Original papers

Med Ultrason 2016, Vol. 18, no. 1, 47-56
DOI: 10.11152/mu.2013.2066.181.zdr

Subclinical myocardial impairment in SLE: insights from novel ultrasound techniques and clinical determinants.

Gabriel Guşetu[1,2], Dana Pop[1,2], Cristina Pamfil[2,3], Raluca Bălaj[3], Lucian Mureşan[1,2], Gabriel Cismaru[1,2], Roxana Matuz[1], Radu Roşu[1,2], Dumitru Zdrenghea[1,2], Simona Rednic[2,3]

[1]Department of Cardiology, Clinical Rehabilitation Hospital, [2]„Iuliu Hatieganu" University of Medicine and Pharmacy, [3]Department of Rheumatology, Emergency Clinical County Hospital, Cluj-Napoca, Romania

Abstract

Aims: Myocardial damage is frequent and often silent in systemic lupus erythematosus (SLE). The aim of the study was to determine the prevalence of myocardial damage by novel ultrasound techniques and to systematically assess the relationship between subclinical cardiac dysfunction and SLE-related clinical parameters. **Material and methods:** Seventy-five consecutive SLE patients without evidence of cardiac disease and seventy-three controls underwent standard transthoracic echocardiography using classical and novel ultrasound techniques: tissue Doppler imaging and speckle tracking echocardiography. Patient characteristics, cumulative organ damage and laboratory data were retrieved by medical chart review. **Results:** Within the cohort, 89.3% of the patients were female; mean±SD age and median (IQR) disease duration were 43.2±12.5 years and 8.03(6.3) years, respectively. SLE patients exhibited a significant decrement in endocardial longitudinal strain (-18.4% vs 19.3%, p=0.001) compared with controls. Diastolic dysfunction was detected in 34 (45.3%) of SLE patients. Major determinants of systolic and diastolic dysfunction were hypertension (p=0.023 and p<0.001, respectively), associated antiphospholipid syndrome (APS) (p<0.001 and p<0.001, respectively), cumulative damage accrual (p<0.001 and p=0.003, respectively), and disease duration (p=0.03 and p<0.001, respectively). Notably, anti-Ro antibodies were present in 37% of the SLE patients who had better systolic longitudinal performance. Neither disease activity, nor specific organ involvement, were associated with myocardial impairment. **Conclusion:** Systolic longitudinal and diastolic performance impairments are frequent findings in SLE patients without overt cardiovascular disease. Cumulative organ damage, disease duration, APS, and hypertension are major determinants for early heart involvement in SLE patients.

Keywords: systemic lupus erythematosus, systolic dysfunction, diastolic dysfunction, tissue Doppler, speckle tracking echocardiography.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown origin characterized by the production of autoantibodies to structures of the cell nucleus which potentially involves all organ systems. Patients with SLE have up to a seven-times higher cardiovascular risk and higher mortality rates compared with the general population [1,2].Cardiovascular mortality remains unchanged in SLE over the last decades, despite significant improvement in diagnosis and therapy [3]. Many factors contribute to the cardiovascular morbidity in SLE; in addition to the classical cardiovascular risk factors, the proatherogenic effect of systemic inflammation, autoantibodies against HDL cholesterol and the thrombotic risk due to antiphospholipid antibodies are a few [1]. Accordingly, the American Guidelines for the Prevention of Cardiovascular Disease in Women include SLE patients in the high risk group for cardiovascular disease [4].

In SLE, myocardial damage occurs secondary to hypoperfusion and inflammation and, even though silent for

Received 23.07.2015 Accepted 24.09.2015
Med Ultrason
2016, Vol. 18, No 1, 47-56
Corresponding author: Prof. dr. Dana Pop, MD, PhD
Department of Cardiology,
Clinical Rehabilitation Hospital,
46-50 Viilor Street,
Cluj-Napoca 400347, Romania
Phone: 0040 744 159 933
Fax: 0040 364 818 027
E-mail: pop67dana@gmail.com

a period of time, it often results in heart failure [5,6]. As subclinical atherosclerosis requires the control of cardiovascular risk factors [1] the detection of subclinical myocardial damage could warrant the initiation of preventive interventions proven beneficial in heart failure.

Echocardiography is a non-invasive and feasible tool used to assess myocardial impairment in conditions which evolve towards heart failure. For instance, the mitral diastolic blood flow and mitral annular diastolic excursion performed by Doppler ultrasound provide detection of diastolic dysfunction (DD) [7]. The systolic performance can be measured by a series of modern ultrasound techniques. These techniques allow the quantification of both segmental and global myocardial deformation. The speckle tracking analysis [8] is a technique independent of the examination angle, that assesses left ventricular myocardial deformation by tracking the systolic (and diastolic) excursion of 20-40 pixel markers (speckles) resulting from the interaction of myocardial tissue with the ultrasound beam; from frame-by-frame analysis of the trajectory of these speckles, the ultrasound machine determines myocardial deformation in longitudinal, circumferential and radial direction [8]. It thus has become the reference tool in the detection of the subtle, early impairment of systolic function in ischemic or valvular heart disease and some metabolic or toxic cardiomyopathies [9-11].

In the setting of these advances, our study aims to assess the impairment of left ventricular (systolic and diastolic) performance, as an early evidence of myocardial involvement in SLE, as well as to provide insight into its possible determinants, in order to help target SLE patients at risk in the absence of overt cardiac disease.

Material and methods

Patients

Seventy-five SLE patients, who fulfilled the 2012 *Systemic Lupus International Collaborating Clinics* classification criteria [12], were compared with seventy-three age and sex matched controls without any known cardiac disease, including hypertension as defined by the ESH/ESC guidelines [13].

Between July 2102 and December 2014 all patients underwent evaluation of cardiovascular risk factors (smoking, obesity, dyslipidemia, diabetes mellitus, and arterial hypertension), a thorough history taking for cardiovascular disease, and standard (12-lead) electrocardiography (ECG). Transthoracic echocardiography was performed to assess heart chambers, valve morphology, hemodynamics and left ventricular longitudinal systolic dysfunction by speckle tracking analysis. Laboratory and immunological data (antiphospholipid antibodies and SLE specific autoantibodies: antinuclear, anti-dsDNA, anti-Ro, anti-Sm), disease characteristics [1,12], disease activity (Systemic Lupus Erythematosus Disease Activity Index - SLEDAI) and damage accrual (Systemic Lupus International Collaborating Clinics damage index- SDI) were retrieved by medical chart review. Disease characteristics were considered if present any time after diagnosis. The SLEDAI and SDI scores were calculated within a maximum 3 month time frame, while the time frame for registering antibody test results was within 1 year from the cardiovascular assessment. Exclusion criteria were: any history of cardiomyopathy, myocarditis, ischemic heart disease, clinically significant valvular heart disease, symptoms or signs (chest pain/discomfort, dyspnea, palpitations, syncope, any heart murmurs or abnormal cardiac sounds) or ECG evidence of cardiac disease (supraventricular or ventricular arrhythmias, abnormal axis deviation, atrial or ventricular enlargement, atrioventricular block, bundle branch block, ST segment deviation or abnormal T wave inversion). Patients with an improper acoustic window for standard transthoracic cardiac ultrasound views were also excluded.

The study was conducted in accordance with the Helsinki Declaration for human studies and was approved by the institutional ethical committee. All patients gave a signed informed consent.

Echocardiography

Transthoracic echocardiography was performed using a 3.5 MHz transducer on an Esaote MyLab50 XVision echo machine. Long axis, short axis, two and four chamber views were obtained in order to perform M-mode and B-mode (2D) measurements of the right ventricle, left atrium and left ventricle (LV) diameters and volumes and LV ejection fraction (LVEF). LVEF was calculated using the modified Simpson's method from an apical four-chamber view. Valvular morphology (prolapse, flail leaflet, vegetations or calcifications) was studied and pulsed, continuous, and color Doppler measurements were applied to quantify valvular regurgitation [14]. Pulmonary arterial systolic pressure was calculated as the estimated right atrial pressure added to the peak tricuspid regurgitation gradient recorded in the four chamber view by continuous-wave Doppler [15].

LV diastolic performance was assessed by pulsed-wave Doppler measurement of the mitral E (early diastolic) and A (late diastolic) inflow velocities. The E/A ratio and deceleration time (DT) of the early filling velocity were also recorded. Additional mitral annular septal early (E'_s) and late (A'_s) diastolic velocities were assessed by tissue Doppler imaging. The E/E' ratio was calculated in

order to estimate LV filling pressure and to distinguish a normal inflow pattern from pseudonormal LV filling (both with an E/A ratio = 0.8-1.5). DD was categorized in three stages [7]: normal (E/A ratio = 0.8-1.5, DT=160-200 ms, $E'_s \geq 8$ cm/s, $E/E_s' < 8$), 1st degree (E/A ratio < 0.8, DT > 200 ms, $E'_s < 8$ cm/s, $E/E_s' < 8$), 2nd degree (E/A ratio = 0.8-1.5, DT=160-200 ms, $E'_s < 8$ cm/s, E/E_s'= 9-14), 3rd degree (E/A ratio > 2, DT <160 ms, $E'_s < 8$ cm/s, $E/E_s' \geq 15$). According to these parameters, the patients were assigned to one of the three DD stages.

Endocardial longitudinal strain was measured by speckle tracking analysis from apical two-chamber (2C) and four-chamber (4C) views. 2D cine-loops recordings (triggered by onset of the R wave on the ECG signal) at a frame rate of 64 fps were acquired and stored on the Esaote Mylab 50 for offline analysis. Offline analysis of the digital loops was performed using XStrain™ software (Esaote, Florence). The endocardial border was drawn by the operator on a single frame; thirteen points were established for the six segments in both apical four-chamber and two-chamber views, with the first point of each segment being the last of the previous one. Endocardial longitudinal strain and strain rate were calculated as the average value of peak systolic strain (strain rate) for the 12 segments; the longitudinal strain is expressed as negative values, a lower strain being represented by a less-negative value [16].

Statistical analysis

Statistical analysis was performed by dedicated software (SPSS for Windows v 20.0, IBM Corporation, Chicago, IL, USA). The Kolmogorov–Smirnov test was used to assess the normal distribution of continuous numerical variables. Results are presented as numbers and percentages for qualitative variables, as mean ± standard deviation for variables with normal distribution and as median values for non-parametric variables.

Comparisons between qualitative variables, variables with normal distribution and non-parametric variables were performed using the χ^2 test, Student t-test, and Man-Whitney u-test, respectively. Spearman's coefficient was

Table I. Clinical features of SLE patients and controls

	SLE patients n=75	Controls n=73	p value
Female, n (%)	67 (89.3)	67 (91.8)	0.611
Age*, years	43.2 ± 12.5	41.8 ± 11	0.494
Age at SLE onset* , years	33.4 ± 10.6	-	-
Time since diagnosis**, years	8.03 (6.3)	-	-
CV risk factors			
Smoking, n (%)	13 (17.3)	16 (21.9)	0.486
Hypertension, n (%)	20 (26.6)	0	-
Diabetes, n (%)	4 (5.3)	6 (8.2)	0.488
Dyslipidemia, n (%)	34 (45.3)	22 (30.1)	0.057
Obesity, n (%)	17 (22.6)	16 (21.9)	0.914
Renal, n (%)	26 (34.6)	-	-
Neuropsychiatric, n (%)	17 (22.6)	-	-
Skin, n (%)	44 (58.6)	-	-
Raynaud's phenomenon	10 (13.3)	-	-
Musculoskeletal, n (%)	64 (85.3)	-	-
Eye, n (%)	3 (4.0)	-	-
Heart ***, n (%)	21 (28.0)	-	-
Pericardial effusion, n (%)	19 (25.3)	-	-
Endocarditis, n (%)	3 (4.0)	-	-
Hematological, n (%)	27 (36.0)	-	-
Pleural effusion, n (%)	18 (24.0)	-	-
Associated AID, n (%)	21 (28.0)	-	-
Vasculitis	11 (14.6)	-	-
Sjogren's syndrome	8 (10.7)	-	-
Other AID	4 (5.3)	-	-

* expressed as mean± standard deviation; **expressed as median (interquartile range); ***with the exception of prior myocarditis and ischemic heart disease; CV- cardiovascular; SD- standard deviation; AID- autoimmune diseases; SLE- systemic lupus erythematosus. Note: disease characteristics were considered according to [1] and [12]

used for correlations and multivariate analysis was performed using linear regression (the stepwise method). Two-sided values of $p < 0.05$ were considered statistically significant.

Results

Out of 110 SLE patients initially assessed, eight had atherosclerotic cardiovascular disease (ischemic heart disease, ischemic stroke and peripheral artery disease), four had symptoms suggestive for a cardiac illness (dyspnea and/or palpitations), two were previously diagnosed with pulmonary embolism, one with myocarditis, and one had moderate mitral regurgitation. A proper ultrasound view was lacking in 19 patients. Among the remaining 75 SLE patients, 89.3% were female with a mean age of 43.2±12.5 years; age and gender were similar with controls, as shown in Table I. Cardiovascular risk factors were present in 50 (66.6%) patients, and hypertension was registered only in the SLE group, according to the study design.

The echocardiographic parameters of SLE patients and controls are presented in Table II. The diameters and volumes of the heart chambers were comparable in both groups, with the exception of the left atrium, which reached higher parameters in SLE patients, although within normal range. No significant structural valvular abnormalities were found. Three patients had a history of Libman-Sacks endocarditis, but valvular regurgitation was mild in all cases.

DD was significantly more prevalent in the SLE group vs. controls (45.3% vs. 8.2%, $p<0.001$), the majority of patients (73.5%) were classified as having 1st degree diastolic dysfunction.

Among cardiovascular risk factors, DD was associated with hypertension ($p<0.001$) and obesity ($p=0.039$); DD remained significantly prevalent in SLE patients without HTN (55 patients) vs. controls (30.9% vs 8.2%, $p=0.002$).

DD was associated with older age and SLE disease duration. Specific organ involvement in SLE did not impact on the accrual of DD (Table III), but cumulative organ damage, strongly correlated with the impairment of the diastolic performance ($p=0.003$). Other disease characteristics, such as specific autoantibodies, hypocomplementemia, or disease activity were not associated with DD parameters. However, we established a strong association between the presence of antiphospholipid syndrome (APS) and DD ($p<0.001$). Furthermore, the systolic pulmonary arterial pressure was higher among DD patients ($p=0.01$). The sPAP values did not differ

Table II. Echocardiographic parameters in SLE patients and controls

	SLE patients n=75	Controls n=73	p value
LV parameters			
LVEF*, %	61.3 ± 7.4	62.5 ± 6.7	0.335
LVEDD*, mm/m2	28.9±3.3	28.1±2.9	0.107
LVEDV*, ml/m2	57.4± 12.9	54.1+12.7	0.115
LA parameters			
LA diameter*, mm/m2	20.9±3.0	19.1±2.56	0.01
LA volume*, ml/m2	27.0±7.1	22.5±4.68	0.001
Pericardial effusion	0	0	
Valvular regurgitation			
AR, n (%)	4 (5.3)	3 (4.1)	0.965
MR, n (%)	42 (56)	29 (39.7)	0.068
TR, n (%)	67 (89.3)	54 (74)	0.028
PSAP*, mmHg	27.1 ± 9.5	19.9 ± 6.7	< 0.001
Diastolic dysfunction, n (%)	34 (45.3)	6 (8.2)	< 0.001
E/A ratio*	1.1 ± 0.35	1.3 ± 0.33	0.001
DT*, ms	219.4 ± 61.5	177.5 ± 27.6	< 0.001
E's*, cm/s	10 ± 2.1	10 ± 2.3	0.243
E/E'* ratio	8.3 ± 3.2	6.6 ± 1.53	0.001
ELS**, %	-18.4 (4.2)	-19.3 (2.3)	0.001
ELSR**, s-1	1.02 (0.23)	1.10 (0.15)	< 0.001

*expressed as mean±standard deviation; **expressed as median (interquartile range); SLE- systemic lupus erythematosus; LV- left ventricle; LVEF- left ventricle ejection fraction; LVEDD- LV end-diastolic diameter; LVEDV- LV end diastolic diameter; LA- left atrium; AR- aortic regurgitation; MR- mitral regurgitation; TR- tricuspid regurgitation; PSAP- pulmonary systolic arterial pressure; DT- deceleration time (of E wave); ELS- endocardial longitudinal strain; ELSR- endocardial longitudinal strain rate; IQR- interquartile range.

however, in the subgroups having DD and APS versus DD without APS (28 vs 24 mmHg, p=0.32)

LV systolic performance, conventionally evaluated by the LVEF, was normal among SLE patients and comparable with controls (Table I). However, longitudinal systolic performance (longitudinal systolic shortening) evaluated by ELS and ELSR was significantly lower in SLE patients (Table II); the difference remained significant after the removal of hypertensive patients (-18.8% vs -19.3%, p=0.015), since none of the controls had hypertension. Furthermore, hypertension proved to be a determinant of both systolic longitudinal and diastolic performance (Table IV). Based on ELS and ELSR, patients with a longer disease duration had significantly diminished longitudinal kinetics (r=-0.251, p=0.03 and r=-0.241, p=0.037, respectively), but longitudinal systolic performance did not correlate with age (p=0.081 and p=0.111). As expected, ELS and ELSR were lower in patients with DD (p<0.01).

Similarly with previous results, cumulative organ damage and APS were determinants of the systolic longitudinal performance. Regarding different serological patterns among APS patients, we observed a tendency of patients with lupus anticoagulant to have lower ELS values (-13.1% vs -15.5% for patients with anti-cardiolipin antibodies), but the number of patients was most likely too small to reach statistical significance (p=0.318). Anti-Ro antibodies were the only disease specific autoantibodies associated with ELS values. The variables found to be associated with ELS by univariate analysis were further analyzed by linear multivariate analysis. APS and SDI predicted systolic longitudinal dysfunction (Table V). Moreover, the systolic performance steeply decreased with each additional 1 point of the SDI (fig 1), although neither the ELS nor the ELSR were influenced by specific organ involvement. No associations were found between disease activity and ELS (p=0.165) or ELSR (p=0.281).

Table III. The impact of disease characteristics on myocardial diastolic performance in SLE patients

	With diastolic dysfunction n=34	**Without diastolic dysfunction n=41**	**p value**
Age*, years	48.1 ± 12.2	39 ± 11.1	0.001
Age at diagnosis*, years	32.5 ± 10.6	34.5 ± 10.29	0.474
Disease duration**, years	10.7 (10.8)	4.8 (6.3)	<0.001
Organ system involvement			
Renal, n (%)	14 (41.1)	12 (29.2)	0.404
Neuropsychiatric, n (%)	8 (26.5)	9 (19.5)	0.66
Skin, n (%)	25(73.5)	19 (46.3)	0.115
Musculoskeletal, n (%)	31 (91.1)	33 (80.4)	1
Hematological, n (%)	10 (29.4)	17 (41.4)	0.208
Pericarditis, n (%)	11 (32.3)	8 (19.5)	0.163
Pleural effusion, n (%)	9 (26.4)	9 (21.9)	0.624
Immunological tests, n(%)			
ANA	31 (91.2)	36 (87.8)	0.722
ANA titer, mean	1/524	1/516	0.494
Anti-dsDNA	11 (32.4)	17 (41.5)	0.567
Anti-Ro	7 (20.6)	21 (51.2)	0.013
Anti-Sm	1 (2.9)	3 (7.3)	0.623
C3 hypocomplementemia	9 (26.4)	16 (39)	0.579
C4 hypocomplementemia	8 (23.5)	12 (29.2)	0.472
CRP, mg/dl	0.5 (0.5; 0.6)	0.5 (0.5; 0.6)	0.3
APS, n (%)	19 (55.9)	2 (4.9)	<0.001
Activity index (SLEDAI)	2.0 (0; 6)	0.5 (0; 6)	0.394
SDI>1, n (%)	22 (82.3)	21 (51.2)	0.003
sPAP*, mmHg	30.4 ± 11.4	24.2 ± 6.2	0.01
ELS**, %	-16 (2.6)	-19.7 (2.0)	<0.01
ELSR**, s^{-1}	0.9 (0.22)	1.08 (0.16)	< 0.01

*expressed as mean±standard deviation; **expressed as median (interquartile range); ANA- antinuclear antibodies; CRP- C-reactive protein; APS- antiphospholipid syndrome; ELS- endocardiallongtudinal strain; ELSR- endocardial longitudinal strain rate; SDI- Systemic Lupus International Collaborating Clinics damage index; SLEDAI- Systemic Lupus Erythematosus Disease Activity Index.

Table IV. Longitudinal systolic performance in SLE versus controls

	ELS, %	p	ELSR, s^{-1}	p
CV risk factors				
Hypertension	-15.7 vs -18.8	0.023	0.89 vs 1.05	0.024
Obesity	-16.2 vs -18.6	0.074	0.93 vs 1.06	0.052
Diabetes	-18.3 vs -18.4	0.768	0.99 vs 1.02	0.981
Dyslipidemia	-18.7 vs -17.7	0.840	1.06 vs 1.01	0.774
Smoking	-17.2 vs -18.4	0.417	0.96 vs 1.02	0.433
Organ involvement				
Renal	-16.9 vs -18.5	0.743	1.00 vs 1.04	0.469
Neuropsychiatric lupus	-16.5 vs -18.9	0.108	0.98 vs 1.05	0.279
Skin	-16.6 vs -19.1	0.106	0.94 vs 1.08	0.096
Musculoskeletal	-18.4 vs -17.7	0.869	1.02 vs 1.07	0.714
Hematological	-18.8 vs -18.0	0.683	1.05 vs 1.00	0.389
Pericarditis	-18.4 vs -18.3	0.435	1.01 vs 1.05	0.135
Pleural effusion	-17.1 vs -18.7	0.547	0.94 vs 1.04	0.289
Immunological tests				
ANA	-18.4 vs -17.6	0.516	1.07 vs 1.02	0.618
Anti-dsDNA	-18.6 vs -18.3	0.948	1.01 vs 1.07	0.463
Anti-Ro	-19.7 vs -17.0	0.003	1.08 vs 0.97	0.002
Anti-Sm	-18.2 vs -18.4	0.680	1.12 vs 1.02	0.264
Low complement				
C3hypocomplementemia	-19.1 vs -18.3	0.617	1.03 vs 1.02	0.468
C4hypocomplementemia	-18.1 vs -18.4	0.783	0.99 vs 1.04	0.971
APS	-15.1 vs -19.2	< 0.001	0.87 vs 1.07	< 0.001
SDI≥1	-16.5 vs -19.8	< 0.001	0.94 vs 1.12	<0.001

ANA – antinuclear antibodies; CRP – C-reactive protein; APS – antiphospholipid syndrome; ELS – endocardiallongtudinal strain; ELSR – endocardial longitudinal strain rate; SDI – Systemic Lupus International Collaborating Clinics damage index; SLEDAI – Systemic Lupus Erythematosus Disease Activity Index.

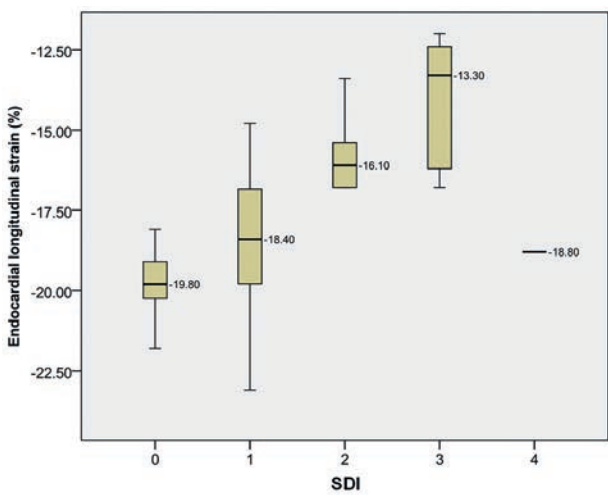


Fig 1. The impact of damage accrual on endocardial longitudinal strain. SDI- Systemic Lupus International Collaborating Clinics damage index.

Table V. The main determinants of endocardial longitudinal strain

	B-coefficient	Significance	95% C.I. for B	
			Lower	Upper
Hypertension	-0.785	0.156	-1.876	0.306
SDI	-0.696	0.003	-1.151	-0.241
APS	-2.834	<0.001	-3.997	-1.672
Anti-Ro	0.726	0.166	-0.309	1.761

SDI – Systemic Lupus International Collaborating Clinics damage index; C.I. – confidence interval; APS – antiphospholipid syndrome.

Discussions

SPECT and cardiac MRI studies on small patient series have shown that myocardial impairment occurs early in SLE, long before symptom onset [5,17]. Our study shows that the latest ultrasound techniques, such as 2-D speckle-tracking strain analysis and tissue Doppler imaging of the mitral ring are able to detect early myocardial

impairment in asymptomatic SLE patients with no history or evidence of cardiovascular disease. Our observations are in line with previous studies, which demonstrated impairment of either diastolic [18] or systolic [19] myocardial performance in SLE, although their precise determinants remain unknown.

Our study found DD in almost half (45.3%) of lupus patients and a significantly decreased systolic longitudinal myocardial performance compared with controls. Several studies assessed DD in SLE patients [18,20] and showed that DD, along with pulmonary hypertension (even mild), are markers of early cardiac involvement in SLE patients. Shang et al showed that DD correlates with the long-term inflammatory burden as assessed by SDI [18]; moreover, another study demonstrated hat DD is diagnosed in patients with clinically inactive disease [21]. Our study confirms the relationship between DD and cumulative organ damage and reinforces this statement by showing that DD further correlates with disease duration. The mean age of the SLE group was less than 50 years (46.6 years), too early for DD to occur as a process of the ageing heart. Importantly, in the present cohort, no patients cumulated SDI damage points from cardiac or peripheral vascular organ domains, the score resulted from other system involvement (neuropsychiatric, renal, pulmonary etc.). Thus, other systems are related to DD by still unknown common factors [22]. This data highlights the complexity of the pathophysiology of DD, which is an end-result of several concurrent factors: inflammation, fibrosis, endothelial dysfunction [23] or therapy (e.g. anti-inflammatory drugs).

The determinants of DD in individuals without cardiac disease have been extensively studied; age, hypertension, obesity, diabetes and non-alcoholic fatty liver disease are the most frequently incriminated factors [24,26]. Our study is consistent with previous findings and shows that hypertension ($p<0.001$) and obesity ($p=0.039$) are strongly related to DD. In the present cohort, the prevalence of diabetes was too low to validate its effect.

The association of antiphospholipid syndrome (APS) and DD has been previously documented [27,28]. APS causes myocardial hypoperfusion by small vessel vasculopathy/ microvascular thrombosis [29] which affect myocardial compliance [30]. Tektonidou et al showed that DD, in particular the right ventricle, is a prominent feature of APS [31]. Another study, which evaluated cardiac dysfunction in patients with SLE and APS, found that LV and right ventricular diastolic dysfunction were significantly more impaired in patients with primary APS and SLE-APS compared with SLE-nonAPS [27]. We determined a significantly altered myocardial diastolic performance in SLE-APS patients, confirming the additional impact of APS on cardiac damage in SLE. One explanation could rely on the influence of possible silent pulmonary embolism, as it was not ruled out by routine measurement of D-dimers, and chronic thromboembolic pulmonary hypertension was previously proven to correlate with DD [32]. In our study however, even if sPAP was slightly elevated in patients with DD, it did not differ according to the presence/absence of APS. That is why in our study with asymptomatic patients and normal mean values of sPAP (27 mmHg vs 44 mmHg in the study of Olson) the relation APS – DD via pulmonary embolism is questionable.

A strength of our study is the use of the *speckle tracking* technique which assesses myocardial deformation independently from the ultrasound beam angle. Its feasibility and accuracy, proven by MRI studies [33,34], has allowed its employment in the study of valvular heart disease [34], heart failure with preserved EF [35] or toxic heart damage [11]. Furthermore, the speckle tracking technique has demonstrated that myocardial systolic longitudinal deformation is early impaired, long before LVEF deterioration. We found significantly lower ELS values in SLE patients compared to controls (-18.4% vs -19.3%, $p<0.001$). The values were further decreased in the subgroups of patients with cumulative organ damage. Moreover, the higher the SDI, the lower the GLS was. By linear multivariate analysis the SDI was independently and positively associated with longitudinal systolic performance. These findings support the premise that, similar to other mechanisms of diastolic dysfunction, SLE-related pathophysiology is responsible for the alterations of the systolic function. Systolic impairment may be further augmented in patients with APS (-15.1% vs -19.2%, $p<0.001$), which, similar to SDI, is independently associated with ELS.

Previous studies have reported conflicting results regarding the association between disease activity and early cardiac dysfunction. A study which evaluated cardiac abnormalities in SLE patients failed to show a clear association between disease activity and DD [36]. Conversely, Yip et al demonstrated that disease activity may provide incremental predictive value for systolic dysfunction [37] . Another study observed that a SLEDAI $\geq$6 was associated with echocardiographic markers of both systolic and diastolic dysfunction, such as the decrement of late diastolic septal velocity [38]. Our study did not reveal an association between disease activity and DD. The explanation may rely on the fact that the majority of our SLE patients were in disease remission; only 15% had a SLEDAI$\geq$1.

No association with SLE-specific autoantibodies was demonstrated, except for anti-Ro, which positively cor-

related with systolic longitudinal strain. In SLE patients, the anti-Ro titers are associated with neonatal lupus and the risk for congenital heart block. In adults, heart's electrical disturbances (e.g. QTc prolongation) are explained by an inhibiting cross-reaction of the anti-Ro antibodies with several cardiac ionic channels, particularly the calcium channels and the potassium channel hERG [39]. In the present cohort 37% of SLE patients had positive anti-Ro antibodies but none exhibited QTc prolongation. It is unclear how anti-Ro antibodies may influence systolic longitudinal performance; it may be speculated that the interaction of anti-Ro antibodies with specific ionic channels (L and T-type calcium channels) may have an agonistic effect on these and finally improve the activity of contractile proteins similar with increased cellular calcium content induced by digoxin (via Na-K ATP-ase). Further studies are required to confirm this association.

In our study, ELS, a parameter of the systolic function, was significantly lower in patients with DD. Our study confirms the findings of Hasselberg et al, who demonstrated the correlation between DD and longitudinal systolic dysfunction [35].

To date, certain questions remain to be answered. Whether longitudinal systolic performance precedes the onset of DD (as suggested by smaller studies [41,14]), or whether it is an event that succeeds it - a sign of progression towards systolic heart failure? And what is the predictive value of longitudinal performance impairment for the progression towards heart failure? These questions are waiting to be addressed by prospective studies, which are also expected to determine a clear cut-off value of ELS and ELSR, in order to allow a more accurate assessment of the relationship between systolic longitudinal performance and various SLE features. Therefore, ELS could represent a feasible method for early detection of subtle myocardial dysfunction also in SLE patients, and could become an alternative to cardiac MRI which is more costly and laborious.

There are limitations to the current study. Our analysis is a cross-sectional study which gives no indication about the sequence of occurrence of the systolic and diastolic dysfunction. We included patients with mostly clinically inactive disease, which may have hindered a definite conclusion regarding the impact of disease activity on myocardial performance in SLE. However, our study had a larger cohort size compared to most previous studies and all patients originated from the same tertiary center, which warrants confident results. Given the retrospective nature of the study, it is possible that some patient information could have been missed despite careful efforts by the authors to record all pertinent details. In this regard, it must also be noted that some data related to specific diagnoses were collected from patients' files. Likewise, the imunological data, collected within 1 year time frame could influence the correlation between some autoantibodies and myocardial performance. In addition, the fact that data were collected from a single center may have introduced bias. Thus, further research is warranted to prospectively evaluate myocardial impairment in SLE using increased numbers of patients and perhaps, a multicenter design.

In **conclusion**, early myocardial involvement in SLE patients can be detected by modern ultrasound techniques and its major determinants are disease duration, cumulative damage accrual and APS. Our results emphasize the need for early echocardiographic detection of cardiac impairment in SLE patients, in order to improve cardiac morbidity and mortality rates. We suggest that SLE patients, especially those with associated APS, should undergo periodical echocardiographic evaluations of both systolic and diastolic performance.

Conflict of interest: none

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