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PREMATURE AORTIC STIFFNESS IN SYSTEMIC LUPUS ERYTHEMATOSUS BY TRANSESOPHAGEAL ECHOCARDIOGRAPHY

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SUMMARY

To assess aortic stiffness by transesophageal echocardiography (TEE) and to determine its clinical predictors and relation to age, blood pressure, renal function, and atherosclerosis, 50 patients with systemic lupus erythematosus (SLE), 94% women, with a mean age of 38 ± 12 years and 22 age and gender matched healthy controls underwent clinical and laboratory evaluations and multiplane TEE to assess stiffness, intima-media thickness (IMT), and plaques of the proximal, mid, and distal descending thoracic aorta. At each level and overall aortic stiffness by the pressure-strain elastic modulus was higher in patients than in controls after adjusting for age (overall, 8.25 ± 4.13 versus 6.1 ± 2.5 Pascal units, $p = 0.01$). Patients had higher aortic stiffness than controls after adjusting both groups to the same mean age, blood pressure, creatinine, and aortic IMT ($p = 0.005$). Neither IMT nor plaques were predictors of aortic stiffness. Moreover, normotensive patients, those without aortic plaques, and non-smokers had higher stiffness than controls (all $p < 0.05$). Age of SLE diagnosis, non-neurologic damage score, and mean arterial pressure during TEE were the only independent predictors of aortic stiffness (all $p \leq 0.02$). Thus, aortic stiffness may be a primary form of premature functional vasculopathy in SLE.

Keywords

aortic stiffness; systemic lupus erythematosus; transesophageal echocardiography; atherosclerosis

INTRODUCTION

Patients with systemic lupus erythematosus (SLE) have a high prevalence of hypertension and premature coronary and carotid atherosclerosis that substantially increases their morbidity and mortality (1–7). Patients with SLE also develop arterial stiffness, but it is uncertain if arterial stiffness occurs independently of age, hypertension, renal function, or atherosclerosis (8,9). In addition, aortic stiffness may be causally related to the development of hypertension and premature aortic atherosclerosis (10). Therefore, this study was designed with 3 objectives: 1) to directly assess aortic stiffness using transesophageal echocardiography (TEE) in young SLE patients as compared to age and gender matched healthy controls; 2) to determine the clinical predictors of aortic stiffness; and 3) to determine if aortic stiffness occurs independently of age, blood pressure, renal function, and aortic atherosclerosis.

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PATIENTS AND METHODS

Study populations

Fifty consecutive patients with diagnosis of SLE according to criteria by the American College of Rheumatology, 46 women, with a mean age of 38 ± 12 years (range, 18–60) and 22 healthy volunteers, 19 women, with a mean age of 34 ± 12 years (range, 18–57) agreed to participate in the study. Patients with SLE were recruited from a well-characterized population of about 200 patients between 18 to 60 years old regularly followed at the Rheumatology Clinics of the University of New Mexico Health Sciences Center. This study protocol was approved by the Institutional Review Board and all participating subjects signed an approved informed consent.

Clinical and laboratory evaluations

Patients and controls underwent clinical and laboratory evaluations including specific parameters of inflammation (Table 1). Also, SLE patients were further characterized with regard to their disease duration, activity, severity, therapy, and serology including antiphospholipid antibodies (Table 2).

Transesophageal Echocardiography

All subjects underwent multiplane TEE with Philips I-E33 imaging systems using a 7 MHz transducer with an axial resolution of approximately 0.1 mm. At a low depth (3–4 cm) and using a narrow sector scan to improve image resolution, two-dimensional guided M-mode images were used to assess aortic systolic and diastolic diameters and intima-media thickness (IMT) of the aortic anterior wall at the proximal (25–30 cm from the incisors), mid (30–35 cm) and distal descending thoracic aorta (35–40 cm). Aortic diameters were measured from the short and long axis views during end-systole and end-diastole (peak to end of T wave and after P wave on the electrocardiogram, respectively) Figure 1). At each aortic level, 3–6 measurements of diameters and IMT were averaged. Far field decreased resolution and common off axis views precluded accurate assessment of diameters and IMT of ascending aorta and arch. All studies were codified, digitally stored, and those of patients and controls were randomly intermixed. Also, all studies were interpreted and measured off line using electronic calipers by experienced observers blinded to subjects' all clinical data. To further avoid interpretation bias, one observer (JJ) assessed aortic diameters and a second observer (CAR) assessed IMT and plaques. Finally, to assess intraobserver reliability 26 randomly selected studies (from 16 patients and 10 controls) had repeated measurements of aortic diameters.

Blood pressures

During TEE and at each aortic level multiple blood pressure measurements were obtained from the brachial artery using an automatic Dash 2000 sphygmomanometer. Blood pressures were matched in time with aortic measurements.

Assessment of aortic stiffness and atherosclerosis

Aortic stiffness was assessed with the ***Pressure-Strain Elastic Modulus (PSEM*** *as* ***= [k(sBP − dBP)/(sD-dD/dD)]/100*** where **k** = 133.3 is a conversion factor from mmHg to Pascal units, **sBP** = systolic blood pressure, **dBP** = diastolic blood pressure, **sD** = systolic diameter, and **dD** = diastolic diameter (11). ***PSEM*** is a well-established and validated parameter of arterial stiffness that defines the amount of force (pulse pressure) required to distend a vessel. This parameter allows assessment of aortic stiffness independently of IMT or plaques. **Atherosclerosis** was defined as aortic plaques manifested as >50% focal or protruding wall thickening as compared with surrounding walls (4,5,12).

Statistical Analysis

Student's *t* test or Wilcoxon rank-sum test (for normally or non-normally distributed data) and Fisher's exact test were used for comparison of continuous and categorical variables among groups, respectively. Analysis of aortic stiffness was performed with repeated measures ANOVA where the 3 aortic locations of measurements constitute a repeated factor and SLE patients versus control subjects constitute the group factor. The "best" multivariate models were obtained by stepwise regression and verified by "all subsets" regression for the stiffness parameter on the candidate predictors (those with $p<0.05$ in univariate analysis). The effect size for a predictor in both univariate and multivariate models are reported as correlations or standardized betas (regression coefficients of the standardized outcome and predictor variables). To further determine that aortic stiffness in SLE patients occurs independently of age, blood pressure, renal function, and atherosclerosis we adjusted by multivariate regression each individual's PSEM at each aortic location to the same mean age (37 years old), arterial blood pressure (86 mmHg), creatinine (0.80 mg/dl), and IMT (0.81 mm). These means are for the pooled data of patients and controls. A two-tail p value <0.05 was considered significant.

RESULTS

Clinical characteristics of patients and controls

SLE patients and controls were similar in age, gender, and body mass index. However, SLE patients had higher ambulatory blood pressures, more atherogenic risk factors, higher creatinine (only 3 patients had values >1mg/dL) and lower hematocrit, platelets, and albumin than controls (all $p \leq 0.04$, Table 1). Clinical, therapy, and laboratory data specific to SLE patients are delineated in Table 2.

Blood pressures, aortic diameters, aortic intima-media thickness and plaques in patients and controls

During TEE, patients had higher systolic, diastolic, and mean arterial blood pressures than controls (123 ± 18, 71 ± 16, and 89 ± 16 mmHg versus 113 ± 12, 64 ± 12, and 81 ± 11 mmHg, respectively, all $p \leq 0.05$). However, pulse pressures were similar in both groups (51 ± 13 versus 49 ± 12 mmHg, respectively, $p = 0.39$). Although, patients and controls had similar systolic and diastolic aortic diameters (1.99 ± 0.26 and 1.81 ± 0.28 versus 1.94 ± 0.22 and 1.74 ± 0.24 cm, respectively, both ≥0.25), the differential diameter was lower in patients than in controls (0.18 ± 0.05 versus 0.20 ± 0.04 cm, respectively, $p = 0.03$). Also, patients had higher IMT values and more aortic plaques than controls (0.87 ± 0.35 versus 0.68 ± 0.18 mm and 28% versus 0%, respectively, both $p \leq 0.02$). The percent error in the measurement of systolic and diastolic diameters at the proximal, mid, and distal aorta were 6% and 6%, 2% and 3%, and 4% and 6%, respectively.

Aortic stiffness in patients and controls

Stiffness was higher in all SLE patients, in normotensive SLE patients (sBP≤ 135 and dPB ≤85 mmHg), in those without aortic plaques, and in non-smokers as compared to controls (all $p<0.05$) (Table 3). Also, aortic stiffness was higher in patients with than without pre or hypertension on TEE and aortic plaques (12.3 ± 5.6 versus 7.4 ± 3.2 and 9.4 ± 4.3 versus 7.8 ± 4 units, $p = 0.03$ and $p = 0.26$, respectively). By repeated measures ANOVA and adjusted for age, aortic stiffness was higher in patients than in controls ($p = 0.02$) and progressively increased from proximal to distal aorta ($p = 0.04$) (Figures 2). In addition, after adjustment of both groups to the same mean age, arterial blood pressure, creatinine, and IMT, SLE patients still had significantly higher aortic stiffness as compared to controls ($p = 0.005$) with a linear trend up of stiffness from proximal to distal aorta ($p= 0.04$) (Figure 3).

Predictors of aortic stiffness in patients with SLE (Table 4

By univariate analyses including all clinical, therapy, and laboratory variables listed in Tables 1 & 2, age of SLE diagnosis, mean arterial blood pressure during TEE, non-neurologic and total SLE damage scores, C3a, IgG anticardiolipin antibodies, total cholesterol and platelets levels were predictors of aortic stiffness (all $p \leq 0.05$). However, aortic IMT, aortic plaques, smoking, and any atherogenic risk factor, were not predictors. By multivariate analyses, age of SLE diagnosis, non-neurologic SLE damage score, and mean arterial blood pressure during TEE (expectedly since blood pressure is a factor in the calculation of stiffness) were the only independent predictors of aortic stiffness (all $p < 0.02$).

DISCUSSION

Major Findings

There are three major findings in this study: 1) aortic stiffness is higher in young SLE patients as compared to matched controls after adjusting for age; 2) in SLE patients, age of SLE diagnosis, non-neurologic damage score, and mean arterial blood pressure are the only independent predictors of aortic stiffness; and 3) aortic stiffness in SLE occurs independently of age, renal function, blood pressure, and aortic atherosclerosis. To our knowledge this is the first TEE series in young SLE patients to directly demonstrate the occurrence of aortic stiffness independently of age, blood pressure, renal function, atherogenic risk factors, and early aortic atherosclerosis.

This study findings suggest that the later in life SLE is diagnosed the higher the likelihood that untreated immune-mediated inflammation leads to aortic stiffness. However, since the age of SLE diagnosis is known but not the age of SLE onset, it is also possible that the later the age of SLE diagnosis is the higher the likelihood that age related aortic stiffness occurs. Therefore, delayed SLE diagnosis and older age at diagnosis play a role in the pathogenesis of aortic stiffness in SLE.

Also in this study, normotensive SLE patients had higher aortic stiffness than controls. Morover, aortic stiffness was higher in patients with than without hypertension. These findings support that once SLE related aortic stiffness occurs, hypertension may follow and result in a perpetuating vicious cycle of progressive large vessel vasculopathy (3,8,9,10–15). However, SLE related hypertension may also lead to aortic stiffness, which then also perpetuates hypertension. In this study, SLE patients had higher non-hypertensive range blood pressures than controls, 14% of patients had hypertension and 28% were either hypertensive or on vasodilator therapy. This is a significantly higher prevalence of hypertension in young SLE women as compared to that of a similar age and gender general population (~5%) (16). Also, hypertension was not related to the low prevalence of renal disease (6%) and postmenopausal status (15%) nor body mass index since patients and controls had similar values. Similarly high prevalence rates (29%–36%) of hypertension have been reported in several series of premenopausal SLE women (2,3,15,17). Therefore, the putative mechanisms of hypertension in SLE such as inflammatory cytokine mediated endothelial dysfunction, hyperactivity of the renal angiotensin system resulting in increased production of angiotensin II and endothelin-1 (both potent vasoconstrictors), increased oxidative stress, steroid therapy, and insulin resistance may all actually contribute to aortic stiffness and then to hypertension or both simultaneously (2,14,20).

In addition, in this study SLE patients without aortic plaques had higher aortic stiffness than controls. Although not statistically significant, aortic stiffness was also higher in patients with than without aortic plaques. These findings also support that aortic stiffness in SLE may be an important pathogenic or exacerbating factor for aortic atherosclerosis, which then sets up a self perpetuating pathologic cycle (10,13–15). In this study, 28% of patients had

aortic plaques (p = 0.004 versus controls), a similar prevalence to that of coronary (31%) and carotid (37%) atherosclerosis reported in other series (4,15,18).

Therefore, aortic stiffness in SLE may lead or contribute to the development of hypertension, which begets stiffness and both may accelerate aortic atherosclerosis.

Comparison with previous studies

Although no previous series have directly assessed aortic stiffness by TEE in SLE, several series using arterial tonometry have demonstrated either aortic or peripheral arterial stiffness manifested by an increased carotid to femoral pulse wave velocity (PWV) (5,8,9). Selzer et al (3), in a non-controlled study of 214 SLE women without clinical cardiovascular disease with a mean age of 45.2 ± 10.5 years (included patients >60 years old) demonstrated that aortic stiffness by PWV was associated with older age, higher systolic blood pressure, higher C3 levels, lower white blood cell count, higher insulin levels, and renal disease. Bjarnegråd N, et al (8), in 27 SLE women (52 to 68 years old) and 27 controls demonstrated that carotid to femoral PWV was higher in SLE women than in controls after correction for mean arterial pressure and body mass index. Also, aortic PWV was positively associated to C-reactive protein and complement factor 3. Finally, Yildiz M, et al (9), demonstrated higher carotid-femoral PWV in 24 premenopausal SLE women as compared to 24 age- and sex-matched controls. Aortic stiffness was correlated with age, body mass index, waist--to-hip ratio, heart rate and blood pressure. Unlike our study, these series did not demonstrate the occurrence of aortic stiffness independently of age, blood pressure, renal function, and aortic atherosclerosis.

Limitations of the study

An underestimation of aortic stiffness may have occurred because this study population only represents about 25% of patients regularly followed at our institution, thus, patients with severe disease may be underrepresented; the low proportion (6%) of patients with renal dysfunction studied; and the assessment of IMT and plaques of the aortic posterior wall was limited and therefore aortic atherosclerosis may have been underestimated. In contrast, the small healthy control group may have led to an overestimation of the independent effect of SLE on aortic stiffness. Also an independent effect of blood pressure on aortic stiffness could only be partially ascertained because assessment of aortic stiffness includes blood pressure as a factor. However, when patients' and controls' mean arterial blood pressure was adjusted to the same normal value or normotensive patients were compared with controls, aortic stiffness was still significantly higher in patients than in controls. Finally, although the specific effect of different SLE therapies on aortic stiffness was not assessed, they were not predictors in the univariate and multivariate analyses.

Clinical implications

This study may have several clinical implications: 1) aortic stiffness may be a primary form of premature functional vasculopathy in SLE (19), 2) SLE-associated chronic immune-mediated inflammation and damage to the arterial wall cause aortic stiffness, which then may lead to or exacerbate hypertension, and then to atherosclerosis (20); 3) earlier diagnosis and aggressive anti-inflammatory therapy of SLE has the potential to prevent the development and progression of aortic stiffness, hypertension, and atherosclerosis (20,21); and 4) statin, angiotensin converting enzyme inhibitor, and antiplatelet therapy may also have primary and secondary preventive effects due to SLE-associated high prevalence of dyslipidemia, endothelial dysfunction, hypertension, vascular stiffness, and atherosclerosis (22,23). These interventions have the potential to decrease the prevalence and incidence of cardiac and cerebrovascular diseases in SLE and their associated high morbidity and mortality. However, a large prospective controlled cross-sectional and longitudinal study is

necessary to define better the short and long term prognosis of aortic stiffness on cardiac and cerebrovascular outcomes in SLE.

Acknowledgments

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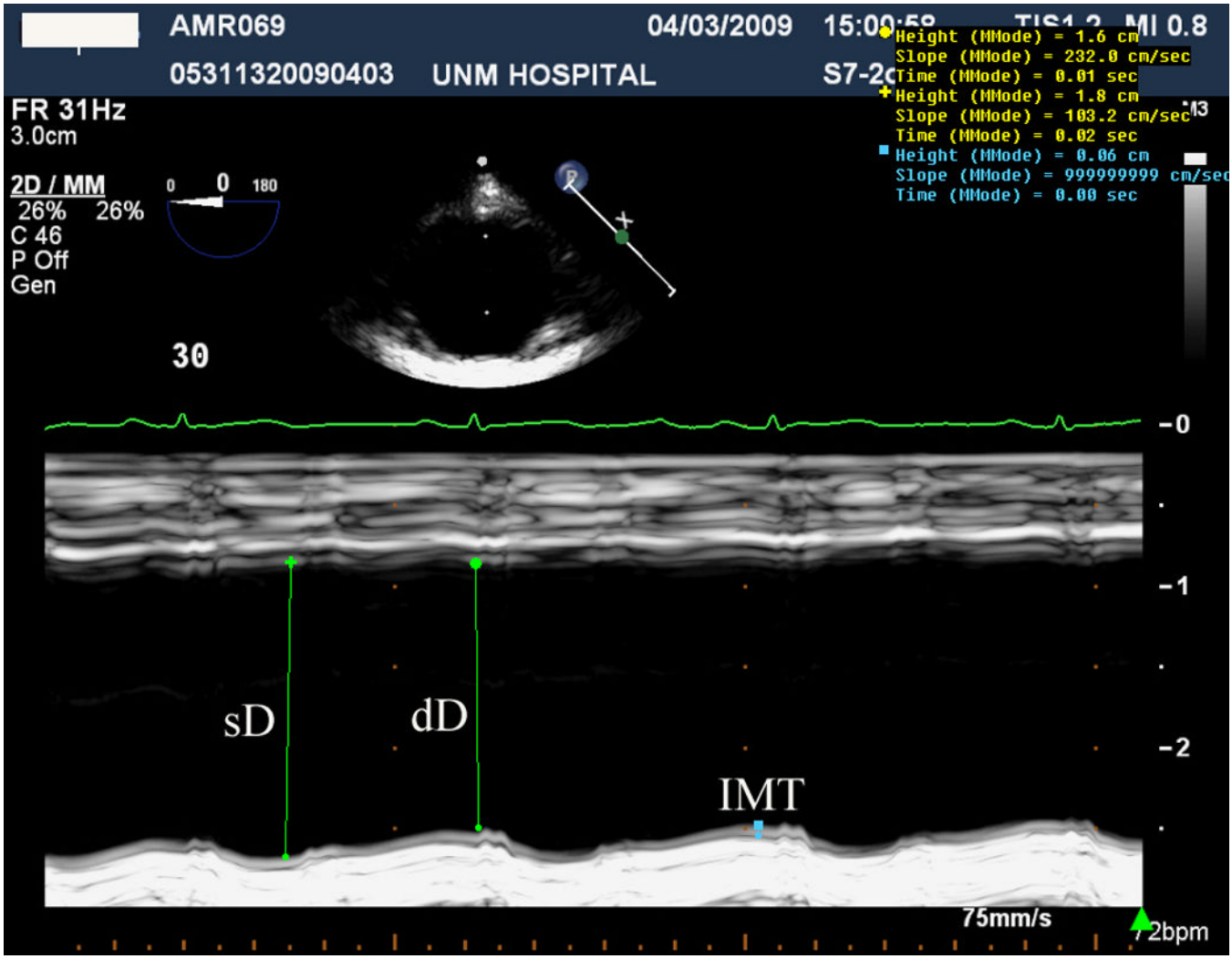

Figure 1. Measurement of Aortic Diameters and Intima-media Thickness

This TEE short axis two-dimensional guided M-mode image of the proximal descending thoracic aorta in a patient with SLE demonstrates the measurements of the aortic systolic diameter (sD) at the peak of the T wave on the electrocardiogram and measurement of the diastolic diameter (dD) and aortic intima-media thickness (IMT) during end-diastole (after the P wave on the electrocardiogram). The systolic and diastolic diameters and IMT measured 1.8 cm, 1.6 cm, and 0.6 mm, respectively.

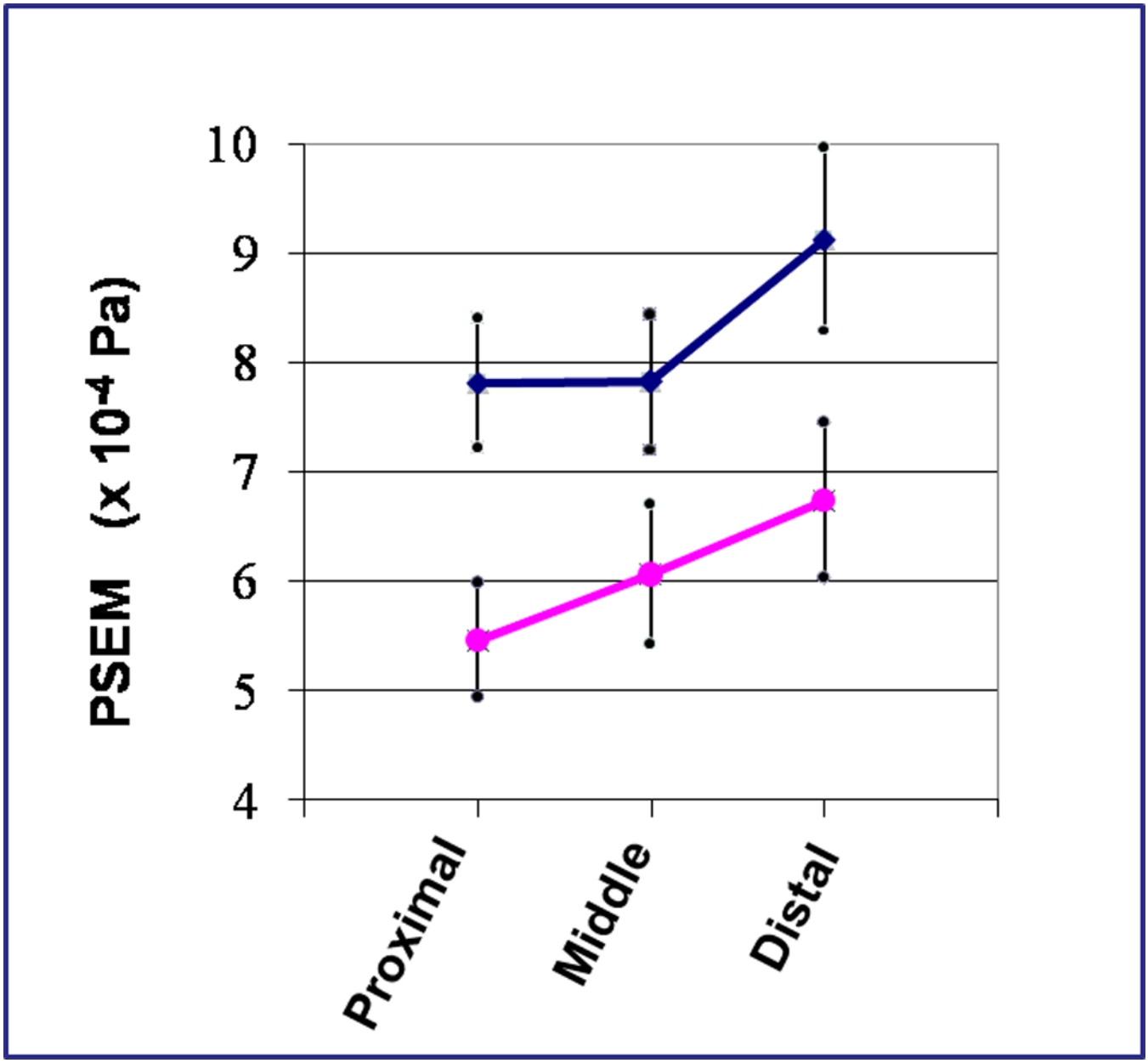

Figure 2. Pressure-Strain Elastic Modulus at the Proximal, Middle, and Distal Descending Thoracic Aorta in Patients with SLE and Controls

Note that the pressure strain elastic modulus (PSEM, mean ± SE) is higher in patients (blue line) than in controls (pink line) at every aortic location. Also note that PSEM progressively increases from the proximal to distal aorta. Unadjusted, p = 0.002 for group and p = 0.05 for location. Adjusted for age, p = 0.02 for group and p = 0.04 for location.

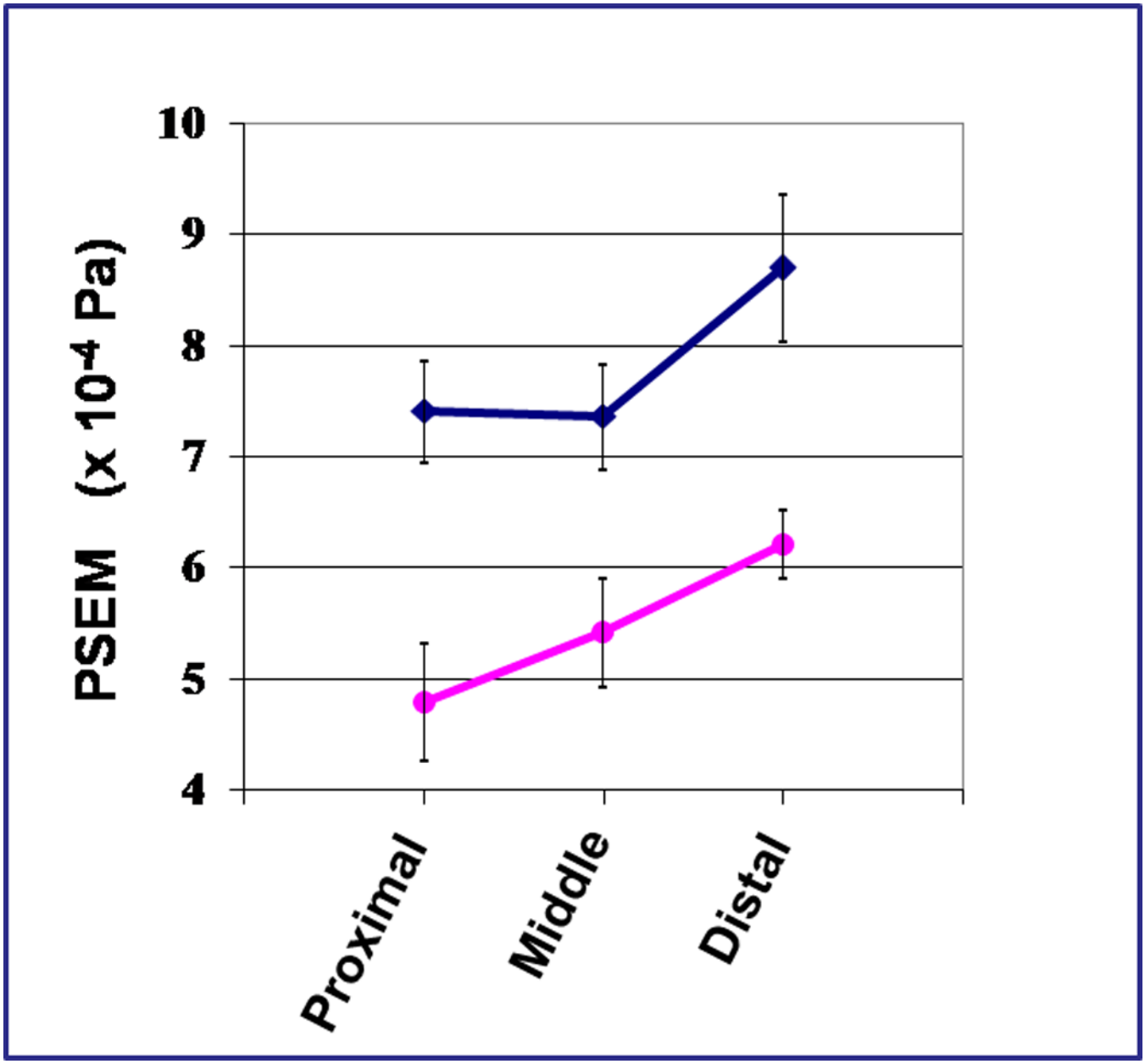

Figure 3. Pressure-Strain Elastic Modulus in Patients and Controls after Adjusting Both Groups to the Same Age, Blood Pressure, Renal Function, and Aortic Intima-media Thickness

SLE patients (blue line) had significantly higher PSEM (mean ± SE) than controls (pink line) at every aortic location ($p = 0.005$) and a linear trend up of PSEM from proximal to distal aorta was noted ($p = 0.04$).

Table 1

Clinical and Laboratory Data in Patients with SLE and Controls

Parameter	Patients (N = 50)	Controls (N = 22)	P Value
Age (years)	38 ± 12	34 ± 12	0.15
Female gender (%)	92	82	0.19
Non hispanic whites and Hispanic (%)	28 and 60	36 and 50	0.71
Body mass index (kg/m^2)	27 ± 5	27 ± 6	0.75
*Systolic blood pressure (mmHg)	124 ± 14	116 ± 8	0.01
*Diastolic blood pressure (mmHg)	77 ± 10	73 ± 7	0.03
*Mean arterial blood pressure (mmHg)	93 ± 10	87 ± 6	0.01
Ambulatory hypertension (%)	14	0	0.09
Hypertension or on vasodilator therapy (%)	28	0	0.004
Smoking	54	23	0.02
Cholesterol (mg/dl)	182 ± 45	185 ± 45	0.82
Triglycerides (mg/dl)	153 ± 77	160 ± 104	0.79
Dyslipidemia	63	38	0.07
Diabetes mellitus (%)	12	0	0.17
Any atherogenic risk factor (%)	72	36	0.01
Post-menopausal status (%)	15	11	1.0
Hematocrit (%)	39 ± 4	41 ± 4	0.02
Platelets (k/mm^3)	240 ± 91	274 ± 44	0.04
White blood cell count (k/mm^3)	5.8 ± 2.3	6.5 ± 1.7	0.19
Creatinine (mg/dl)	0.83 ± 0.32	0.72 ± 0.10	0.04
Albumin (g/dL)	3.9 ± 0.6	4.2 ± 0.4	0.01
P-selectin (ng/mL)	41 ± 21	39 ± 16	0.62
C3a (pg/mL)	2246 ± 3255	2096 ± 2217	0.83
C5a (pg/mL)	31 ± 11	29 ± 10	0.54
Quantitative D-dimer (ug/ml)	1.0 ± 3.0	0.3 ± 0.4	0.15
Platelet derived microparticles (uL)	553 ± 668	517 ± 592	0.83
Monocyte derived microparticles (uL)	442 ± 668	477 ± 487	0.81
Endothelium derived microparticles (uL)	162 ± 235	154 ± 122	0.87

Data presented as mean ± SD or %.

*Ambulatory blood pressure.

Table 2

Clinical, Therapy, and Laboratory Data in Patients with SLE

Characteristic	Patients (N = 50)
Duration of SLE (years)	9 ± 7
Age of SLE diagnosis (years)	30 ± 13
Total SLEDAI (U)	12 ± 10
Non-Neuro-SLEDAI (U)	8 ± 6
Total SLICC (U)	3 ± 2
Non-Neuro-SLICC (U)	2.5 ± 1.7
Prednisone therapy (%)	42
Prednisone average dose (mg/d)	8 ± 7
Prednisone (years)	7.2 ± 6.6
Cyclophosphamide therapy (%)	44
Years of cyclophosphamide therapy (%)	0.7 ± 0.9
Methotrexate, azathioprine, mycophenalate, or retuximab (%)	52
Hydroxycloroquine or cloroquine therapy (%)	62
Warfarin, aspirin, or clopidogrel (%)	38
Positive DNA (%)	44
DNA titer (dilutions)	66 ± 236
ANA titer (dilutions)	374 ± 455
Smith antibody positive (%)	30
SSA antibody positive (%)	38
SSB antibody positive (%)	12
Ribonucleoprotein antibody positive (%)	22
Ribonucleoprotein titer (dilutions)	4.7 ± 20
C3 (mg/dl)	99 ± 33
C4 (mg/dl)	20 ± 25
CH50 (mg/dl)	81 ± 37
C-reactive protein (mg/dl)	1.1 ± 1.5
Erythrosedimentation rate (mm/hr)	25.4 ± 25.2
Antiphospholipid antibody positive (%)	60
IgM anticardiolipin antibody (IU)	10 ± 15
IgG anticardiolipin antibody (IU)	13 ± 20
IgA anticardiolipin antibody (IU)	6 ± 12
Beta 2 glycoprotein antibody positive (%)	23
Lupus-like inhibitor positive (%)	33

Data presented as mean ± SD or %.

SLEDAI = SLE disease activity index; SLICC = SLE International Collaborating Clinics Damage Index; DNA = deoxyribonuclease antibody; ANA = antinuclear antibody.

Table 3

Aortic Pressure-Strain Elastic Modulus (Pascal Units) in Patients and Controls

Location	Patients (n=50)	Controls (n=22)	P-value
Proximal	7.81 ± 4.08	5.46 ± 2.46	0.004
Mid aorta	7.82 ± 4.24	6.06 ± 2.99	0.05
Distal aorta	9.13 ± 5.56	6.74 ± 3.31	0.03
Overall	8.25 ± 4.13	6.1 ± 2.5	0.01
	*Normotensive TEE (N = 41)	*Normotensive TEE (N = 20)	
Overall	7.4 ± 3.2	5.8 ± 2.2	0.03
	*Ambulatory normotensive (N = 37)	*Ambulatory Normotensive (N = 22)	
	7.9 ± 4.4	6.1 ± 2.5	0.04
	No aortic plaques (N = 36)	No aortic plaques (N = 22)	
Overall	7.8 ± 4	6.1 ± 2.5	0.046
	Non-smokers (N = 23)	Non-smokers (N = 17)	
Overall	8.98 ± 4.5	6.0 ± 2.2	0.01

*Normotensive defined as systolic blood pressure ≤135 and diastolic blood pressure ≤85 mmHg.

Table 4

Predictors of Aortic Stiffness in Patients with SLE

	Pressure-Strain Elastic Modulus	
	Pearson Correlations (r)	**P value**
Variable	**Univariate Analyses**	
Age of SLE diagnosis	0.47	0.001
Mean arterial blood pressure during TEE	0.39	0.005
Non-Neuro SLICC	0.31	0.03
Total SLICC	0.32	0.02
C3a	0.32	0.03
IgG aPL	−0.28	0.05
Cholesterol level	0.28	0.05
Platelets count	−0.29	0.04
Aortic IMT	0.23	0.12
Aortic plaques	0.17*	0.23
Smoking	−0.14*	0.34
Any atherogenic risk factor	0.25*	0.08
Variable	**Multivariate Analyses**	
Age of SLE diagnosis	0.42**	0.001
Non-Neuro SLICC	0.30**	0.01
Mean arterial pressure during TEE	0.28**	0.02

*Spearman correlations.

**These correlations (standardized betas) are adjusted for other variables in the model and represents the number of SD change in the outcome for 1 SD change in the predictor variable (i.e., stiffness increased by 0.42 SD above the mean of stiffness for 1SD above the mean of age of SLE diagnosis).

Abbreviations as in previous tables.