Relation of Arterial Stiffness to Left Ventricular Structure and Function in Adolescents and Young Adults with Pediatric-Onset Systemic Lupus Erythematosus

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ABSTRACT. Objective. Limited adult data suggested arterial stiffening in systemic lupus erythematosus (SLE). We investigated the hypothesis that arterial stiffening is related to left ventricular (LV) structure and function in adolescents and young adults with pediatric-onset SLE.

Methods. We studied 32 patients with SLE (28 female) aged 17.3 ± 4.8 years. The arterial stiffness was assessed by the carotid artery stiffness index, while the LV mass and cardiac function were assessed echocardiographically. These indices were compared to those of 15 healthy controls.

Results. Compared with controls, patients with SLE had lower LV shortening fraction, ejection fraction and mean velocity of circumferential fiber shortening, reduced mitral early diastolic inflow velocity and early (eₐ) diastolic myocardial tissue velocity, and lower systolic strain and systolic diastolic strain rates of the LV free wall (all p ≤ 0.02). Their global LV function was impaired as reflected by the significantly higher myocardial performance index (MPI; p = 0.02). The carotid arterial stiffness index (p < 0.001) and LV mass (p < 0.001) were significantly greater in patients than controls. Among patients with SLE, the carotid arterial stiffness index correlated with disease activity index (r = 0.46, p = 0.009).

Multivariate analysis revealed that carotid arterial stiffness was a significant independent determinant of LV mass (ß = 0.52, p < 0.001), MPI (ß = 0.43, p = 0.002), eₐ velocity (ß = –0.46, p = 0.001), and systolic strain rate of the LV free wall (ß = –0.46, p = 0.001).

Conclusion. Arterial stiffening occurs in adolescents and young adults with SLE, which may contribute to the development of LV hypertrophy and subclinical myocardial dysfunction. (First Release May 1 2007; J Rheumatol 2007;34:1345–52)

Key Indexing Terms: ARTERIAL STIFFNESS LEFT VENTRICLE SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic vasculitis is one of the characteristic features of systemic lupus erythematosus (SLE). Studies have demonstrated that systemic arterial stiffness is increased in children with vasculitic disease, including polyarteritis nodosa and Kawasaki disease, and in young adults with Behçet’s disease. Proposed mechanisms include replacement of elastic tissue by the stiffer fibrous scar during the reparative process and induction of metalloproteinases by the inflammatory mediators.

In patients with adult-onset SLE, predominantly women aged 40 to 60+, recent studies have similarly shown an increase in carotid arterial stiffness. Nonetheless, the potential confounding influence of premature atherosclerosis, systemic hypertension, dyslipidemia, longterm steroid and other types of immunosuppressive therapy, and menopause on arterial stiffening in these adult patient cohorts could not be completely excluded.

Arterial function in adolescents and young adults with SLE, on the other hand, has hitherto not been studied. Arterial stiffness and its effects on arterial wave reflection from the periphery contribute to increased left ventricular (LV) afterload. While echocardiographic assessment of LV function by qualitative scoring or load-dependent indices has revealed subclinical LV systolic and diastolic dysfunction in adults with SLE, little is known about the LV function in adolescents and young adults with pediatric-onset SLE. More importantly, no studies have yet been performed to examine possible relationships between arterial stiffness and LV function in young patients with SLE. In our study, we determined their LV function using relatively load-independent indices of LV function and tested the hypothesis that arterial stiffness is related to LV structure and function in adolescents and young adults with pediatric-onset SLE.
MATERIALS AND METHODS

Subjects. Patients with disease onset before 18 years of age who met the SLE diagnostic criteria of the American Rheumatism Association 19 were recruited. The following data were collected: age at study and disease onset, disease duration, sex, SLE Disease Activity Index (SLEDAI), Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index, and current medications. Healthy siblings were recruited as controls. Body weight and height were measured, and body mass index and body surface area were calculated accordingly. All subjects rested for at least 15 min before blood pressure and cardiovascular assessments. Blood pressure in the right arm was measured twice and averaged using an automatic oscillometric device (Dinamap, Critikon Inc., Tampa, FL, USA). The Institutional Review Board approved the study and parents of all patients gave informed consent.

Echocardiographic examination. Trans thoracic echocardiography was performed using a 2- to 4-MHz phased-array scanner interfaced to the Philips Sonos 5500 ultrasound machine. The echocardiographic data were stored in magneto-optical disks for offline analysis. Values from 3 consecutive cardiac cycles were averaged for subsequent analyses.

Pulsed-wave Doppler echocardiography was performed to obtain the following indices: peak mitral inflow velocities at early (E) and late (A) diastole, early and late diastolic deceleration times, time interval from cessation to onset of mitral inflow (a), and LV ejection time (b). The LV myocardial performance index (MPI) was calculated as (a – b)/b. 20

Standard M-mode echocardiography was performed from the parasternal short-axis view to obtain the following: LV systolic dimension (LVIDs), LV end-diastolic dimension (LVIDd), and thickness of the interventricular septum and posterior LV wall at diastole. The LV fractional shortening, ejection fraction, and mass were calculated according to standard formulae. 21 The rate-corrected mean velocity of circumferential fiber shortening (MVCFc) was calculated as: (LVIDd – LVIDs)/LVIDd x LV ejection time/√R–R interval. 22 A relatively load-independent index of contractility was determined by calculating the difference between measured and predicted velocity of circumferential fiber shortening (ΔMVCFc) 23 for the calculated peak systolic wall stress. 22

Pulse-wave tissue Doppler imaging of the apical 4-chamber view with the sample volume positioned at the basal LV free wall-mitral annular junction was performed to obtain the following: peak early (e’a) and late (a’) diastolic myocardial tissue velocity, e’/a’ ratio, and peak systolic myocardial tissue velocity (s’a). The ratio of transmitral velocity at early diastole to peak early diastolic mitral annular velocity (E/e’), reported to correlate with left ventricular filling pressure, 24 was calculated.

Color tissue Doppler imaging of the LV free wall was obtained from the apical 4-chamber view using the smallest possible color sector and analyzed offline using QLAB (Philips Ultrasound, Bothell, WA, USA). A multisection curved M-line was positioned from the basal to the apical segments of the LV lateral wall to provide a spatial average of the peak systolic strain (ε), systolic strain rate (SR), early diastolic SR, and late diastolic SR. The ε and systolic and diastolic SR have been shown to be homogeneous from the apex to the base of the heart. 25,26 This spatial averaging further reduces the noise problems commonly associated with strain rate tracings.

Measurement of carotid arterial stiffness. A 7- to 15-MHz linear-array transducer was used to image the right and left common carotid arteries at about 1 cm below their bifurcation. The end-diastolic (Dd) and systolic (Ds) diameters were measured and the carotid arterial stiffness index was calculated as: ln [(SBP/DBP)/(Dd – Ds)/Dd] 27, where SBP and DBP are systolic and diastolic blood pressure. The stiffness index is considered relatively independent of systemic blood pressure. 27 The average of the right and left carotid arterial stiffness index, each derived from the values of 3 consecutive cardiac cycles, was used for subsequent analyses.

Statistical analysis. All data are presented as mean ± SD unless stated otherwise. Demographic and echocardiographic variables between patients and controls were compared by unpaired Student’s t test and Fisher’s exact test where appropriate. Pearson correlation analysis was used to assess for possible relationships between arterial stiffness and indices of LV function. Significant positive correlations were reexamined after adjustment for sex using multiple regression analysis. Multivariate stepwise regression analysis was used to identify independent determinants of carotid arterial stiffness index, indexed LV mass, MPI as an indicator of global myocardial function, εa as a marker of global LV diastolic function, 28 and systolic SR as a marker of LV systolic function. 29The absolute values of ε and SR were used to facilitate interpretation. A p value < 0.05 was considered statistically significant. All statistical analyses were performed with SPSS version 11 software (SPSS Inc., Chicago, IL, USA).

RESULTS

Subjects. Thirty-two patients and 15 control subjects were studied. The age at diagnosis of SLE in patients was 11.7 ± 3.4 years (range 4–17), the duration of disease was 6.3 ± 4.3 years (range 1–18), their SLEDAI was 4 ± 4 (median 4, range 0–13), and their SLICC/ACR Damage Index was 1.0 ± 1.5 (median 0, range 0–6). Of the 32 patients, 21 had nephritis, 11 had antiphospholipid antibodies, and 2 had antiphospholipid syndrome. At the time of study, 28 patients were taking prednisolone at a daily dose of 5.4 ± 3.9 mg, 20 hydroxychloroquine, 8 azathioprine, 8 mycophenolate mofetil, 6 nonsteroidal antiinflammatory drugs, 4 enalapril, and 1 each sulphasalazine, ramipril, and nifedipine. Table 1 shows demographic data and systemic blood pressure of patients and controls. There were no significant differences in age, sex distribution, body weight, body mass index, and systemic blood pressure between the 2 groups.

Echocardiographic measures. No patient had pericardial effusion or valvar abnormalities. Table 2 summarizes the M-mode and Doppler echocardiographic findings. Compared with controls, patients had thicker interventricular septum (p < 0.001), thicker LV posterior wall (p < 0.001), and greater indexed LV mass (p < 0.001). Patients had significantly lower LV fractional shortening (p = 0.02), ejection fraction (p = 0.02), and MVCFc (p = 0.02) than controls. Their ΔMVCFc were significantly more negative (p < 0.001), suggesting that measured MVCFc for the calculated wall stress was significantly lower than predicted.

Conventional Doppler echocardiography revealed that patients had significantly lower E wave velocity (p = 0.02), E deceleration time (p = 0.001), and E/A ratio (p = 0.006) compared to those of controls. The LV MPI was significantly higher in patients than controls (p < 0.001), which was related to a
shorter ejection time ($p < 0.001$) and a longer total duration of isovolumic contraction and relaxation times ($p < 0.001$).

Tissue Doppler imaging showed that patients had significantly lower $e_m$ velocity ($p < 0.001$), $e_m/a_m$ ratio ($p = 0.004$), and $s_m$ velocity ($p = 0.01$) than controls. The LV $\varepsilon$ and systolic and diastolic SR were all significantly reduced in patients with SLE ($p \leq 0.01$).

LV systolic dysfunction was reflected by more negative $\Delta$MVCFc, reduced LV free wall $\varepsilon$ and SR, and lower $e_m$ velocity, while diastolic dysfunction was evident from the reduced mitral E velocity, $e_m$ velocity, E/A and $e_m/a_m$ ratios, and diastolic SR and the longer mitral E deceleration time in patients with SLE. These cardiac measurements did not differ between patients with and those without antiphospholipid antibodies.

Carotid arterial stiffness. The right carotid arterial stiffness index was highly correlated with that of the left ($r = 0.81$, $p < 0.001$). The average arterial stiffness index of patients was significantly greater than that of controls ($4.9 \pm 1.0$ vs $3.5 \pm 0.5$; $p < 0.001$; Figure 1).

Univariate analysis showed that in patients with SLE, the carotid arterial stiffness index correlated significantly with SLEDAI ($r = 0.46$, $p = 0.009$; Figure 2) and SBP ($r = 0.49$, $p = 0.005$), but not with age, body mass index, DBP, SLICC/ACR Damage Index, daily steroid dose, and duration of disease. Stepwise multiple linear regression analysis revealed that SLEDAI ($8 = 0.37$, $p = 0.019$) and SBP ($8 = 0.43$, $p = 0.008$) remained significant correlates of carotid stiffness index after adjustment of the above variables.

Relation between arterial stiffness and LV structure and function. For the entire cohort, the average carotid arterial stiffness index correlated positively with LV posterior wall thickness ($r = 0.36$, $p < 0.001$), interventricular septal thickness ($r = 0.36$, $p = 0.02$), indexed LV mass ($r = 0.49$, $p = 0.001$), and MPI ($r = 0.43$, $p = 0.002$). On the other hand, the arterial stiffness correlated negatively with E wave velocity ($r = -0.32$, $p = 0.03$), $e_m$ velocity ($r = -0.46$, $p = 0.001$), LV $\varepsilon$ ($r = -0.59$, $p < 0.001$), LV systolic SR ($r = -0.51$, $p < 0.001$), early diastolic SR ($r = -0.61$, $p < 0.001$), and late diastolic SR ($r = -0.40$, $p = 0.009$) (Figures 3 and 4). These correlations remained statistically significant after adjustment for sex. Stepwise multiple linear

| Table 2. Comparisons of echocardiographic indices between patients and controls. |
|----------------------------------|----------------|----------------|-----|
|                                | Patients,     | Controls,      | p   |
|                                | $n = 32$      | $n = 15$       |     |
| M-mode measurements            |               |                |     |
| LV internal dimension at end-diastole, cm | $4.18 \pm 0.46$ | $4.43 \pm 0.33$ | 0.07 |
| LV internal dimension at systole, cm | $2.67 \pm 0.48$ | $2.76 \pm 0.28$ | 0.47 |
| Interventricular septum thickness at end-diastole, cm | $0.78 \pm 0.12$ | $0.60 \pm 0.08$ | <0.001* |
| LV posterior wall thickness at end-diastole, cm | $0.84 \pm 0.15$ | $0.63 \pm 0.07$ | <0.001* |
| LV mass index, g/m$^2$          | $72.6 \pm 11.5$ | $55.1 \pm 7.7$ | <0.001* |
| LV shortening fraction, %      | $34.9 \pm 4.0$ | $37.8 \pm 3.3$ | 0.02* |
| LV ejection fraction, %        | $72.3 \pm 4.9$ | $75.7 \pm 3.8$ | 0.02* |
| MVCFc, cm/s                    | $1.08 \pm 0.10$ | $1.16 \pm 0.12$ | 0.02* |
| $\Delta$MVCFc, cm/s            | $-0.10 \pm 0.11$ | $0.04 \pm 0.10$ | <0.001* |
| Mitral inflow Doppler indices   |               |                |     |
| E, cm/s                        | $84.7 \pm 17.1$ | $97.2 \pm 13.9$ | 0.02* |
| A, cm/s                        | $47.0 \pm 8.8$ | $43.4 \pm 7.8$ | 0.19 |
| E deceleration time, ms         | $166.0 \pm 29.0$ | $144 \pm 15$ | 0.001* |
| A deceleration time, ms         | $100 \pm 28.0$ | $86 \pm 11$ | 0.06 |
| E/A ratio                       | $1.9 \pm 0.5$ | $2.3 \pm 0.4$ | 0.006* |
| LV myocardial performance index | $0.33 \pm 0.08$ | $0.23 \pm 0.09$ | <0.001* |
| Sum of isovolumic contraction and relaxation times, ms | $93 \pm 24$ | $62 \pm 21$ | <0.001* |
| LV ejection time, ms            | $285 \pm 23$ | $307 \pm 15$ | <0.001* |
| Mitral annular myocardial tissue velocities |    |                |     |
| $e_m$, cm/s                     | $15.6 \pm 2.7$ | $18.9 \pm 2.1$ | <0.001* |
| $a_m$, cm/s                     | $6.9 \pm 1.4$ | $6.6 \pm 1.8$ | 0.57 |
| $s_m$, cm/s                     | $8.7 \pm 2.4$ | $10.6 \pm 2.0$ | 0.01* |
| $e_m/a_m$ ratio                 | $2.4 \pm 0.6$ | $3.1 \pm 1.0$ | 0.004* |
| $E/e_m$ ratio                   | $5.5 \pm 1.1$ | $5.2 \pm 0.8$ | 0.34 |
| LV free wall strain and strain rates |               |                |     |
| Systolic strain, %              | $10.6 \pm 2.1$ | $14.3 \pm 2.1$ | <0.001* |
| Systolic strain rate, /s        | $0.9 \pm 0.3$ | $1.4 \pm 0.6$ | 0.01* |
| Early diastolic strain rate, /s | $1.6 \pm 0.4$ | $2.3 \pm 0.6$ | <0.001* |
| Late diastolic strain rate, /s  | $0.6 \pm 0.3$ | $1.0 \pm 0.5$ | 0.01* |

A: mitral inflow peak velocity at late diastole; $a_m$: mitral annular late diastolic myocardial tissue velocity; E: mitral inflow peak velocity at early diastole; $e_m$: mitral annular early diastolic myocardial tissue velocity; LV: LV left ventricular; MVCFc: rate-corrected mean velocity of circumferential fiber shortening; $s_m$: mitral annular systolic myocardial tissue velocity. * Statistically significant.
regression analysis revealed that carotid arterial stiffness was a significant determinant of indexed LV mass \((p < 0.001)\), MPI \((p = 0.002)\), \(e_m\) velocity \((p = 0.001)\), and LV systolic SR \((p = 0.001)\) after adjustment for age, sex, body mass index, and systolic and diastolic blood pressure (Table 3). Among patients, these latter 4 indices of LV structure and function did not correlate with SLEDAI and SLICC/ACR Damage Index. On the other hand, among patients, the correlations between carotid arterial stiffness and indexed LV mass \((r = 0.43, p = 0.02)\), MPI \((r = 0.40, p = 0.033)\), \(e_m\) velocity \((r = -0.44, p = 0.014)\), and LV systolic SR \((r = -0.37, p = 0.042)\) remained significant. However, subgroup analysis of control subjects failed to find such correlations.

**DISCUSSION**

Our study provides the first evidence that systemic arterial stiffening is associated with LV hypertrophy and dysfunction in a young cohort of patients with pediatric-onset SLE. The carotid arterial stiffness, being significantly increased in patients with SLE, correlates with the disease activity score. Further, we have shown using multivariate analysis that carotid arterial stiffness is an independent determinant of LV mass and relative load-independent indices of LV systolic and diastolic function.

Comparatively little is known about systemic ventricular function of children and adolescents with SLE\textsuperscript{30, 31}. Studies in
adults with SLE have revealed echocardiographic abnormalities consistent with LV systolic dysfunction, albeit indices used were either qualitative or load-dependent. Using relatively load-independent indices, we have demonstrated the presence of LV systolic dysfunction even in our young cohort of patients with SLE, as reflected by more negative ΔMVCFc, reduced LV free wall systolic strain and strain rate, and lower mitral annular systolic velocity. Further, our findings of reduced mitral E velocity, $e_m$ velocity, E/A and $e_m/a_a$ ratios, and diastolic strain rates and the longer mitral E deceleration time in patients with SLE are consistent with LV diastolic dysfunction due to impaired relaxation. These findings corroborate and extend those reported in adults. While Cacciapuoti and colleagues attributed the increased LV MPI, and hence worse global myocardial performance, in patients with SLE to isolated impairment of LV relaxation, our findings suggest that both systolic and diastolic LV dysfunction contribute to an increase in LV MPI.

The cause of LV dysfunction in our young cohort of patients with pediatric-onset SLE remains speculative. In adults, LV dysfunction has been attributed to several factors including coronary arteritis, premature coronary artery arteriosclerosis, and myocardial inflammation and fibrosis. The possible association between anti-Ro/SSA and anti-La/SSB antibodies and myocarditis in children with SLE has been reported. In adults, anticardiolipin antibodies have been associated with LV dysfunction, although the mechanism remains elusive. Additionally, right ventricular dysfunction has been reported in lupus patients with anticardiolipin antibodies and antiphospholipid syndrome. In our study, however, we did not find associations between antiphospholipid antibodies and LV dysfunction. As only 2 patients had antiphospholipid syndrome, we did not explore its association with LV dysfunction. Myocardial perfusion studies performed in adolescent patients at a median age of 15.9 years revealed a 16% prevalence of coronary perfusion defects. These patients may thus be predisposed to early-onset ischemic heart disease and ventricular dysfunction. Indeed, carotid intimal-medial thickness, a surrogate marker of coronary arteriosclerosis, is significantly increased in patients with SLE. Our findings of a negative effect of carotid arterial stiffness on LV function suggest that arterial stiffening may also be contributory in the framework of ventriculo-arterial interaction.

We have demonstrated increased arterial stiffness in systemic vasculitis related to polyarteritis nodosa and Kawasaki disease. Recent studies performed in adult patients with SLE, aged 40 to 60 years, have similarly found an increase in stiffness of the carotid, carotid-femoral, and popliteal arterial segments. Our study extends the previous observations and shows that arterial stiffening in SLE may occur as early as adolescence. It is probable that immune complex-induced complement activation and inflammatory cell infiltration in the arterial wall may lead to elastase production and release of fibroblast growth factors that result in degradation of elastin and increased collagen synthesis, respectively. Indeed, we found a positive correlation between disease activity score and arterial stiffness in our young patients, which agrees with our previous findings in children with polyarteritis nodosa. It might be expected that arterial stiffness should relate to the disease duration, a relation that we failed to show. Nonetheless, its association with disease activity suggests that subjects with longstanding disease of low activity might be spared longterm cardiovascular dysfunction.

Our findings of arterial stiffening and its relations to LV function in a young adolescent cohort of patients with SLE have significant implications. Increased arterial stiffness has emerged as an independent cardiovascular risk factor. This is particularly relevant, as patients with SLE are known to be at risk of premature coronary artery disease. Arterial stiff-
ening increases the input impedance presented to the left ventricle and results in an unfavorable LV-arterial interaction\textsuperscript{42}. The increase in pulsatile afterload probably also contributes in part to increased LV mass in our normotensive patients. The decrease in central diastolic pressure as a result of arterial stiffening, in conjunction with myocardial hypertrophy and increased afterload, may predispose to subendocardial ischemia and interstitial fibrosis, which in turn can impair myocardial relaxation and reduce ventricular compliance\textsuperscript{43}. Indeed, the association between arterial stiffness and LV diastolic dysfunction has been reported in patients with hypertension\textsuperscript{43-45} and diabetes mellitus\textsuperscript{45,46}. The negative effect of arterial stiffness on LV contractility has similarly been reported in patients with beta-thalassemia major by our group\textsuperscript{47}.

Several limitations to our study deserve comments. First, myocardial perfusion scan was not performed to ascertain potential coronary arterial involvement. Nonetheless, the 16\% prevalence of perfusion defect in a previously reported cohort of similar age\textsuperscript{38} suggests that subclinical myocardial ischemia cannot wholly account for LV dysfunction. Second, the potential confounding effects of steroid and immunosuppressive therapy on ventricular function could not be assessed as most of our patients were on treatment. Nonetheless, immunomodulatory\textsuperscript{40} and cytotoxic\textsuperscript{41} therapy has been shown to improve cardiac dysfunction in lupus patients. It is also unlikely that steroid-induced systemic hypertension is the culprit as our patients were normotensive. Third, healthy siblings who might also be genetically predisposed to SLE were recruited as controls. They were nonetheless asymptomatic at the time of the study. Even if the genetic predisposition were to have any influence on the findings, the chance of detecting a significant difference between groups would be minimized rather than exaggerated. Fourth, the brachial systolic pressure may overestimate the carotid systolic pressure due to amplification along the arterial tree\textsuperscript{52}. The amplification is reduced in subjects with stiffer arteries\textsuperscript{53}, hence the observed arterial stiffening in patients with SLE is likely to be underestimated.

Arterial stiffening in adolescents and young adults with pediatric-onset SLE, albeit free of cardiac symptoms, probably contributes to subclinical LV dysfunction and hypertrophy. Whether strategies to reduce arterial stiffness would improve the ventricular function and reduce the risk of premature cardiovascular disease in these at-risk patients requires longitudinal studies for clarification.

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