29 mm Hg vs 115.5 ± 8.02 mm Hg and 71.12 ± 8.68 mm Hg, respectively, both $P \leq 0.02$) but had no significantly higher frequency of hypertension (10 [13%] vs 0%, $P = 0.06$). Patients as compared with controls also had lower hemoglobin, platelets, albumin, and peak thrombin generation; and higher creatinine, quantitative D-dimer, and tissue plasminogen activator antigen (tPA; all $P \leq 0.04$; Supplemental Table 1). Clinical, therapy, and laboratory data were typical of young adult SLE patients (Supplemental Table 2).

Table 1. Aortic Pressure-Strain Elastic Modulus in SLE Patients and Controls

Aortic Location	Patients, n = 76	Controls, n = 26	*P* Value[a]
Aortic PSEM, U			
Proximal	7.77 ± 4.09	5.40 ± 2.28	<0.001/<0.001
Mid	7.87 ± 4.65	6.15 ± 2.93	0.03/0.006
Distal	9.08 ± 6.62	6.37 ± 3.17	0.01/0.003
Overall[b]	8.14 ± 4.25	5.97 ± 2.31	0.002/<0.001
Aortic strain, stiffness, and distensibility in SLE patients and controls			
Overall strain, %[b]	10.7 ± 4	12.3 ± 3	0.049
Overall stiffness, U[b]	6.55 ± 3.20	5.26 ± 1.88	0.02
Overall distensibility, U[b]	0.446 ± 0.25	0.568 ± 0.18	0.01

Abbreviations: PSEM, pressure-strain elastic modulus; SD, standard deviation; SLE, systemic lupus erythematosus.
Data are presented as mean ± SD.
[a]Second *P* value after standardizing both groups to the same pooled mean heart rate and blood pressure using regression coefficients.
[b]Overall refers to the average of proximal, mid, and distal thoracic aortic PSEM, strain, stiffness, and distensibility.

Aortic Stiffness in Patients and Controls

As shown in Supplemental Table 3, during TEE patients as compared with controls had similar pulse pressures, and yet the differential aortic diameters were smaller in patients, suggesting that aortic stiffness may occur independent of blood pressure. Aortic PSEM was higher in patients as compared with controls even after standardizing both groups to the same mean heart rate and MAP ($P < 0.001$; Table 1). Furthermore, PSEM was higher in 59 patients vs 23 controls who were normotensive during TEE (7.55 ± 3.71 vs 5.58 ± 1.99 units, $P = 0.003$), in 47 patients vs 23 controls who were normotensive during TEE and on no antihypertensive therapy (7.22 ± 3.58 vs 5.58 ± 1.99 units, $P = 0.02$), in 66 patients vs 26 controls who were normotensive during initial enrollment clinical evaluation (8.03 ± 4.34 vs 5.97 ± 2.31 units, $P = 0.004$), in 54 patients vs 25 controls who were neither hypertensive nor prehypertensive during initial enrollment clinical evaluation (8.07 ± 4.29 vs 5.95 ± 2.35 units, $P = 0.006$), and in 59 patients vs 26 controls who had no aortic plaques (7.74 ± 4.20 vs 5.97 ± 2.31 units, $P = 0.01$). Aortic strain, stiffness, and distensibility were also worse in patients than in controls (all $P < 0.05$; Table 1).

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Table 2. TEE Doppler Echocardiographic Findings in Systemic Lupus Erythematosus Patients and Controls

Variable	Patients (n = 76)	Controls (n = 26)	*P* Value[a]
Heart rate, bpm	76.14 ± 13.24	66.60 ± 11.82	0.001
Mean arterial BP, mm Hg	87.70 ± 16.20	79.56 ± 10.55	0.005
LVEDD, cm	4.65 ± 0.64 (74)	4.66 ± 0.48	0.94
LV wall-motion abnormalities, n (%)	2 (3)	0	1.00
LVEF <50%, n (%)	2 (3)	0	1.00
LV inferior wall thickness, cm	0.81 ± 0.20 (73)	0.71 ± 0.10	<0.001/0.001
LV anterior wall thickness, cm	0.78 ± 0.18 (73)	0.65 ± 0.10	<0.001/<0.001
LV mass, g	123 ± 50 (73)	99 ± 23	0.002/0.007
LVMI, g/m^2	67 ± 26 (73)	54 ± 11	<0.001/0.003
LA volume, mL	44.43 ± 19.07 (71)	37.76 ± 11.03	0.04/0.88
LAVI	24.63 ± 9.99 (71)	20.76 ± 6.03 (25)	0.02/0.82
Mitral E velocity, cm/sec	80 ± 23 (75)	79 ± 16	0.90/0.77
Mitral A velocity, cm/sec	64 ± 25 (75)	45 ± 9	<0.001/<0.0001
Mitral E/A ratio	1.39 ± 0.61 (75)	1.81 ± 0.43	<0.001/<0.001
Mitral E deceleration time, msec	177 ± 38 (73)	166 ± 35 (24)	0.19/0.15
Septal IVRT, msec	115 ± 16 (74)	72 ± 14	0.02/0.03
Septal E′ velocity, cm/sec	9 ± 3 (75)	12 ± 3	<0.001/0.006
Septal A′ velocity, cm/sec	8.47 ± 2.05 (75)	8.35 ±1.69	0.78/0.16
Septal E′/A′ ratio	1.14 ± 0.48 (75)	1.44 ± 0.43	0.004/0.001
Lateral E′ velocity, cm/sec	12 ± 4	15 ± 2	0.001/0.002
Lateral A′ velocity, cm/sec	8.91 ± 2.28 (74)	8.40 ± 1.66 (25)	0.24/0.07
Lateral E′/A′ ratio	1.55 ± 0.76 (73)	1.92 ± 0.62 (23)	0.008/0.003
Septal E/E′ ratio	9.99 ± 4.66 (75)	7.27 ± 1.96 (25)	<0.001/<0.001
Lateral E/E′ ratio	7.68 ± 4.64 (75)	5.59 ± 1.35 (25)	<0.001/0.004
Average, septal/lateral E/E′ ratio	8.46 ± 4.29 (75)	6.27 ± 1.52 (25)	<0.001/0.002
PV systolic velocity, cm/sec	21.55 ± 15.16 (73)	15.63 ± 4.04	0.003/0.006
PV diastolic velocity, cm/sec	13.96 ± 13.90 (73)	10.56 ± 3.48	0.06/0.37
PV systolic/diastolic ratio	1.84 ± 0.66 (73)	1.56 ± 0.44	0.02/0.002

Abbreviations: BP, blood pressure; IVRT, isovolumic relaxation time; LA, left atrium; LAVI, left atrial volume index; LV, left ventricle; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; PV, pulmonary vein; SD, standard deviation; TEE, transesophageal echocardiography.
Cell formats are mean ± standard deviation (SD) or mean ± SD (n) for subsets.
[a]The first *P* value is unadjusted, and the second *P* value is after standardizing patients and controls to same mean heart rate and blood pressure using regression coefficients.

Left Ventricular Wall Thickness, Mass, and Diastolic Function

Unadjusted and after standardizing each subject to the same pooled mean heart rate (73.7 bpm) and blood pressure (85.6 mm Hg), patients as compared with controls had (1) greater inferior and anterior wall thickness and higher LV mass and index; (2) lower E/A and E′/A′ ratios, longer IVRT, and lower septal and lateral mitral annulus E′ velocities consistent with impaired LV relaxation; and (3) higher mitral E/septal E′, mitral E/lateral E′, and average mitral E/E′ velocities ratios suggestive of decreased LV compliance (all $P \leq 0.03$; Table 2). Left ventricular size, wall motion, and systolic function were similar among groups.

Correlation of Aortic Stiffness With Left Ventricular Mass, Left Atrial Volume, and Left Ventricular Diastolic Dysfunction

In SLE, PSEM was correlated with LV mass and LA volume indexes and with parameters of LV diastolic dysfunction (all $P < 0.05$; Table 3). Aortic strain, stiffness,

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Table 3. Correlation of Aortic Stiffness With LV Mass, LA Volume, and Parameters of LV Diastolic Function in SLE Patients

	PSEM	
Variable	Pearson Correlations (*r*)	*P* Value
SLE patients		
LVMI, g/m² (n = 73)	0.23	0.05
LAVI (n = 71)	0.27	0.02
Mitral A peak velocity, cm/sec (n = 75)	0.40	< 0.001
Mitral E′/A′ ratio (n = 75)	−0.37	< 0.001
Septal E′ peak velocity, cm/sec (n = 75)	−0.24	0.03
Septal A′ peak velocity, cm/sec (n = 75)	0.33	0.004
Septal E′/A′ ratio (n = 75)	−0.42	< 0.001
Septal IVRT, msec (n = 74)	0.34	0.004
Lateral E′ peak velocity, cm/sec (n = 76)	−0.45	< 0.001
Lateral A′ peak velocity, cm/sec (n = 74)	0.20	0.08
Lateral E′/A′ ratio (n = 74)	−0.46	< 0.001
Average of septal and lateral E′/A′ ratio (n = 75)	−0.38	< 0.001
Septal E/E′ ratio (n = 75)	0.23	0.045
Lateral E/E′ ratio (n = 75)	0.40	< 0.001
Average E/E′ ratio (n =75)	0.32	0.006

Abbreviations: IVRT, isovolumic relaxation time; LA, left atrial; LAVI, left atrial volume index; LV, left ventricular; LVMI, left ventricular mass index; PSEM, pressure-strain elastic modulus; SLE, systemic lupus erythematosus.

and distensibility were also correlated with parameters of LV diastolic dysfunction in SLE (all $P \leq 0.03$; Supplemental Table 4).

Independent Association of Aortic Stiffness and Other Variables With Left Ventricular Diastolic Dysfunction

By multivariate analysis including all clinical, laboratory, and therapy variables listed in Supplemental Tables 1 and 2, PSEM was independently negatively associated with mitral E/A and E′/A′ ratios and E′ velocity and positively associated with E/E′ ratios after adjustment including MAP and LVMI ($P \leq 0.02$ for each parameter and $P < 0.001$ for all parameters as a profile by rANOVA; Table 4 and Figure 1). These data support that LV diastolic dysfunction in SLE patients can occur independently of hypertension and LV hypertrophy. Mean arterial blood pressure, complement C3 levels, non-neuro–Systemic Lupus International Collaborating Clinics score (SLE damage score), tPA levels, antithrombotic therapy, and SLE duration were also independently associated with LV diastolic dysfunction (all $P \leq 0.04$).

Table 4. Independent Association of Aortic Stiffness (PSEM) and Other Variables with LV Diastolic Function in SLE Patients by Multivariate Analysis[a]

Best Predictors	Standardized β[b]	*P* Value
Mitral E/A ratio		
PSEM	−0.32/−0.34[c]	0.004/0.003[c]
tPA	−0.28	0.009
Septal mitral annulus tissue Doppler E′/A′ ratio		
PSEM	−0.30/−26[c]	0.009/0.03[c]
Mean blood pressure	−0.29	0.01
Complement C3 levels	−0.28	0.009
Mitral annulus tissue Doppler E′ velocity		
PSEM	−0.35/−0.33[c]	<0.001/0.002[c]
tPA	−0.29	0.005
Mean blood pressure	−0.25	0.02
ASA/warfarin	−0.20	0.04
Lateral mitral annulus tissue Doppler E/E′ ratio		
PSEM	0.34/0.34[c]	0.002/0.003[c]
Non-neuro-SLICC	0.32	0.004
Average mitral annulus tissue Doppler E/E′ ratio		
PSEM	0.26/0.27[c]	0.02/0.02[c]
SLE duration	0.31	0.007

Abbreviations: ASA, aspirin; LV, left ventricular; LVMI, left ventricular mass index; PSEM, pressure-strain elastic modulus; SD, standard deviation; SLE, systemic lupus erythematosus; SLICC, Systemic Lupus International Collaborating Clinics; tPA, tissue plasminogen antigen.
[a]Multivariate models were determined by stepwise variable selection and verified by backward regression. Candidate predictor variables include all variables statistically significant and clinically meaningful in univariate analyses. [b]Standardized β represent the number of SD change in the outcome for 1 SD change in the predictor variable (ie, a 1-SD increase in PSEM is associated with a 0.32-SD decrease in mitral E/A ratio). [c]Standardized β and *P* value when LVMI was added in the model.

Discussion

Major Findings

There are 3 major findings in this study: (1) SLE patients as compared with controls have a higher degree of aortic stiffness independently of atherogenic risk factors including hypertension and aortic atherosclerosis, have higher LV mass, and have a greater degree of LV diastolic dysfunction; (2) in SLE patients, aortic stiffness is correlated with increased LV mass, LA volume, and LV diastolic dysfunction; and (3) in SLE patients, aortic stiffness (even after adjusting for LVMI), MAP, inflammation (complement C3 levels and SLE damage score), thrombogenesis (tPA levels and antithrombotic therapy), and SLE duration are independently associated with LV diastolic dysfunction.

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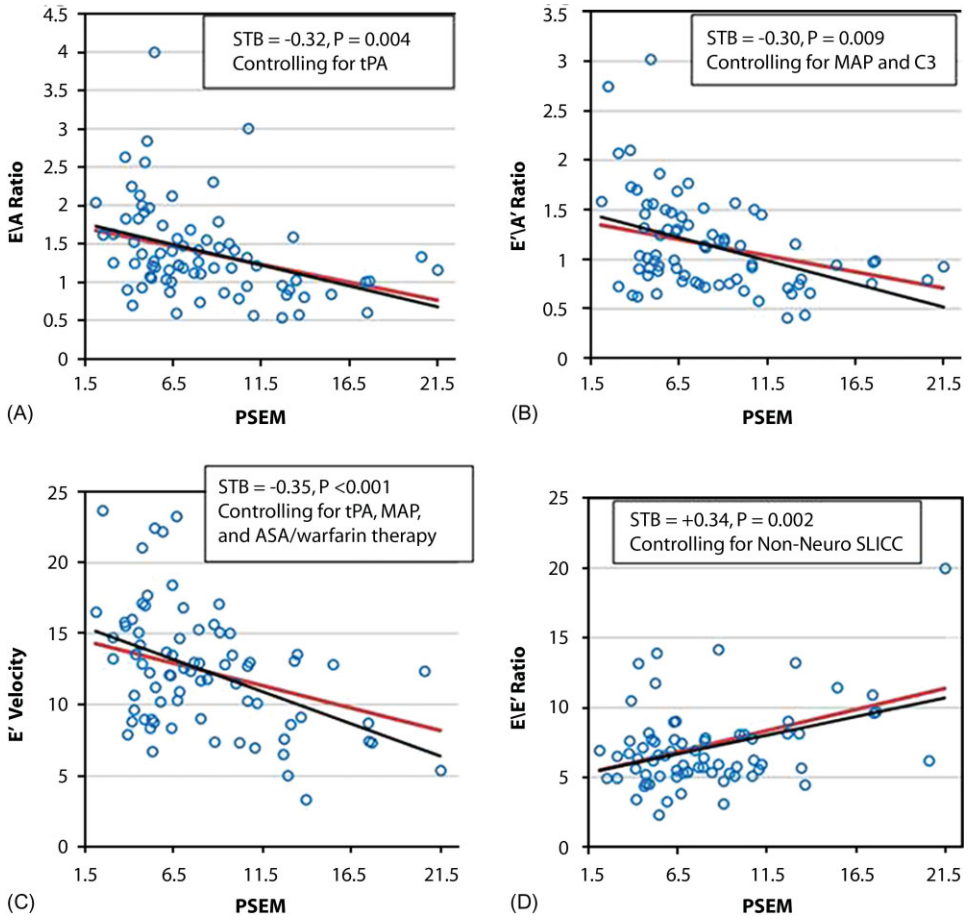

Figure 1. Association of aortic stiffness with LV diastolic dysfunction. Independent association of PSEM (units) with (A) mitral E/A ratio, (B) E′/A′ ratio, (C) E′ peak velocity, and (D) E/E′ ratio ($P \leq 0.009$ for each parameter and $P < 0.001$ by rANOVA as a profile). The association of PSEM with LV diastolic dysfunction was computed as least squares means over the range of PSEM values, controlling for relevant covariates set to their mean values (red lines). The unadjusted linear regression fits (black lines) to the scatter plots of raw data (open blue circles) are shown for comparison purposes. Abbreviations: ASA, aspirin; C3, complement C3; LV, left ventricular; MAP, mean arterial blood pressure; PSEM, pressure-strain elastic modulus; rANOVA, repeated measures analysis of variance; SLICC, Systemic Lupus International Collaborating Clinics; STB, standardized β; tPA, tissue plasminogen antigen.

To our knowledge, this is the first study to demonstrate that aortic stiffness is independently associated with LV diastolic dysfunction in SLE even after adjusting for blood pressure and LVMI. These findings suggest that SLE and other autoimmune diseases–associated chronic or recurrent systemic inflammation may cause endothelial dysfunction and apoptosis, increased thrombogenesis, smooth-muscle-cell proliferation, intima-media thickening, vessel stiffness and increased impedance, and consequently prehypertension or hypertension—which, in combination and a self-perpetuating vicious cycle, may cause further aortic stiffness, increased blood pressure, and LV afterload; may or not increase LV mass; and ultimately may cause LV diastolic dysfunction.[8,13–15] Arterial hypertension is highly prevalent (29% to 36%) in SLE patients.[3,13,16] In this study, SLE patients had higher nonhypertensive-range blood pressures than controls, 10 patients (13%) were hypertensive on enrollment, 24 patients (32%) were either ambulatory hypertensive or on vasodilator therapy, and aortic stiffness was highly correlated with hypertension or vasodilator therapy (standardized β: 0.37, $P = 0.001$). The rates of hypertension in this study are similar to those reported in studies of premenopausal women with SLE[16,17] but higher than those reported in similar general populations (~5%).[18]

Aortic stiffness in SLE may be associated with reduced coronary flow reserve or microvascular coronary artery disease, leading to LV diastolic dysfunction.[8,14,15,19] Previous series demonstrated decreased in coronary flow reserve during dipyridamole or adenosine Doppler TTE and vasodilatory stress-induced reversible, fixed, or mixed myocardial perfusion defects in young SLE patients with normal or minimally diseased epicardial coronary arteries on angiography.[19,20] In this study, 17 patients (22%) had atherosclerosis of the descending thoracic aorta, and other studies have reported an association of carotid arterial stiffness with similar rates of subclinical carotid and coronary atherosclerosis.[21,22]

Comparison With Previous Studies

To our knowledge, there are no previous studies correlating aortic stiffness with LV diastolic dysfunction in autoimmune inflammatory diseases, including SLE. Previous studies

using TTE for assessment of LV diastolic dysfunction and arterial tonometry for assessment of carotid-to-femoral-artery pulse wave velocity as an indicator of arterial stiffness have shown that SLE patients do develop premature LV diastolic dysfunction and arterial stiffness independently of age and hypertension, but an association of arterial stiffness with LV diastolic dysfunction was not reported in those studies.[2–6,23,24]

Study Limitations

The strength of association of aortic stiffness with LV diastolic dysfunction may have been underestimated by (1) study of a low proportion (8%) of patients with renal dysfunction and therefore of less severe SLE, (2) exclusion of patients age >60 years with expected longer SLE duration and greater vascular disease, (3) no application of myocardial strain and strain rate for detection of LV diastolic dysfunction, and (4) assessment of aortic stiffness and LV diastolic dysfunction during conscious sedation. Although the study lacks a gold standard of invasively measured LV end-diastolic pressure, studies in non-SLE populations have shown a high correlation of LV diastolic dysfunction by Doppler echocardiography with that by cardiac catheterization.[25,26] Finally, the use of 24-hour ambulatory blood-pressure monitoring and blood pressure assessed in response to stressors may have reflected better the prevalence and impact of systemic hypertension on aortic stiffness and LV diastolic function in both study groups (SLE patients and controls). In this study, systemic hypertension was more common during a stressor such as TEE than during enrollment clinical evaluation (22% vs 13% in SLE patients and 12% vs 0% in controls, respectively), and therefore the prevalence and effect of systemic hypertension may have been overestimated. However, after adjustment to blood pressure and exclusion of subjects with hypertension during TEE and initial clinical evaluation, aortic stiffness and LV diastolic dysfunction were still higher in patients than in controls. Thus, these tests should be considered in future studies of the association of systemic hypertension, aortic stiffness, and LV diastolic dysfunction.

Conclusion

Systemic lupus erythematosus-associated aortic stiffness may not only be associated with, but also may be a marker or risk factor for, hypertension, LV hypertrophy, and LV diastolic dysfunction.[17,21,22,27] This study suggests that subsets of SLE patients are at higher risk for LV diastolic dysfunction and include those with (1) longer SLE duration, (2) severe SLE (high damage score), (3) elevated acute-phase reactants (C3 levels), (4) hypercoagulability (requiring antithrombotic therapy or with elevated tPA), and (5) inadequately treated hypertension. Therefore, an earlier diagnosis of SLE; effective immunosuppressive, anti-inflammatory, and antithrombotic therapy; and treatment of commonly associated traditional atherogenic risk factors may prevent the development or progression of aortic stiffness, hypertension, atherosclerosis, LV diastolic dysfunction, and clinical diastolic heart failure. In fact, immunosuppressive therapy, statins, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers or calcium channel blockers, and antiplatelet therapy have shown to have a beneficial effect on aortic stiffness in SLE and non-SLE populations.[28–30] The findings of this study may also apply to other autoimmune-mediated inflammatory diseases such as rheumatoid arthritis, spondyloarthropathies, scleroderma, and polymyositis/dermatomyositis. Furthermore, in SLE patients undergoing TEE for appropriate indications, assessment of aortic stiffness and LV diastolic dysfunction is feasible and clinically relevant. Finally, a larger controlled cross-sectional and longitudinal study is needed to confirm our findings and determine the short- and long-term prognosis and effect of therapy on the incidence and progression of aortic stiffness and LV diastolic dysfunction in young adult SLE patients.

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