Original Article

Quantitative assessment of left ventricular systolic function in patients with systemic lupus erythematosus: a non-invasive pressure-strain loop technique

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Background: Systemic lupus erythematosus (SLE) is associated with a variety of cardiovascular diseases, even in the early stage of disease development. The purpose of this study was to quantitatively evaluate left ventricular (LV) systolic function in patients with SLE using a novel non-invasive pressure-strain loop (PSL) technique.

Methods: This prospective case-control study included 132 patients with SLE and 99 normal controls, all of whom underwent traditional transthoracic echocardiography. The LV myocardial work was evaluated with the PSL technique based on speckle tracking and brachial artery blood pressure. The differences among groups were compared, and the correlations between myocardial work, laboratory data, and disease activity were analyzed in the SLE group.

Results: Compared with the normal group, SLE patients had significantly higher global wasted work {GWW; SLE: 109 [82–150] mmHg%; controls: 66 [45–109] mmHg%; P<0.001} and impaired global work efficiency [GWE; SLE: 95% (94–97%); controls: 97% (96–98%); P<0.001]. Global work index (GWI) and global constructive work (GCW) did not show significant differences (P>0.05). Further subdivision analysis found that the increase of GWW and the damage of GWE were more obvious in SLE patients with high disease activity or severe diastolic dysfunction. Multivariate analysis revealed that increased erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), anti-phospholipid antibodies, peak strain dispersion, and SLE Disease Activity Index (SLEDAI) were independently associated with increased GWW (β=0.189, 0.230, 0.444, 0.111, and 0.180, respectively; all P<0.05) and damaged GWE (β=–0.184, –0.130, –0.468, –0.149, and –0.191, respectively; all P<0.05).

Conclusions: The non-invasive PSL can quantitatively evaluate the LV systolic function in SLE patients. This technique may provide a new method for monitoring cardiac function in chronic diseases.

Keywords: Systemic lupus erythematosus (SLE); pressure-strain loop (PSL); myocardial work

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Introduction

Systemic lupus erythematosus (SLE) is a multi-system autoimmune disease that is associated with a variety of complex cardiovascular diseases (incidence 48–78%). It often manifests as valvular disease, Libman-Sacks endocarditis, pericarditis, cardiomyopathy, coronary artery disease, arrhythmia, and pulmonary hypertension (1-3). Cardiac injury is the most common single cause of death in patients with SLE (4). Therefore, preclinical detection of left ventricular (LV) dysfunction is crucial to preventing adverse events for patients with SLE. Traditional echocardiography can evaluate cardiac systolic and diastolic function. However, cardiac function parameters and the ejection fraction are usually within the normal range in the early stages of SLE development; the effectiveness of traditional echocardiography is limited when there is only minor cardiac dysfunction (3,5).

In the last years, two-dimensional (2D) speckle tracking echocardiography (STE) has been widely applied in the detection of asymptomatic myocardial dysfunction in a variety of diseases, including SLE. It can accurately estimate longitudinal, radial, and axial deformation and function of the myocardium, and can be used to predict adverse cardiac events (6). Nevertheless, speckle tracking is load-dependent; preload and afterload can influence the result of STE, which may lead to underestimation of the true myocardial systolic function (7). Recently, Russell *et al.* (8) proposed a novel non-invasive LV pressure-strain loop (PSL) method to quantify myocardial work (MW), which corresponded well with invasive and direct measurement of MW. The PSL method improves the analysis of cardiac load dependence based on STE by taking into account the LV global longitudinal strain (GLS) and the afterload (9). Currently, MW has been used to evaluate the effect of cardiac resynchronization therapy on coronary heart disease and primary cardiomyopathy (10,11). Accordingly, we sought to assess subclinical cardiac damage with the aid of MW in SLE patients. We present the following article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-21-951/rc).

Methods

Study population

In accordance with the diagnostic criteria of SLE revised by the American College of Rheumatology and Systemic Lupus International Collaborating Clinics (ACR and SLICC) in 2012 (12), 150 SLE patients admitted to the Second Affiliated Hospital of Nanchang University between January 2020 and February 2021 were randomly selected for a prospective case-control study. Disease activity and disease-related damage were determined with the 2000 version of the SLE Disease Activity Index (SLEDAI-2K), which included 24 items that related to disease activity that was present within 10 days of interview (13).

All participants underwent standard trans-thoracic echocardiography to evaluate their cardiac structure and function, and their blood samples were examined with the following laboratory tests: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), cholesterol, triglyceride, and anti-nuclear antibody profile. Demographic, clinical, and laboratory results were obtained retrospectively via interviews and chart reviews. The exclusion criteria included any systemic disease, chronic kidney disease, intractable hypertension, congenital or acquired heart disease, and other connective tissue diseases. The control group consisted of 99 healthy individuals who were examined by us at the same time and of similar age, gender, and body mass index (BMI) as the SLE patients. The echocardiographic data of the control group showed that they had structurally normal hearts. All the patients had a normal LV ejection fraction (LVEF; >50%). The collection, storage, and use of all research data in this study were in accordance with the Helsinki Declaration (as revised in 2013). The study protocol was approved by the Ethics Committee of the Second Affiliated Hospital of Nanchang University, and individual consent for this prospective analysis was waived.

Standard echocardiographic assessment

Transthoracic echocardiography, using a 3.5-MHz electronic transducer equipped with the Vivid E95 ultrasound system (General Electric Vingmed Ultrasound, Milwaukee, WI, USA), was performed by the same experienced cardiac sonographer. The ultrasonic data were collected in accordance with the guidelines of the American Society of Echocardiography (ASE) and European Association for Cardiovascular Imaging (EACVI) (14). The end-diastolic interventricular septum thickness, LV posterior wall thickness, and end-systolic left atrial diameter (LAD) were measured on the parasternal long-axis section. The LV end-diastolic and end-systolic volumes (LVEDV, LVESV), LVEF, stroke volume (SV), and LA volume (LAV) were measured with Simpson's biplane method

from the apical 4- and 2-chamber views. The LV volume index (LVEDVI, LVESVI) and LA volume index (LAVI) were indexed to the body surface area (BSA). In the apical 4-chamber view, mitral peak early diastolic velocity (E) and peak late diastolic velocity (A) and tricuspid regurgitation (TR) velocity were measured with a pulsed wave Doppler, and the septal velocity (e') was measured with tissue Doppler imaging, which showed the average value of early peak velocity of the septal and lateral annuli.

Diastolic classification

According to the 2016 ASE guidelines, the LV diastolic function was classified as normal (E/A ratio ≥0.8; E/e' ratio <10; TR <2.8 m/s; LAVI ≤34 mL/m^2), grade I diastolic dysfunction (E/A ratio ≤0.8; E/e' ratio <10; TR<2.8 m/s; LAVI ≤34 or >34 mL/m^2), grade II diastolic dysfunction (E/A ratio >0.8:<2; E/e' ratio =10–14; TR >2.8 m/s; LAVI >34 mL/m^2), and grade III diastolic dysfunction (E/A ratio>2; E/e' ratio >14; TR >2.8 m/s; LAVI >34 mL/m^2) (15). The SLE patients were categorized into the following groups: group A, normal group (n=40); group B, grade I diastolic dysfunction (n=38); group C, grade II diastolic dysfunction (n=30); and group D, grade III diastolic dysfunction (n=24). The diastolic function of the included controls was in class I or normal.

Quantification of LV myocardial work

All participants assumed the left lateral position, and their brachial artery pressure was measured (taking the average value of 3 measurements) in the natural breathing state while connected to the electrocardiogram (ECG). Then, 2D images of apical 2-chamber, 3-chamber, and 4-chamber views of at least 3 cardiac cycles were digitally stored at a speed of 50–80 frames per second. Participants were encouraged to adjust their breathing during the acquisition to obtain high-quality images. Some participants with incomplete LV wrapping, blurred endocardial boundary, or obvious artifacts were excluded. Analysis of the images was done off-line on dedicated software (EchoPAC PC version 203; GE Healthcare, Horten, Norway).

Using the automated function imaging mode, the 3-, 4-, and 2-chamber views were selected in turn. The software automatically sketched the endocardial and epicardial boundaries to form regions of interest (ROIs) and manually adjusted to include the entire myocardial thickness. The system automatically analyzed the bovine eye map of 17 LV segments, as well as the GLS and peak strain dispersion (PSD) of the LV.

The PSL was derived using software which integrated LV strain and brachial blood pressure (BP). The apical 3-chamber view was used to identify openings and closures of mitral and aortic valves to define the duration of isovolumic contraction, ejection, and isovolumic relaxation (16,17). Subsequently, MW software constructed a global non-invasive LV PSL, and the following MW parameters were generated: (I) global work index (GWI; mmHg%): total work of the LV during a cardiac cycle; (II) global constructive work (GCW; mmHg%): the work of the function to lengthen during diastole and shorten during systole; (III) global wasted work (GWW; mmHg%): the work of LV myocardial lengthening/shortening that does not occur in the appropriate cardiac phase; and (IV) global work efficiency (GWE; %): the comprehensive estimation of LV performance calculated as [GCW/(GCW + GWW)] ×100%, which reflects the efficiency of energy expended during the cardiac cycle (*Figure 1*).

Statistical analysis

Statistical analysis was processed using a standard statistical software program (SPSS version 25.0; IBM Corp., Armonk, NY, USA). The normality of samples was evaluated using the Kolmogorov-Smirnov test. Continuous data that had a normal distribution were reported as mean ± standard deviation (SD); data with a non-normal distribution were reported as median (range). The unpaired Student's *t*-test was used to assess normally distributed data, and the Mann-Whitney test was used to compare non-normally distributed data. Categorical data were presented as absolute frequencies and percentages and compared with the chi-squared test or a Fisher exact test. For more than two groups of continuous variables which conformed to a normal distribution, one-way analysis of variance (ANOVA) was used to compare them; otherwise, the Kruskal-Wallis test was implemented. Pearson's correlation analysis was used to evaluate the correlation between different variables. A multiple linear regression model was used to determine whether the baseline parameters were independently correlated with the MW index. First, possible influencing factors were selected based on relevant expertise, such as SLEDAI score covered anti-double-stranded DNA antibodies; LAVI = LAV/BSA; E/A included E, A; and so on. Second, univariate analysis was performed, and independent variables with P<0.1 were

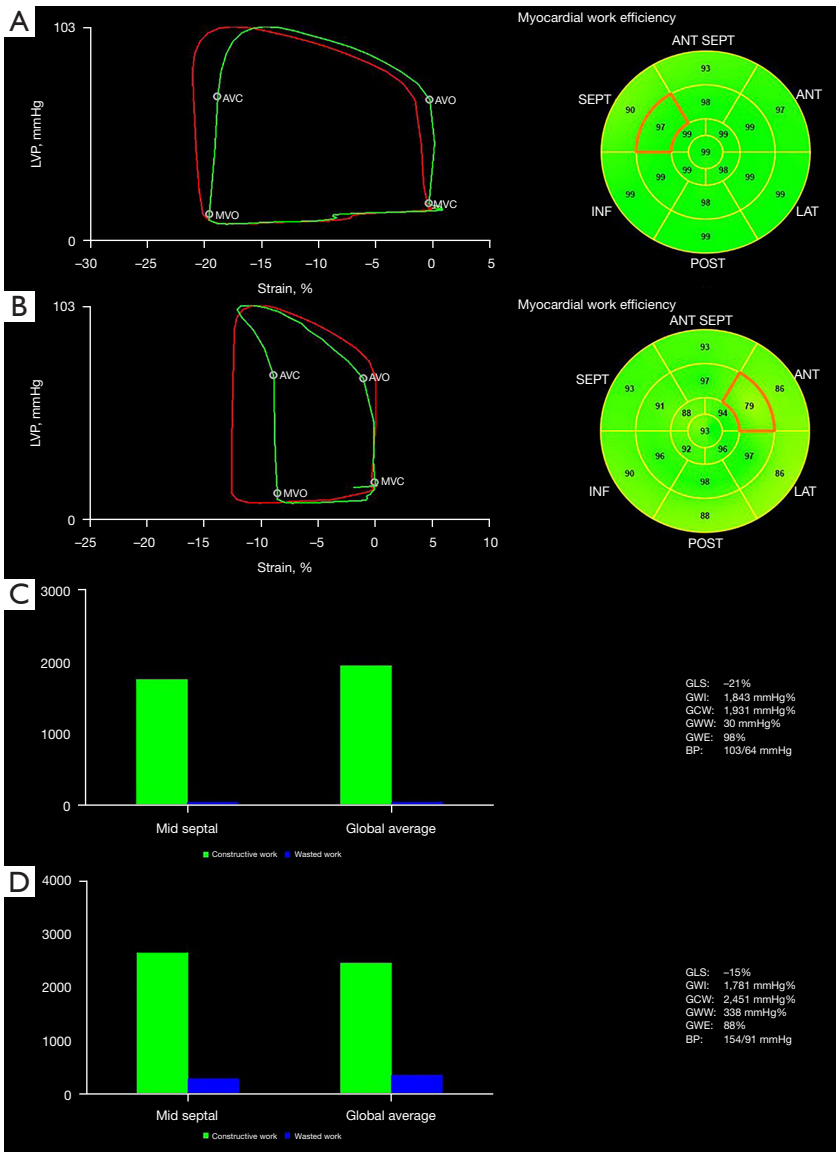

Figure 1 LV myocardial work of control and SLE. (A,C) Control. (B,D) SLE. For (A) and (B), the left side shows the PSLs and their area represents the work index (red ring refers to global; green refers to a segment); the right side is the bullseye plot of 17 segments, which shows the global work efficiency (GWE). For (C) and (D), the left side represents the constructive work (GCW, green column) and wasted work (GWW, blue column) of the mid-septal and the global, respectively; the right side shows the specific values of the parameters. Note the LV myocardium was damaged in SLE. LVP, left ventricular pressure; ANT, anterior; SEPT, septal; INF, inferior; LAT, lateral; POST, posterior; BP, blood pressure; LV, left ventricular; SLE, systemic lupus erythematosus; PSL, pressure-strain loop; GLS, global longitudinal strain; GWI, global work index; GWE, global work efficiency; GCW, global constructive work; GWW, global wasted work.

included in the multivariate analysis. All eligible variables were entered together to enable a comprehensive analysis. In the multivariate model, there was no multicollinearity between variables. All tests were bilateral, and $P<0.05$ was considered statistically significant.

Results

Baseline characteristics

Of the 150 patients, 18 were excluded; the final analysis was performed on 132 SLE patients. The patient screening

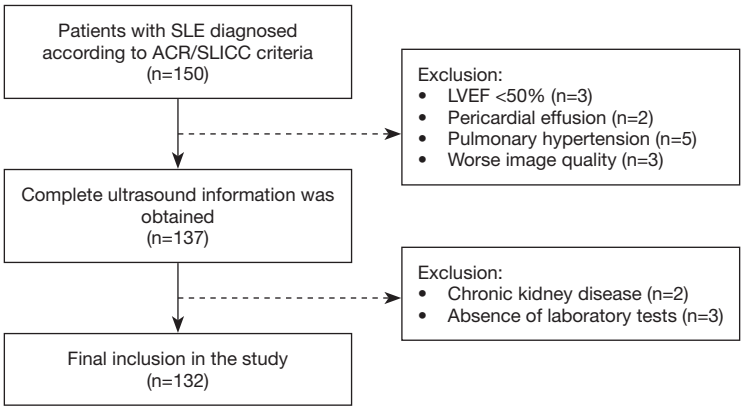

Figure 2 Patient screening flow diagram. SLE, systemic lupus erythematosus; ACR/SLICC, American College of Rheumatology/Systemic Lupus International Collaborating Clinics; LVEF, left ventricular ejection fraction.

process is shown in *Figure 2*. The demographic and clinical characteristics of the overall population are illustrated in *Table 1*. The SLE patients' mean age was 40.61±13.05 years, 116 (87.9%) were female, and their average disease duration was 5.61±4.19 years. The SLEDAI score range was 2 to 32 (13.08±6.46). Regarding laboratory examination: 35 patients (26.5%) showed positive anti-phospholipid antibodies, 102 (77.3%) showed positive anti-nuclear antibody, 48 (36.4%) showed positive anti-double-stranded DNA, and 20 (15.2%) showed positive anti-Smith antibodies. There was no significant difference in age, BMI, BSA, BP, and heart rate (HR) between SLE patients and healthy controls.

Standard echocardiographic parameters

Echocardiographic features are shown in *Table 2*. There was no significant difference in cardiac structure between SLE patients and the controls. The LAVI and E/e' ratios, which represent LV diastolic function, were significantly increased in the SLE group (P<0.05). The LVEF of all participants were within the normal range (>50%). The Tei index showed no significant difference (P=0.855). Meanwhile, the parameters of LV systolic function and synchronization, that is, GLS, were significantly reduced (–18.60%±1.92% *vs.* –20.22%±1.63%), and PSD was increased (47.96±15.34 *vs.* 38.42±9.59 ms) in the SLE group compared to the controls. According to the subdivision analysis of LV diastolic function and SLEDAI score, patients with worse diastolic function or a higher the SLEDAI score had lower GLS and higher PSD (*Table 3*).

Myocardial work analysis

Compared with the normal control group, GWW of SLE patients increased significantly {SLE: 109 [82–150] mmHg%; controls: 66 [45–109] mmHg%; P<0.001}, while GWE decreased significantly [SLE: 95% (94–97%); controls: 97% (96–98%); P<0.001], but there was no significant difference in GWI and GCW (P>0.05; *Table 2*). We hypothesized that disease activity would affect MW, and SLE patients were subdivided into the following groups based on the SLEDAI-2K: no or mild activity group (SLEDAI ≤9; n=39), moderate activity group (9< SLEDAI <15; n=49), and severe activity group (SLEDAI ≥15; n=44; *Figure 3A*). The GWW increased and GWE decreased in the severe activity group {176 [143–221] mmHg%; 93% (90–94%)} compared with the no or mild activity group {83 [66–101] mmHg%; 96% (95–97%)}. No statistically significant difference was found in GWI and GCW among the 3 groups (P>0.05).

Patients with abnormal diastolic function accounted for 69.7% of SLE patients, of which 28.8% were grade I, 22.7% were grade II, and 18.2% were grade III. The difference of MW parameters manifested in higher GWW and lower GWE in grade II {P<0.05; 136 [101–180] mmHg%; 94% (92–95%)}, and was further aggravated in grade III {P<0.05; 192 [126–252] mmHg%; 92% (89–94%); *Figure 3B*}. In addition, we further grouped SLE patients according to the presence or absence of traditional risk factors (concomitant hypertension, diabetes, hyperlipidemia). Pairwise comparison showed that there was no significant difference between the two groups of SLE patients, and GWE and GWW were significantly different from those of normal controls (*Table 3*).

Table 1 Baseline clinical characteristics of SLE patients and healthy controls

Variables	Controls (N=99)	SLE (N=132)	P value
Clinical characteristics			
Age (years)	41.02±13.32	40.61±13.05	0.817
Female gender, n (%)	80 (80.8)	116 (87.9)	0.138
BMI (kg/m^2)	21.98±1.98	22.29±2.68	0.085
BSA (m^2)	1.56±0.11	1.58±0.09	0.186
SBP (mmHg)	121.99±12.43	121.72±19.08	0.902
DBP (mmHg)	76.84±8.75	78.36±12.61	0.306
HR (beats/min)	74±11	77±8	0.078
Diabetes mellitus, n (%)	0 (0)	11 (8.3)	0.003
Hypertension, n (%)	0 (0)	20 (15.2)	<0.001
Hypercholesterolemia, n (%)	0 (0)	29 (21.97)	<0.001
Duration of SLE (years)	–	5.61±4.19	–
SLEDAI score	–	13.08±6.46	–
Positive anti-phospholipid antibodies, n (%)	–	35 (26.5)	–
Positive anti-nuclear antibody, n (%)	–	102 (77.3)	–
Positive anti-double-stranded DNA, n (%)	–	48 (36.4)	–
Positive anti-Smith antibodies, n (%)	–	20 (15.2)	–
Medications, n (%)			
Steroid	–	66 (50.0)	–
Cyclophosphamide	–	15 (11.4)	–
Methotrexate	–	9 (6.8)	–
Rituximab	–	4 (3.0)	–
Hydroxychloroquine	–	58 (43.9)	–
Tacrolimus	–	13 (9.8)	–
Mycophenolate mofetil	–	8 (6.1)	–
Cyclosporine	–	1 (0.8)	–

Values are presented as mean ± SD (continuous data) or numbers (%) (categorical data). SLE, systemic lupus erythematosus; BMI, body mass index; BSA, body surface area; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; SLEDAI, SLE Disease Activity Index; SD, standard deviation.

Associations between baseline characteristics and MW index in SLE

We used linear-regression analysis to examine indicators that affected MW parameters. Univariate analysis was used to screen the relevant indexes, and all variables with P<0.1 were included in the multivariate analysis. Finally, the multiple linear regression model was found to be statistically significant (GWW: R^2=0.883; F=91.545; P<0.001. GWE: R^2=0.804; F=49.627; P<0.001). The increases of ESR, CRP, anti-phospholipid antibodies, PSD, and SLEDAI were independently correlated with GWW (β=0.189, 0.230, 0.444, 0.111, 0.180, respectively; all P<0.05) and GWE (β=–0.184, –0.130, –0.468, –0.149, –0.191 respectively; all P<0.05; *Table 4*). In addition, GLS correlated with GWE and GWW (GEW: r=–0.667; P<0.001. GWW: r=0.665; P<0.001). The E/A was independently correlated with

Table 2 Comparison of conventional echocardiography and myocardial work data in SLE and controls

Variables	Controls (N=99)	SLE (N=132)	P value
LAD (mm)	31.32±2.71	31.45±3.26	0.745
LAVI (mL/m^2)	28.19 (27.06–29.87)	29.73 (28.7–30.96)	<0.001
IVSd (mm)	9.00 (8.00–10.00)	9.00 (8.00–10.00)	0.316
PWTd (mm)	9.00 (8.00–9.00)	9.00 (8.00–10.00)	0.420
E/A ratio	1.29 (1.18–1.43)	1.28 (0.79–1.59)	0.394
E/e' ratio	8.55 (7.60–9.42)	9.90 (8.34–12.32)	<0.001
Tei index	0.29 (0.23–0.36)	0.29 (0.24–0.35)	0.855
LVEDVI (mL/m^2)	56.32±5.71	55.03±8.02	0.152
LVESVI (mL/m^2)	20.58±3.07	21.69±4.35	0.816
LVEF (%)	63.51±3.72	62.48±4.36	0.060
SV	55.70±6.14	54.04±7.78	0.072
GLS (%)	–20.22±1.63	–18.60±1.92	<0.001
PSD (ms)	38.42±9.59	47.96±15.34	<0.001
GWE (%)	97 [96–98]	95 [94–97]	<0.001
GWI (mmHg%)	1,865±325	1,846±334	0.657
GCW (mmHg%)	2,103±309	2,198±318	0.024
GWW (mmHg%)	66 [45–109]	109 [82–150]	<0.001

Continuous values are presented as mean ± standard deviation (normally distributed) or median (range) (non-normally distributed). LAD, left atrial diameter; LAVI, left atrial volume index; IVSd, interventricular septum thickness in diastole; PWTd, posterior wall thickness in diastole; E/A, peak early diastolic velocity/peak late diastolic velocity; E/e', peak early diastolic velocity (by pulsed-wave Doppler)/early diastolic peak velocity (by tissue Doppler); LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end- systolic volume index; LVEF, left ventricular ejection fraction; SV, stroke volume; GLS, global longitudinal strain; PSD, peak strain dispersion; GWE, global work efficiency, GWI, global work index; GCW, global constructive work; GWW, global wasted work.

GWW (β=0.074; P<0.05; *Figure 4*).

Reproducibility of MW analysis

Repeated measurements of MW parameters were performed on 15 randomly selected participants, and the intra-observer and inter-observer reliability were analyzed by intra-class correlation coefficient (ICC). All ICC values were >0.75, which indicated good inter-observer and intra-observer repeatability (*Table 5*).

Discussion

The main finding of this study was that it is feasible to quantify LV MW in SLE patients using a non-invasive PSL analysis. Compared with the control group, PSD and GWW of SLE patients increased significantly, while GLS and GWE decreased, but there was no significant difference between GWI and GCW. In addition, disease activity impacted LV function. When the disease was highly active, GWW increased and GWE decreased significantly. Finally, ESR, CRP, anti-phospholipid antibodies, PSD, and disease activity were independently correlated with the GWW and GWE. Therefore, GWW and GWE of LV may provide further insights into early LV remodeling in SLE. As far as we know, this was the first study to quantitatively evaluate LV MW in SLE using non-invasive PSL analysis.

Recently, the prevalence of SLE has increased (18). Long-term chronic inflammation and an abnormal immune system can lead to different degrees of cardiovascular disease, which has become one of the main causes of death in patients (19). Studies have found that 40–50%

Table 3 Subdivision analysis of patients with or without traditional diseases, disease activity, and diastolic function in SLE

Groups	GLS (%)	PSD (ms)	GWE (%)	GWI (mmHg%)	GCW (mmHg%)	GWW (mmHg%)
With or without traditional risk						
Controls (n=99)	−20.22±1.63	38.42±9.59	97 [96–98]	1,865±325	2,103±309	66 [45–109]
No traditional risk SLE (n=93)	−18.72±1.99*	46.45±13.80*	95 [94–97]*	1,823±331	2,189±318	106 [78–148]*
With traditional risk SLE (n=39)	−18.31±1.75*	51.56±18.20*†	95 [92–96]*	1,897±337	2,219±319	110 [84–165]*
SLEDAI score						
≤9 (n=39)	19.82±1.43	40.00±11.26	96 [95–97]	1,842.31±312.28	2,133.89±296.52	83 [66–101]
10–14 (n=49)	19.14±1.58*	45.98±15.07*	96 [95–97]	1,873.10±342.82	2,221.31±312.53	97 [82–114]*
≥15 (n=44)	16.91±1.43*†	57.23±14.20*†	93 [90–94]*†	1,818.25±347.72	2,229.89±339.67	176 [143–221]*†
LV diastolic function						
Normal (n=40)	19.3±1.77	41.43±11.30	96 [95–97]	1,861.50±307.36	2,194.63±265.00	91 [71–110]
Grade I (n=38)	19.29±1.63	43.00±9.91	96 [95–97]	1,860.61±323.25	2,160.29±305.39	86 [69–109]
Grade II (n=30)	18.27±1.87*†	49.97±13.02*†	94 [92–95]*†	1,811.73±366.92	2,174.27±346.19	136 [101–180]*†
Grade III (n=24)	16.75±1.29*†‡	64.21±18.90*†‡	92 [89–94]*†	1,838.33±367.58	2,293.88±376.96	192 [126–252]*†

*, P<0.05: significantly different compared with Controls, SLEDAI ≤9 or normal; †, P<0.05: significantly different compared with no traditional risk SLE, SLEDAI 10–14 or Grade I; ‡, P<0.05: significantly different compared with Grade II. SLE, systemic lupus erythematosus; GLS, global longitudinal strain; PSD, peak strain dispersion; GWE, global work efficiency; GWI, global work index; GCW, global constructive work; GWW, global wasted work; SLEDAI, SLE Disease Activity Index; LV, left ventricular.

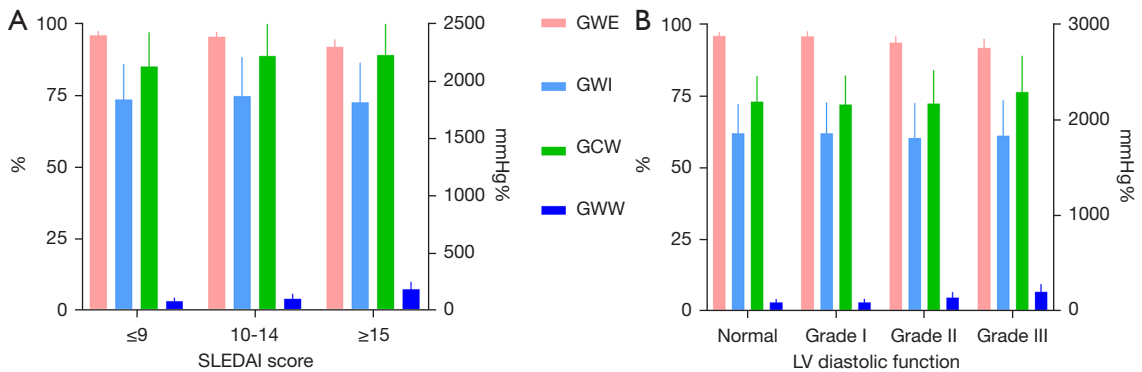

Figure 3 Grouping analysis was performed according to SLEDAI score (A) and LV diastolic function (B). The Y axis on the left corresponds to GWE, while the right corresponds to GWI, GCW, and GWW. SLEDAI, systemic lupus erythematosus Disease Activity Index; LV, left ventricular; GWE, global work efficiency; GWI, global work index; GCW, global constructive work; GWW, global wasted work.

of SLE patients without cardiovascular-related clinical manifestations before death have histological evidence of myocardial involvement at autopsy, which indicates the existence of subclinical cardiovascular damage (20,21). In these patients, cardiovascular damage tends to progress faster and cannot be explained by traditional disease factors, such as hypertension, hyperlipidemia, or diabetes (22). Previous animal models and clinical studies have shown that lupus-related risk factors play a key role in the pathogenesis of cardiovascular disease, but the mechanism of accelerated disease progression is still unclear (23). Early cardiac involvement in SLE is difficult to detect because of subtle clinical manifestations and limitations of current diagnostic tools.

Table 4 Potential associated factors of GWW and GWE in SLE patients

Variables	Univariable analysis		Multivariable analysis	
	β-coefficient	P value	β-coefficient	P value
GWW				
ESR	0.539	<0.001	0.189	<0.001
CRP	0.695	<0.001	0.230	<0.001
Anti-phospholipid antibodies	0.817	<0.001	0.444	<0.001
Anti-nuclear antibody	0.095	0.279		
Anti-Smith antibodies	–0.004	0.966		
HP	0.087	0.322		
SLEDAI score	0.719	<0.001	0.180	<0.001
Duration	0.159	0.069	0.048	0.140
LAVI	0.313	<0.001	0.039	0.305
IVSd	0.172	0.048	0.035	0.290
PWTd	0.093	0.291		
E/A	0.409	<0.001	0.074	0.049
E/e’	0.444	<0.001	–0.003	0.932
PSD	0.675	<0.001	0.111	0.009
GWE				
ESR	–0.498	<0.001	–0.184	<0.001
CRP	–0.610	<0.001	–0.130	0.013
Anti-phospholipid antibodies	–0.796	<0.001	–0.468	<0.001
Anti-nuclear antibody	–0.091	0.298		
Anti-Smith antibodies	–0.035	0.688		
HP	–0.067	0.444		
SLEDAI score	–0.689	<0.001	–0.191	0.001
Duration	–0.161	0.066	–0.059	0.167
LAVI	–0.293	0.001	–0.053	0.276
IVSd	–0.153	0.079	–0.021	0.635
PWTd	–0.111	0.205		
E/A	–0.386	<0.001	–0.081	0.095
E/e’	–0.373	<0.001	0.081	0.110
PSD	–0.665	<0.001	–0.149	0.007

GWW, global wasted work; GWE, global work efficiency; SLE, systemic lupus erythematosus; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; HP, hypertension; SLEDAI, SLE Disease Activity Index; LAVI, left atrial volume index; IVSd, interventricular septum thickness in diastole; E/A, peak early diastolic velocity/peak late diastolic velocity; E/e’, peak early diastolic velocity (by pulsed-wave Doppler)/early diastolic peak velocity (by tissue Doppler); PSD, peak strain dispersion; PWTd, posterior wall thickness in diastole.

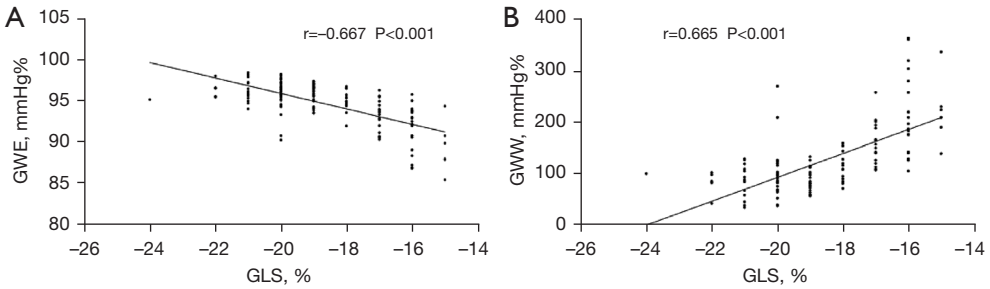

Figure 4 Correlation between myocardial work parameters and GLS. (A) Correlation between GWE and GLS. (B) Correlation between GWW and GLS. GLS, global longitudinal strain; GWE, global work efficiency; GWW, global wasted work.

Table 5 Interobserver and intraobserver variability

Variables	Interobserver variability			Intraobserver variability		
	ICC	95% CI	P value	ICC	95% CI	P value
GLS	0.959	0.884–0.986	<0.001	0.956	0.875–0.985	<0.001
PSD	0.984	0.953–0.994	<0.001	0.993	0.978–0.998	<0.001
GWI	0.942	0.839–0.980	<0.001	0.948	0.854–0.982	<0.001
GCW	0.997	0.996–1.000	<0.001	0.993	0.980–0.998	<0.001
GWW	0.964	0.945–0.994	<0.001	0.981	0.946–0.994	<0.001
GWE	0.950	0.859–0.983	<0.001	0.978	0.938–0.993	<0.001

ICC, intraocular correlation coefficient; CI, confidence interval; GLS, global longitudinal strain; PSD, peak strain dispersion; GWI, global work index; GCW, global constructive work; GWW, global wasted work; GWE, global work efficiency.

In the past few years, speckle tracking has become an effective means of evaluating LV function in SLE patients, and early use of GLS can improve its risk stratification. However, GLS is load-dependent and may be limited by changes in hemodynamic conditions. Russell *et al.*'s (8,24) non-invasive LV PSL is a new technique for indirectly measuring myocardial metabolism and oxygen consumption, which studies show is clinically beneficial and can identify early abnormalities of LV function. Currently, MW has made significant progress in the diagnosis and treatment of cardiovascular diseases, such as cardiac resynchronization therapy (10,11), acute coronary syndrome (25,26), hypertension (27), dilated/hypertrophic cardiomyopathy (28), cardiac amyloidosis (29). These studies have shown that MW provides incremental value for the evaluation of LV function. A study conducted in 2020 (17) showed that non-invasive PSL can be used to evaluate LV function in patients with chronic kidney disease. Both GLS and MW are sensitive indexes that assess LV systolic function and may guide the early treatment of asymptomatic patients with subclinical LV dysfunction (30). Previous studies have also shown that MW is superior to GLS in predicting outcomes and detecting coronary heart disease and may find subclinical disorders that GLS cannot show (17,31,32). Furthermore, previous studies have considered patients with absolute GLS values <18% to have LV systolic insufficiency (33-35). In this regard, we performed further analysis: we divided SLE patients into ≥18% and <18% groups and found that the differences in GWE and GWW were statistically significant from the normal group regardless of whether GLS was impaired in SLE patients, and were more pronounced in those with <18%, which suggested that PSL parameters may be able to detect subclinical myocardial damage earlier than current methods (*Table 6*).

In this study, MW and GLS parameters of SLE patients without typical cardiovascular symptoms were compared with those of normal controls. The results showed that GLS, PSD, and MW in SLE patients with normal LVEF were significantly different from controls, indicating that GWW and GWE may reflect subclinical myocardial

Table 6 Subdivision analysis of whether GLS is impaired in SLE

Groups	GWE (%)	GWI (mmHg%)	GCW (mmHg%)	GWW (mmHg%)
Controls (n=99)	97 [96–98]	1,865±325	2,103±309	66 [45–109]
≥18% (n=90)	96 [95–97]*	1,859±330	2,185±313	89 [72–114]*
<18% (n=42)	93 [90–94]*†	1,815±344	2,227±330*	186 [141–222]*†

*, P<0.05: significantly different compared with controls; †, P<0.05: significantly different compared with ≥18%. GLS, global longitudinal strain; GWE, global work efficiency; GWI, global work index; GCW, global constructive work; GWW, global wasted work; SLE, systemic lupus erythematosus.

function damage. The increase of GWW led to the decrease of GWE, suggesting that the myocardial energy metabolism was abnormal in SLE patients. The MW parameters in SLE patients were close to normal values, which is similar to previous studies (36,37). The difference in LV systolic function between SLE patients and healthy controls was not significant, which indicated that systolic function was well protected during the first years of the disease. Moreover, LV systolic dysfunction in SLE patients is time-dependent, with reduced LVEF that usually occurs in patients with a disease duration of more than 10 years (38). Most of the SLE patients included in this study had the disease for <10 years, and myocardial damage may not have been significant, leading to results close to normal values. At the same time, ESR, CRP, antiphospholipid antibodies, and disease activity were independently associated with GWW and GWE. This is consistent with previous findings that inflammatory status (measured by CRP levels), disease activity (measured by SLEDAI-2K, faster ESR also indicates that the disease is in the active stage), and increased antiphospholipid antibodies may individually or synergistically affect cardiovascular health (39). In addition, E/e' and E/A correlated with PSL parameters, although E/e' lost statistical significance in the multifactorial analysis. This shows that there are many factors affecting systolic function, but this does not affect the overall conclusion of the study. The study showed that PSD was significantly increased, indicating that there was LV contraction asynchrony. A large amount of energy was wasted on the segments of non-synchronous contraction, which could not effectively promote LV ejection, and this led to the increase of GWW. This may be related to various inflammatory factors, immune factors, and cytokines that act on cardiomyocytes or the conduction system, which may result in diffuse fibrosis, edema, myocyte necrosis, endothelial damage, ventricular remodeling, and premature atherosclerosis (30,40,41). All these events are associated with increased cardiovascular mortality.

The factors affecting MW are complex, and the geometry, volume, and wall stress of the LV significantly affect the estimation of MW. The non-invasive PSL technique can be widely used in patients with no significant LV remodeling in the early stage of the disease, such as cardiotoxicity caused by hypertension, diabetes, chemotherapy, and chronic diseases. The main advantage of the non-invasive PSL technique is that brachial artery BP replaces the invasive measurement of LV pressure, which overcomes the inevitable afterload of GLS.

Limitations

This study had several limitations. Our study was a single-center cross-sectional study with possible selection bias and lacked long-term follow-up of patients. Therefore, a larger-scale prospective study is needed to further explore the prognostic significance of the findings. Non-invasive PSL is novel and advanced, requires extremely high image quality, and it is necessary to clearly display the endocardial boundaries and the opening and closure of mitral and aortic valves. In addition, data suggested that mitral regurgitation had an effect on PSL, which was not considered in this study. Finally, the drugs used by patients may have protective or promoting effects on cardiovascular injury.

Conclusions

Our study revealed that the efficiency of myocardial energy utilization in SLE patients is significantly impaired. Furthermore, ESR, CRP, antiphospholipid antibody, and disease activity may be potential drivers for the impaired myocardial energy consumption. This simple and non-invasive PSL technique may become a new method to assess and monitor LV systolic function of SLE patients. Further prospective studies are needed to confirm these results and to explore whether MW has incremental value in risk

stratification in these patients.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-21-951/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-21-951/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of the Second Affiliated Hospital of Nanchang University, and individual consent for this prospective analysis was waived.

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