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Echocardiographic Assessment of Diastolic Function in Children with Incident Systemic Lupus Erythematosus

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Abstract

Background: The timing and etiology of diastolic impairment in pediatric-onset systemic lupus erythematosus (SLE) are poorly understood. We compared echocardiographic metrics of left ventricular diastolic function in children at SLE diagnosis to controls and identified factors associated with diastolic indices.

Methods: Echocardiograms of children aged 5–18 years within 1 year of SLE diagnosis and age-/sex-matched controls were retrospectively read by blinded cardiologists. Clinical characteristics were abstracted separately. Z-scores for diastolic indices (E/A, e', E/e', and isovolumetric relaxation time (IVRT)) were calculated using published normative data and study controls, and compared using linear mixed-effects models adjusted for blood pressure. Pericardial effusions and valvular disease were also evaluated. Linear regression was used to identify factors associated with diastolic measures.

Results: 85 children with incident SLE had echocardiograms performed a median of 6 days after diagnosis (interquartile range (IQR) 1–70). Prior cumulative prednisone exposure was minimal

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(median 60 mg, IQR 0–1652). SLE cases had lower E/A, lower e', higher E/e', and longer IVRT compared to controls. Though none met criteria for Grade I diastolic dysfunction, Z-scores for e', E/e' and IVRT were abnormal in 30%, 25%, and 6% of SLE cases, respectively. Greater disease activity was associated with lower septal e' ($p<0.01$), higher E/e' ($p=0.02$), and longer IVRT ($p<0.01$).

Conclusion: Children with incident SLE have worse diastolic indices at diagnosis compared to peers without SLE, independent of blood pressure and prior to significant prednisone exposure. Longitudinal studies will determine whether diastolic dysfunction develops in this population over time.

Keywords

Pediatrics; Systemic lupus erythematosus; Echocardiography; Diastolic Function; Valvular Heart Diseases

Introduction

Echocardiographic evidence of chronic cardiac dysfunction has been described in adults with systemic lupus erythematosus (SLE), who have a 4.6-fold higher risk of heart failure compared to the general population [1]. The increased risk of heart failure is most pronounced in younger adults, with a 20-fold increased relative risk in those under age 35, and over a 50-fold increased risk in those ages 18–25 [1]. Youth with onset of SLE in childhood have more severe disease and are exposed to greater cumulative disease duration and medication use [2, 3]. Therefore, children with SLE may be at higher life-time risk for cardiac dysfunction or face the complications of heart failure at an earlier age.

While cardiac manifestations of SLE have traditionally included pericardial involvement, myocarditis, and Libman-Sacks endocarditis, awareness of other subclinical echocardiographic findings in both children and adults with SLE has increased in recent years [4–6]. Up to 72% of adults with SLE have echocardiographic evidence of left ventricular (LV) diastolic dysfunction [7–9], and valvular disease can be identified in up to 40–50% of adult patients by transthoracic echocardiogram [10, 11]. Evidence of diastolic impairment has also been described in small cross-sectional studies of children with SLE with varying disease duration [5, 12, 13]. These echocardiographic findings are frequently present in asymptomatic patients [14, 15] and may be potential precursors to heart failure. However, the etiology of diastolic dysfunction in SLE is not well understood and likely confounded by a high prevalence of cardiovascular risk factors, chronic medication exposure, and other secondary factors. Characterizing the prevalence of diastolic impairment in children near the initial onset of SLE and assessing the relationship between SLE manifestations and echocardiographic measures of diastolic health can inform the potential etiology of cardiac dysfunction in SLE and implementation of appropriate screening and treatment protocols.

The objectives of this study were to: 1) compare measures of LV diastolic function among children with SLE at the time of diagnosis compared to controls without SLE, and 2)

identify patient and disease characteristics associated with diastolic indices and other echocardiographic abnormalities.

Methods

Study Design:

This was a retrospective study of children with SLE at initial presentation to our tertiary care center. The study was approved by the Children's Hospital of Philadelphia (CHOP) Institutional Review Board.

Study Population:

All children and adolescents who were 1) diagnosed with SLE at CHOP between 2008 – 2016, 2) age 5–18 years old at the time of SLE diagnosis, 3) met revised American College of Rheumatology (ACR) [16] or Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE [17] and 4) underwent transthoracic echocardiography within one year of initial SLE diagnosis were eligible for inclusion. Patients with a history of congenital heart disease, familial cardiomyopathy, or acute rheumatic fever were excluded. Subjects with SLE were matched 1:1 by age and sex to a randomly selected control without SLE. The control population included children and adolescents evaluated with echocardiograms in the CHOP cardiology clinic during the same time period for the primary indication of benign murmur or chest pain who had no structural defects as determined by the initial echocardiogram. Patients with congenital heart disease, familial cardiomyopathy, acute rheumatic fever, other rheumatologic disorder, malignancy, hypertension, chronic kidney disease, or diabetes were excluded from the control population.

Study Procedures:

Each echocardiogram was re-read by one of two pediatric cardiologists (MDE and BRW) who were blinded to the group assignment and all clinical data, save age, sex, and body surface area. For diastolic parameters using tissue Doppler (mitral e' and E/e'), both medial and lateral mitral valve annulus measurements were recorded in the apical 4-chamber view. Isovolumetric relaxation time (IVRT) was measured offline using pulse wave tissue Doppler in the apical 4-chamber view.

Ten randomly selected echocardiograms were independently read by both readers and the intraclass correlation coefficient (ICC) was used to test the inter-rater reliability of each diastolic measurement. An ICC greater than 0.85 was considered excellent agreement. Baseline demographic and clinical characteristics as well as the indication for echocardiography were abstracted separately from the electronic medical record.

Study Measures:

The primary outcomes were echocardiographic parameters of LV diastolic function, including the mitral E/A ratio (peak early over peak late diastolic filling velocity), septal and lateral e' (early diastolic mitral annular velocity), E/e' ratio (peak early diastolic filling velocity over early diastolic mitral annular velocity), and isovolumetric relaxation time (IVRT, the time between aortic valve closure and mitral valve opening). As no single echocardiographic parameter alone defines diastolic dysfunction, each parameter was

analyzed both separately and in aggregate to determine the presence of LV diastolic dysfunction as defined by published American Society of Echocardiography (ASE) guidelines [18]. Two separate Z-scores for each diastolic parameter were also calculated using 1) published normative data in children and 2) the study control population [19]. Z-scores greater than +2 or less than -2 were considered abnormal.

Secondary outcome measures included the presence of pericardial effusion, valvular insufficiency, and left ventricular systolic function. Pericardial effusion was graded by size, and the presence of tamponade physiology was determined by right atrial or right ventricular collapse and exaggerated inspiratory decrease in mitral valve Doppler inflow velocity greater than 30%. Valvular insufficiency was assessed using color Doppler and graded as absent, trivial, mild, moderate or severe according to jet area and vena contracta [20]. LV systolic function was assessed by measuring the ejection fraction (LVEF) via Simpson's method via the apical 4- and 2-chamber views and shortening fraction (LVSF) from M-mode derived from 2D parasternal short-axis views.

Covariates for the comparison of SLE cases and controls included age, sex, race, ethnicity, body mass index percentile (BMI%ile) for age and sex, body surface area (BSA), hypertension (defined as a physician diagnosis of hypertension or ≥ 3 previously recorded office measurements above the 95th percentile for age, sex, and height), and systolic and diastolic blood pressure percentiles (BP%ile) at the time of echocardiography. For the analysis of SLE cases only, the primary exposure was the modified SLE disease activity index 2000 (SLEDAI-2K), which is a validated measure of disease activity in adults and children [21–23]. A SLEDAI-2K score of < 6 is considered low disease activity, 6–12 is moderate activity, and > 12 is high activity, up to maximum of 105). In addition, we abstracted baseline clinical manifestations (including nephritis, serositis, mucocutaneous features, hematologic features, neuropsychiatric involvement, arthritis, myositis, and vasculitic lesions as defined by ulcerations, gangrene, tender finger nodules, splinter hemorrhages, or biopsy/angiography proven vasculitis), laboratory values (complement C3 and C4 levels, urine protein:creatinine (UPC) ratio, serum albumin, sedimentation rate (ESR), C-reactive protein (CRP), low-density lipoprotein (LDL) and antiphospholipid antibodies), cardiovascular signs (tachycardia, murmur, gallop, rub), cardiovascular symptoms (chest pain, dyspnea), and cumulative oral glucocorticoid exposure preceding echocardiogram. A cumulative prednisone dose of 2500 mg (approximately 60 mg per day over 6 weeks) was considered chronic high dose steroid exposure.

Statistical Analysis:

Baseline clinical factors, demographic characteristics, and echocardiographic findings were summarized using standard descriptive statistics and compared using Student's t-test for continuous variables and chi-square or Fisher's exact tests for categorical variables. Normality of continuous variables was assessed using the Shapiro-Wilk test, and variables were natural log-transformed or dichotomized as appropriate.

Linear mixed-effects models accounting for matching were used to compare Z-scores (based on published normative data) for each of the diastolic indices among SLE cases to controls, with or without adjustment for BP%iles for age, sex and height. Other covariates, including

race, ethnicity, BMI%ile, and BSA were tested in the model and retained if the coefficient of interest changed by more than 15%. We performed several sensitivity analyses excluding SLE cases with non-trivial pericardial effusions, mitral valve insufficiency, and hypertension from the mixed-effects model to assess whether these SLE manifestations explained the differences in diastolic parameters between SLE cases and controls.

To explore which additional SLE patient factors might be associated with diastolic indices, we used univariable linear regression to estimate unadjusted associations between diastolic indices and SLE disease activity, as well as the covariates listed above and other echocardiographic findings. Covariates with p-values <0.1 on univariable analysis were included in multivariable models using stepwise forward selection. Additional covariates determined a priori to be of clinical significance (including hypertension, tachycardia, non-trivial pericardial effusions, non-trivial MR) were forced into the models and retained if coefficients of interest changed by more than 15%.

To identify laboratory markers or clinical signs and symptoms associated with the presence of non-trivial pericardial effusions or mitral valve insufficiency, we performed bivariate comparisons using Fisher's exact and Student's t-tests. All statistical analyses were performed using STATA (College Station, TX) version 14.2, and p-values <0.05 were considered statistically significant.

Results:

A total of 85 children met ACR and/or SLICC classification criteria for SLE and had baseline echocardiograms available for review. Median time from SLE diagnosis to echocardiogram was 6 days (interquartile range 1–70). The majority of baseline echocardiograms were performed for screening purposes (61%), while 16% were for cardiovascular symptoms/signs, and 23% were for other reasons including abnormal chest radiographs or hypertension. Baseline demographic and clinical characteristics of SLE cases and matched controls are shown in Table 1. Compared to age and sex-matched controls, a significantly higher proportion of SLE cases were non-White or had hypertension. There were no significant differences in BMI or BSA. Among SLE cases, disease activity at diagnosis was moderate to high (mean SLEDAI score 16.8 ± 9), however the median cumulative oral glucocorticoid exposure preceding echocardiogram was low (60 mg prednisone equivalents, IQR 0–1652 mg).

Echocardiographic Findings

Pericardial effusions were present in 33% of all SLE cases and 25% of SLE cases without cardiovascular symptoms, though the majority of effusions were trivial or mild (Table 2). Two of the five children with moderate sized effusions had evidence of early tamponade physiology. Mild valvular abnormalities were also common in SLE cases, including trivial aortic valve insufficiency (17%) and mild mitral insufficiency (6%), of which the majority were asymptomatic (Table 2). Trivial mitral insufficiency was identified in both SLE cases and controls, but significantly more prevalent among SLE cases (53% versus 35%, $p < 0.01$). In addition, one SLE case without referable cardiovascular symptoms had regional wall motion abnormalities in association with suspected coronary artery thrombosis due to

antiphospholipid antibody syndrome, and was excluded from the subsequent analysis of diastolic function.

LV Diastolic Function

Excellent inter-rater reliability was achieved for echocardiographic measures of diastolic function (ICC E/A 0.96 [95%CI 0.84 – 0.99]; septal E/e' 0.97 [0.87 – 0.99]; lateral E/e' 0.97 [0.85 – 0.99]; IVRT 0.88 [0.52 – 0.97]). Among SLE cases, 70 (83%) and 59 (70%) had evaluable tissue Doppler tracings at the septal annulus and lateral annulus, respectively. By ASE criteria, 5 (8%) SLE cases with evaluable tracings had abnormal lateral e' measurements (< 10 cm/s) and 1 (1%) had abnormal septal e' (< 7 cm/s), but none met criteria for Grade I diastolic dysfunction. In addition, 25/68 (37%) had prolonged IVRT > 70 ms corrected for age. Using published pediatric normative data, 31% of SLE cases had tissue Doppler e' Z-score < -2, 24% had E/e' Z-score > 2, and 6% had IVRT Z-score > 2 (Table 3). In comparison to study controls, SLE cases had significantly lower Z-scores for E/A and e', higher E/e', and longer IVRT, despite adjustment for diastolic blood pressure (Table 3). Results were similar among the subset of SLE cases without cardiovascular symptoms (N=60) and matched controls. In contrast, LV systolic function was preserved among SLE cases compared to controls (LVEF mean difference 1.6% (95%CI [-1.9, 5.1], p=0.36) and LVSF mean difference 1.6% (95% CI [0.16, 3.0], p=0.03)).

The sensitivity analysis excluding SLE cases with non-trivial pericardial effusions did not result in any significant changes in the estimates (Supplemental Table 1a). Exclusion of non-trivial mitral regurgitation from the analysis attenuated the estimated effect of SLE on septal E/e' (mean Z-score difference 0.2, 95% CI [-0.2, 0.6], p-value 0.23), but not on lateral E/e' (mean Z-difference 0.7, 95% CI [0.2, 1.1], p-value <0.01) or other diastolic parameters (Supplemental Table 1b). In contrast, exclusion of cases with a hypertension diagnosis attenuated the estimated effect of SLE on IVRT (mean Z-difference 0.3, 95% CI [-0.1, 0.7], p-value 0.14) (Supplemental Table 1c).

Clinical factors associated with diastolic measures

On univariable analysis, higher disease activity (particularly the vasculitis component of the SLEDAI) was significantly associated with worse diastolic indices, including lower septal e', higher E/e', and longer IVRT (Table 4). Markers of active nephritis, including proteinuria and hypoalbuminemia, were associated with lower E/A ratio, lower septal e' and longer IVRT. In contrast, mild-moderate pericardial effusions, presence of serositis (pericarditis or pleuritis), mild mitral insufficiency, and elevated C-reactive protein were most strongly associated with higher average E/e'. Of note, ESR, antiphospholipid antibodies, parenchymal lung disease (interstitial lung disease or pulmonary hemorrhage), and cumulative oral glucocorticoid use were not associated with any of the diastolic measures.

After multivariable adjustment, the presence of vasculitis was the only disease activity component independently associated with all tissue Doppler indices. Holding all other independent variables constant, the presence of vasculitis was associated with an average 1.5 cm/s decrease in septal e' (p<0.01), 1.2 cm/s decrease in lateral e' (p=0.13), 1.0 unit increase in average E/e' ratio (p=0.02), and 12.2 ms increase in IVRT (p<0.01) (Supplemental Table

2). Markers of renal disease activity were independently associated with septal e' and IVRT, with each log unit increase in urine protein:creatinine ratio resulting in a 0.3 cm/s decrease in septal e' ($p<0.01$) and 1.7 ms increase in IVRT ($p=0.10$), and each log decrease in C3 levels corresponding to a 6.4 ms increase in IVRT ($p=0.04$). The presence of non-trivial effusions and MR were independently associated with 3.1 cm/s and 3.4 cm/s decreases in e' ($p=0.01$ and $p=0.06$, respectively), and with 2.9 and 1.6 unit increases in E/e' ($p=0.01$ for both).

Clinical factors associated with valvular insufficiency and pericardial effusion

The presence of anti-cardiolipin IgG and anti-cardiolipin IgM antiphospholipid antibodies were the only clinical characteristics significantly associated with any degree of mitral valve insufficiency ($p=0.01$ and $p=0.03$, respectively). Restricting the analysis to the 5 SLE cases with greater than trivial mitral insufficiency also yielded a significant association with anti-cardiolipin IgG ($p=0.03$) but not anti-cardiolipin IgM antibodies ($p=0.13$) or cardiac murmurs ($p=1.00$). The presence of mild-moderate sized pericardial effusions were associated with non-White race ($p=0.05$), fever ($p=0.02$), tachycardia ($p<0.01$), and dyspnea ($p=0.02$). Hypoalbuminemia and elevated CRP levels were the laboratory abnormalities significantly associated with a higher prevalence of pericardial effusions ($p=0.03$ and $p=0.05$, respectively).

Discussion

We performed a retrospective analysis of echocardiographic measures of left ventricular diastolic function in a large pediatric SLE inception cohort as well as age- and sex-matched controls. The majority of echocardiograms were performed for screening purposes and within days of SLE diagnosis. There are several important findings from our study that have implications for echocardiographic assessment of cardiac function in this population. First, while no pediatric SLE cases met ASE criteria for diastolic dysfunction, nearly one-third of SLE cases had abnormal tissue Doppler Z-scores based on normative pediatric data, and all of the diastolic indices assessed were worse in SLE cases compared to controls despite preserved systolic function. Secondly, pericardial effusions and valvular insufficiency were common amongst SLE cases, but did not completely account for the differences in diastolic measures observed between SLE cases and controls. Lastly, increased SLE disease activity, especially the presence of vasculitis, was associated with worse parameters of diastolic function, suggesting that lupus-related inflammation may have detectable effects on myocardial function early on in the disease course.

The interpretation of diastolic function in pediatric-onset SLE is complicated by a number of factors, including the lack of pediatric-specific guidelines for evaluation of diastolic dysfunction, the heterogeneous disease phenotype, and treatment-related comorbidities. In our cohort, while individual diastolic parameters were significantly different in SLE cases compared to healthy controls and pediatric reference values, no patients met criteria for diastolic dysfunction according to ASE guidelines. This may reflect the limitations of applying cutoff values and diagnostic flowcharts based on an adult paradigm of diastolic dysfunction, which is frequently insufficient to correctly classify cardiac dysfunction in

children [24]. In addition, it is often unclear whether the differences in diastolic measures in this population are due to intrinsic properties of the myocardium, extrinsic factors such as pericardial effusions and valvular disease, or to an increased prevalence of traditional cardiovascular risk factors, such as hypertension and obesity. The evidence that measures of diastolic function are affected very early in the disease course of children with SLE provides some insight into the factors contributing to diastolic dysfunction in SLE. First, this population had not yet accumulated traditional cardiovascular risk factors, with the exception of hypertension among those with renal involvement, which was of relatively short duration and did not fully account for the differences in diastolic function between SLE cases and controls in our sensitivity analyses. Secondly, as the majority of baseline echocardiograms were performed within days of SLE diagnosis, the cumulative glucocorticoid exposure was small. Thus, it is reasonable to infer that these results are not due to accumulated medication toxicity or chronic exposure to steroid-induced hypertension.

With regard to other SLE manifestations which have the potential to exert secondary effects on diastolic measures, pericardial effusions and mild mitral valve insufficiency had the greatest magnitude of effect on lateral e' and E/e' measurements, and therefore need to be factored in when interpreting these values. In contrast, septal e' and IVRT appeared to be more influenced by measures of active renal disease such as proteinuria and hypocomplementemia, independent of hypertension. Thus, the effects of SLE on measures of diastolic function are multifactorial, and it may not be possible to determine a single metric by which diastolic health can be trended in this population. Rather, the echocardiographer needs to synthesize an overall diastolic assessment in the context of disease-specific factors. Of note, exclusion of children with non-trivial pericardial effusions, mitral valve insufficiency, and hypertension did not completely ameliorate the differences in diastolic function between SLE cases and controls. This suggests that there may still be intrinsic factors affecting myocardial stiffness in child-onset SLE that should be explored further.

In our study, diastolic parameters were associated with SLE disease activity, and in particular, vasculitic manifestations of SLE, which suggests that inflammation may play a direct role in diastolic function. Other authors have also hypothesized that a combination of direct myocardial injury [25] and chronic inflammation [26], may contribute to chronic ventricular dysfunction in adults with SLE. Interestingly, systolic function was preserved in our cohort relative to diastolic parameters. This is consistent with findings from studies in adults with SLE and the limited studies in children with SLE, suggesting that LV diastolic dysfunction frequently occurs in the setting of normal ejection fraction and may be present earlier in the disease course than systolic dysfunction [9, 12, 27]. Proposed mechanisms for inflammation resulting in increased diastolic stiffness include the generation of reactive oxygen species, endothelial activation and reduced nitric oxide bioavailability, coronary microvascular dysfunction, and intramyocardial immune deposits [28–31]. While no patients in our incident cohort had clinically significant alterations in diastolic function based on published guidelines, our findings suggest that the processes leading to diastolic dysfunction may begin at the initial onset of disease.

Although the level of disease activity at SLE presentation may correlate with baseline diastolic measures, it remains unclear whether diastolic measures improve with treatment or if cumulative disease burden contributes to future progression toward diastolic dysfunction. Based on cross-sectional studies in adults with prevalent SLE, we can hypothesize that at least a subset of patients may have worsening diastolic function over time, as longer disease duration has been shown to be significantly associated with LV diastolic dysfunction [8, 9]. Other studies in adults with SLE have shown that measures of cumulative disease burden such as the SLICC damage index (SDI) are more strongly associated with diastolic dysfunction than disease duration [32]. Therefore, future studies of diastolic function in children with SLE will need to consider both the impact of overall inflammatory burden starting from initial onset of disease and the potentially beneficial effects of SLE therapy. In addition, follow-up echocardiograms with reporting of diastolic measures should be considered in children who have had several years of disease, refractory disease, or accrual of disease damage.

There are several strengths of our study. First, to our knowledge this is one of the largest pediatric echocardiographic cohorts described for child-onset SLE. Second, the echocardiograms were performed close to the time of initial diagnosis, and therefore findings are less likely to be confounded by cumulative medication toxicity and chronic hypertension. Third, we demonstrated evidence of early diastolic impairment in children who largely underwent echocardiograms for screening purposes. Lastly, we have characterized the potential impact of lupus-specific factors on the interpretation of diastolic parameters. Our study is limited by its retrospective nature, in particular the risk of ascertainment bias. Not every provider routinely referred SLE patients for baseline echocardiograms, and those who did had echocardiograms performed for a variety of indications, including screening as well as diagnostic purposes. Additionally, the echocardiographic protocol was not prospectively standardized with the result that tissue Doppler imaging was not evaluable in all patients. Lastly, we do not have longitudinal data to study progression of disease. However, this study serves as a baseline from which prospective studies could be performed to evaluate changes in diastolic function and valvular health over time.

In conclusion, children with SLE have worse diastolic indices at onset of disease compared to peers without SLE, and a number of disease-related factors may influence measures of LV diastolic function, thus the relationship between cardiac function and SLE in childhood is complex. Therefore, it is our recommendation that diastolic parameters should be reported for all echocardiograms performed in children with SLE. While it remains unclear whether all children with SLE warrant routine screening echocardiograms, baseline assessment of diastolic function should be considered for children with severe disease. Longitudinal studies will determine whether early echocardiographic findings progress into diastolic dysfunction and whether they are prognostic of future cardiac complications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Baseline subject characteristics

	SLE (N=85)	Controls (N=85)	p-value
Age, mean (SD)	14.6 (2.9)	14.6 (2.9)	-
Female, n (%)	68 (80)	68 (80)	-
Race, n (%)			
White	28 (33)	50 (59)	<0.01
African American	32 (38)	15 (18)	
Asian	17 (20)	6 (7)	
Other	8 (9)	14 (16)	
Ethnicity, n (%)			
Non-Hispanic	68 (80)	76 (89)	0.17
Hispanic	11 (13)	6 (7)	
Hypertension, n (%)	18 (21)	0 (0)	<0.01
BMI %ile, mean (SD)	62.5 (28.8)	56.5 (29.1)	0.16
Body Surface Area	1.5 (0.3)	1.5 (0.3)	0.85
<i>SLE Disease Characteristics</i>			
Serositis, n (%)	20 (24)		
Nephritis	37 (44)		
Neuropsychiatric manifestation	9 (11)		
Arthritis	51 (60)		
Mucocutaneous manifestation	48 (56)		
Vasculitis	23 (27)		
Myositis	6 (7)		
Antiphospholipid antibodies ^a	46 (54)		
Absolute lymphocyte count < 1000/mm ³	34 (41)		
Absolute white blood cell count < 4000/mm ³	39 (47)		
Platelet count < 100,000/mm ³	20 (24)		
SLEDAI-2K ^b , mean (SD)	16.8 (9.1)		
Cumulative prednisone dose (mg) ^c , median [IQR]	60 [0–1652]		
Duration of prednisone use (days), median [IQR]	0 [0–3]		
Cardiac symptom ^d , n (%)	24 (28)		
Cardiac exam abnormality ^e	9 (11)		

^a Presence of medium-high titer anti-cardiolipin IgG/IgM, anti-β2 glycoprotein IgG/IgM, abnormal dilute Russell Viper Venom confirmatory test, or false positive rapid plasma reagin at initial evaluation

^b SLE disease activity index 2K (<6=low activity, 6–12=moderate, >12=high, max 98)

^c Cumulative oral glucocorticoid dose in prednisone equivalents before echocardiogram

^d Chest pain, dyspnea

^e Murmur, rub, gallop, tachycardia

Table 2.

Baseline echocardiographic findings in children with SLE versus controls

	Control N = 85	All SLE N = 85	p [*]	SLE without symptoms N = 61	p [^]
Effusion, n (%)	4 (5%)	28 (33%)	<0.01	15 (25%)	0.01
Trivial	4 (5%)	15 (18%)	<0.01	10 (16%)	0.02
Mild	0 (0%)	8 (9%)	-	2 (3%)	-
Moderate	0 (0%)	5 (6%)	-	3 (5%)	-
Tamponade physiology	0 (0%)	2 (2%)	0.25	1 (2%)	0.50
Regional wall abnormality	0 (0%)	1 (1%)	0.50	1 (2%)	0.50
AI, n (%)					
Trivial	1 (1%)	14 (17%)	0.01	9 (15%)	0.01
MR					
Trivial	30 (35%)	45 (53%)	<0.01	33 (54%)	0.02
Mild	0 (0%)	5 (6%)	-	2 (3%)	-

* All SLE cases (N=85) compared to age and sex-matched controls

[^] Children with SLE without cardiovascular symptoms compared to matched controls

AI = aortic valve insufficiency; MR = mitral regurgitation/insufficiency

Table 3.

Diastolic function in SLE cases compared to published reference values and study controls

Mitral	Evaluable N	Z > 2.0 ^a n (%)	Z _c > 2.0 ^b n (%)	Adjusted mean Z-score difference		
				β^c	95% CI	p-value
E/A ratio	72	0 (0%)	0 (0%)	-0.3	[-0.6, -0.0]	0.05
e' (septal)	70	19 (27%)	14 (20%)	-0.4	[-0.7, -0.1]	<0.01
e' (lateral)	59	18 (31%)	8 (13%)	-0.6	[-1.0, -0.3]	<0.01
E/e' (septal)	70	14 (20%)	12 (17%)	0.3	[-0.1, 0.7]	0.09
E/e' (lateral)	59	14 (24%)	23 (39%)	0.9	[0.4, 1.4]	<0.01
IVRT	68	4 (6%)	7 (10%)	0.4	[0.05, 0.8]	0.03

SLE cases with evaluable tracings (N) found to have abnormal diastolic measures according to Z-scores calculated from published normative pediatric data and study controls ($Z < -2.0$ for E/A or e', and $Z > 2.0$ for E/e' or IVRT were considered abnormal). One SLE case was excluded from the analysis due to regional wall abnormalities from suspected coronary thrombosis.

^aZ-scores according to published reference values (Eidem et al.)

^bZ-scores according to study controls

^cBeta coefficients represent mean differences in Z-scores between SLE cases and controls in linear mixed-effects models, adjusted for matching and diastolic blood pressure percentile-for-age-sex-height. Other baseline characteristics did not meet criteria for inclusion in the models.

Table 4.

Univariable associations between SLE characteristics and diastolic measures

Characteristic	E/A	Septal e'	Lateral e'	Average E/e'	IVRT
SLEDAI-2K	0.0	-0.1 ***	-0.1	0.1 **	0.9 ***
Nephritis	-0.2	-1.5 ***	-1.1	0.2	15.9 ***
ln(UPC)	-0.1 **	-0.3 ***	-0.3	0.1	2.6 ***
ln(C3)	0.0	1.1 ***	0.7	-0.2	-10.1 ***
Neurologic	-0.2	-1.8 **	-1.5	0.7	13.9 **
Vasculitis	0.0	-1.6 ***	-1.4	1.0 **	12.7 ***
Arthritis	-0.1	-0.3	-0.7	0.4	8.9 **
Myositis	-0.1	0.6	1.9	-0.5	16.3 **
Serositis	-0.1	-0.2	-2.0 **	1.6 ***	-1.9
Pleural effusion	-0.4 *	-0.9	-0.5	1.2 *	-0.4
Pericardial effusion	0.0	0.1	-3.0 **	1.3 **	0.9
Other echo findings					
MR, mild	-0.1	-0.4	-3.0	3.0 ***	-7.0
AI, any	-0.3 **	-1.3 *	-0.9	0.5	8.6
Lung disease	0.0	0.5	0.8	-0.2	13.1 *
Hypertension	-0.1	-0.8	-0.6	-0.2	14.5 ***
Albumin, serum	0.2 ***	0.8 **	0.9 *	-0.2	-5.2 **
Elevated CRP	-0.3 **	0.3	-1.0	0.9 **	-6.0

Beta coefficients from univariable linear regression models representing the expected change in each diastolic parameter for every one unit increase in the predictor of interest. No significant associations were observed between diastolic measures and demographic characteristics, BMI%ile, mucocutaneous features, hematologic manifestations, fever, Raynaud's, ESR, antiphospholipid antibodies or cumulative oral glucocorticoid dose (not shown).

SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; eGFR = estimated glomerular filtration rate; ln(UPC) = log transformed urine protein:creatinine ratio; ln(C3) = log-transformed complement component 3; MR = mitral regurgitation; AI = aortic insufficiency; LDL = low density lipoprotein; CRP = C-reactive protein

* p 0.10,

** p 0.05,

*** p 0.01