ORIGINAL ARTICLE

Left Ventricle Functional Assessment by Three-Dimensional Echocardiography in Patients with Systemic Lupus Erythematosus

Evaluación de la función del ventrículo izquierdo en pacientes con lupus eritematoso sistémico mediante ecocardiografía tridimensional

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ABSTRACT

Background: Systemic lupus erythematosus frequently presents subclinical myocardial involvement; this has an early onset and predicts mortality. The analysis of myocardial deformation (strain) by three-dimensional speckle tracking echocardiography could be useful in the assessment of myocardial function.
Objective: The aim of this study was to assess left ventricular structure and systolic function through the analysis of three-dimensional deformation.
Methods: Thirty seven women with systemic lupus erythematosus (age 35±10 years) and no history of structural heart disease and 20 controls (34±8 years) were included in the study. Two-dimensional and three-dimensional echocardiography was performed according to the recommendations of the American Society of Echocardiography to acquire global longitudinal strain, radial strain, circumferential strain and strain area. Systemic lupus erythematosus activity was estimated with the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI), considering a score ≥4 as active disease.
Results: There were no differences in age, risk factors, blood pressure, and heart rate between both groups. From a structural point of view, both atria presented larger size in the systemic lupus erythematosus group. This group of patients presented lower global longitudinal strain (-19.7±2.7 vs. -21.1±2.5, p=0.009), global radial strain (50.7±8.7 vs. 56.5±5.6; p=0.02) and global strain area (-32.1±3.9 vs. -34.7±2.1, p=0.004). This decrease was even more marked in women with active systemic lupus erythematosus.
Conclusions: All deformation parameters were reduced in patients with systemic lupus erythematosus, which could be due to incipient alterations of left ventricular systolic function.

Keywords: Three-dimensional Echocardiography - Systemic Lupus Erythematosus - Left Ventricular Dysfunction/imaging diagnosis - Left Ventricular Dysfunction/physiology

RESUMEN

Introducción: El lupus eritematoso sistémico tiene un compromiso miocárdico subclínico frecuente, que se inicia precozmente y predice mortalidad. El análisis de la deformación miocárdica (*strain*) mediante el método de *speckle tracking* tridimensional podría ser de utilidad en la evaluación de la función miocárdica.
Objetivo: Evaluar la estructura y la función sistólica ventricular izquierda mediante el análisis de la deformación tridimensional.
Material y métodos: Se estudiaron 37 mujeres con lupus eritematoso sistémico (edad 35 ± 10 años) sin antecedentes de enfermedad cardíaca estructural y 20 controles (34 ± 8 años) a quienes se realizó un ecocardiograma bidimensional y tridimensional según recomendaciones de la Sociedad Americana de Ecocardiografía *(American Society of Echocardiography)*. Se obtuvo el strain global longitudinal, radial, circunferencial y el área de *strain*. La actividad del lupus eritematoso sistémico se estimó mediante el *Systemic Lupus Erythematous Disease Activity Index 2000 (SLEDAI)* considerándose como enfermedad activa una puntuación ≥4.
Resultados: No hubo diferencias de edad, factores de riesgo, tensión arterial y frecuencia cardíaca entre ambos grupos. Desde el punto de vista estructural se observó mayor tamaño de ambas aurículas en el grupo con lupus eritematoso sistémico. Este grupo de pacientes presentó menor strain longitudinal global (-19,7 ± 2,7 vs -21,1 ± 2,5; p=0,009), strain radial global (50,7 ± 8,7 vs. 56,5 ± 5,6; p=0,02) y área de strain global (-32,1 ± 3,9 vs -34,7 ± 2,1; p=0,004). Esta disminución fue aún más acentuada en aquellas mujeres con lupus eritematoso sistémico activo.
Conclusiones: Todos los parámetros de deformación se encontraron disminuidos en los pacientes con lupus eritematoso sistémico, lo cual podría obedecer a incipientes alteraciones de la función sistólica del ventrículo izquierdo.

Palabras clave: Ecocardiografía Tridimensional - Lupus Eritematoso Sistémico - Disfunción Ventricular Izquierda/diagnóstico por imágenes - Disfunción Ventricular Izquierda/fisiología

Abbreviations

CGS	Circumferential global strain	**RGS**	Radial global strain
GSA	Global strain area.	**SLE**	Systemic lupus erythematosus
LGS	Longitudinal global strain		

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INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease with as yet not completely clarified etiology and multiple organ involvement.

Several epidemiological studies point to a wide regional variation in its incidence and prevalence, which suggests the importance of genetic, hormonal and environmental factors.

Systemic lupus erythematosus mainly affects women of gestational age and non-Caucasian race, representing between 80-90% of patients. (1)

Although survival has improved in the last decade, cardiovascular morbidity and mortality of patients with SLE is twice that observed in individuals without the disease and with the same risk profile. (2)

Cardiac involvement is very frequent and all its structures can be affected by the disease: pericardium, myocardium, endocardium, coronary arteries and conduction tissue. (3) In autopsy studies, myocardial involvement has been observed in up to 40-50% of patients. Various factors may be implicated in the pathophysiological mechanism, such as the presence of autoantibodies (particularly associated with early disease damage), traditional risk factors (hypertension, dyslipidemia), accelerated atherosclerosis due to inflammatory mechanisms and side effects of drugs used in SLE treatment such as corticosteroids and hydroxychloroquine. In addition, in most cases, myocardial involvement occurs subclinically and even in quiescent periods of the disease. (4)

Previous studies have revealed subclinical alterations with both tissue Doppler echocardiography (5) and two-dimensional (2D) cardiac strain (6), as well as with magnetic resonance imaging (MRI), with increased T1 and T2 signals and greater late gadolinium enhancement. (7)

Unlike 2D strain, the study of three-dimensional (3D) myocardial deformation has the advantage of not losing information on the displacement of myocardial speckles, as well as faster analysis and processing and, compared with MRI, has lower cost and no need to use contrast. (8) In addition, it allows simultaneous analysis of longitudinal, circumferential, and radial deformation of the entire left ventricle (LV) in the same sequence of heartbeats.

The purpose of the present study was to compare left ventricular 3D deformation in patients with SLE without cardiovascular symptoms with a control group.

METHODS

Population

The initial study population consisted of 50 patients diagnosed with SLE according to the 1997 criteria of the American College of Rheumatology, evaluated at the Rheumatology Division of Hospital de Clinicas "José de San Martin" (UBA, Buenos Aires, Rep. Argentina) between August 2014 and March 2015.

Patients with structural heart disease of any etiology (ischemic, hypertrophic, valvular, idiopathic, etc.), as well as those with history of atrial fibrillation, diabetes mellitus, pulmonary hypertension and inadequate ultrasonic window were excluded from the study.

The results were compared with a control group matched by sex, age and cardiovascular disease risk factors, selected among individuals who had requested a routine assessment in the outpatient clinic of the same hospital. Finally, 37 women with SLE (mean age 35±10 years) and 20 control women (mean age 34±8 years) were included in the study.

Echocardiographic assessment

The study was performed in the Echocardiography laboratory with a Vivid E9 ultrasound machine (GE Health Care, Milkwaukee, USA) equipped with two multi-frequency transducers: the M5S for 2D assessment, and the 4V for 3D assessment. Left ventricular chamber dimensions and wall thickness, as well as transvalvular blood flow assessment was carried out according to the guidelines of the American Society of Echocardiography (9, 10).

For the 3D analysis, a full volume image was obtained from the apical 4-chamber view of 4 to 6 beats, taking special care to cover the entire LV, at a frame rate of no less than 35% of the patient's heart rate in order to achieve suitable speckle tracking.

Strain analysis was performed offline, with the EchoPAC PC v112 software provided by the same manufacturer, by means of the following sequence: correct alignment of the 3 apical views, manual marking of two points (one located at the apex and the other at the base of the LV in the 4-chamber view at end-diastole and end-systole), from which the endocardial chamber border is automatically traced with the possibility of making the adjustments that are considered necessary. Subsequently, the program determines the ventricular volumes, the ejection fraction and the sphericity index. Then, the automatic tracing of the epicardial border is performed with the possibility of manual correction to determine ventricular mass, and finally the region of interest is established for longitudinal global strain (LGS), circumferential strain (CGS), radial strain (RGS) and strain area (GSA) calculation.

The quality of speckle tracking is validated both by the program and by the operator, having the possibility of excluding from the analysis those segments with defective tracking (Figure 1).

Clinical assessment of systemic lupus erythematosus patients

The degree of disease clinical activity was assessed prior to the echocardiographic study with the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI). A score ≥4 points was considered as active disease. (11)

Statistical analysis

Data analysis was carried out with IBM SPSS™ Statistics v20 statistical software package. Nominal variables were expressed as percentage of the total number of cases, and quantitative variables as mean and standard deviation or median and interquartile range, as appropriate.

Normality of distributions was analyzed with the Kolmogorov-Smirnov or Shapiro-Wilk tests.

Statistical comparison between groups was performed with the corresponding hypothesis tests (Student's t-test, Mann-Whitney test, chi-square test), according to the type of variable and data distribution.

Intraobserver and interobserver variability was analyzed with the intraclass correlation coefficient. Significance was considered at a threshold $p=0.05$.

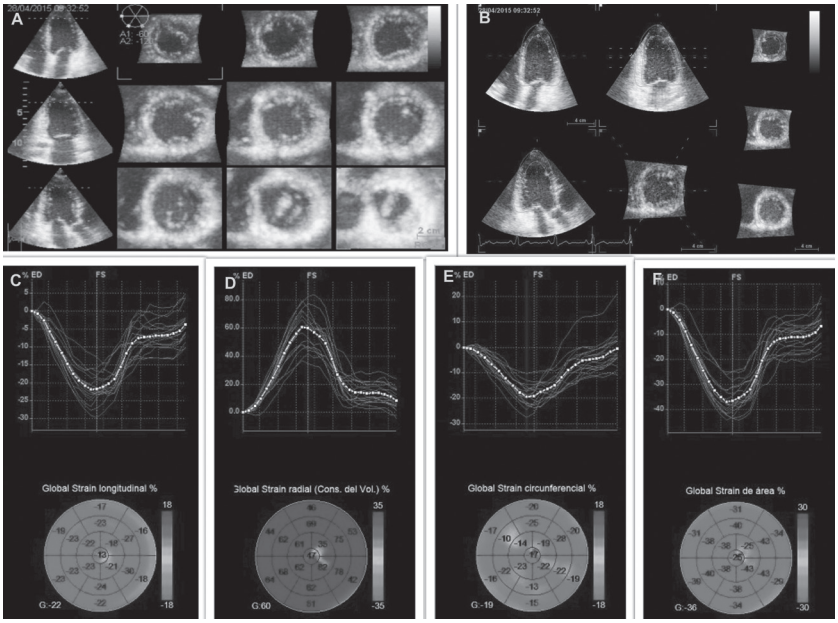

Fig. 1. Complete left ventricular volume (**A**). Region of interest in different views (**B**). Longitudinal strain (**C**). Radial strain (**D**). Circumferential strain (**E**). Strain area (**F**).

Ethical considerations

The study was approved by the institutional Ethics Committee and was carried out in accordance with the regulations in force for observational studies in agreement with the Declaration of Helsinki. The patients authorized the anonymous use of their data by signing an informed consent.

RESULTS

Population Characteristics

There were no differences between groups in terms of age, heart rate, blood pressure and cardiovascular risk factor profile. In contrast, in patients with SLE, weight (67±16 kg vs. 59±8 kg, p=0.01) and body mass index (25.9±5.2 kg/m2 vs. 23±2.7 kg/m2, p=0.01) was higher than in the control group. Median time evolution of the disease was 84 months (IQR: 24-126 months) and 100% of patients had positive antinuclear antibodies. A total of 24% of patients had active disease (SLEDAI ≥4) with mean SLEDAI of 8.2 ± 4.2. Seventeen percent of patients with SLE had some positive dosage for antiphospholipid antibodies.

Seventy-one percent of patients were treated with corticosteroids, 88% received hydroxychloroquine, 22% mycophenolate, 12% methotrexate, 6% azathioprine and 4% cyclophosphamide, as detailed in Table 1.

Conventional Doppler Echocardiography

Structurally, patients with SLE presented greater left atrial area (17.3±2.7 cm2 vs. 14.9±2.1 cm2; p=0.006) and right atrial area (13.9±2 cm2 vs. 12.5±1.5 cm2, p=0.02), enhanced interventricular septal thickness (8.6±1.1 mm vs. 7.9±0.8 mm; p=0.02) and a tendency to lower E/A ratio of diastolic transmitral flow (1.5±0.5 vs. 2.1±0.7, p=0.06).

No differences were observed in the E/e ratio of both ventricles or in the pulmonary artery systolic pressure.

Conversely, control patients had higher, though not significant, shortening fraction (42.2±6.5% vs. 38.4±6%, p=0.07) (Table 2).

Three-dimensional echocardiogram

The analysis of the full-volume left ventricular image showed no differences in terms of volume, mass, ejection fraction and sphericity index between the two groups (Table 3). Patients with SLE presented lower LGS (-19±2.7% vs. -21.1±2.5%, p=0.009), RGS (50.7±8.7% vs. 56.2±2.3%; p=0.02), and GSA (-32.1±.9% vs.-34.7±2.3%, p=0.004).

The results of SLE patients who had active disease according to the SLEDAI score showed less deformation in all directions than those with quiescent disease and controls (Table 4).

There was no correlation between strain values and patients' weight or body mass index (patients with SLE had higher weight and BMI).

Intra and interobserver correlation

The reproducibility of the different deformation indexes was analyzed in 20 randomized patients.

The intraobserver intraclass correlation was 0.95 (95% CI 0.86-0.98, p≤0.0001) for LGS, 0.97 (95% CI 0.92-0.99, p≤ 0.0001) for RGS, 0.94 (95% CI 0.85-0.98, p≤0.0001) for CGS and 0.97 (95% CI 0.91-0.99, p≤0.0001) for GSA.

The interobserver intraclass correlation was 0.99 (95% CI 0.99-1, p≤0.0001) for LGS, 0.99 (95% CI 0.98-0.99, p≤0. 0001) for RGS, 0.99 (95% CI 0.99-1,

p≤0.0001) for CGS and 0.99 (95% CI 0.99-1, p≤0.0001) for GSA.

DISCUSION

In our work we have observed that lupus patients, despite age and low prevalence of traditional cardiovascular risk factors, presented incipient alterations in the structure (greater atrial size) and systolic function of the heart, with lower values of longitudinal, radial and strain area deformation with an excellent intra and interobserver correlation. These findings were more evident the greater the degree of disease activity.

Although all cardiac structures can be affected as a result of the disease, myocardial involvement is the most common characteristic. (3) Myocarditis, vascular disease due to early atherosclerosis, vasculitis, secondary effects due to prolonged use of various drugs, pul-

Table 1. General characteristics of the study groups

	SLE group (n=37)	Control group (n=20)	p
Age (years)	35± 10	33.9±8	0.62
Weight (kg)	67.4±16.2	58.9±7.9	0.02
Body mass index (kg/m2)	26±5.2	23±2.6	0.04
Body surface area (m2)	1.7±0.21	1.6±0.11	0.06
Heart rate	71±9.9	71±7	0.94
SBP (mmHg)	117±16	113±14	0.94
DBP (mmHg)	71± 16	73±5	0.63
HTN	11%	6%	0.51
Smoking	16%	6%	0.50

SLE: Systemic lupus erythematosus; SBP: Systolic blood pressure. DBP: Diastolic blood pressure. HTN: Hypertension.

Table 2. Results of two-dimensional and Doppler echocardiography assessment

	SLE group (n=37)	Control group (n=20)	p
LVDD (mm)	45.1±4.2	43.9±3.8	0.35
LVSD (mm)	27.8±3.7	25.5±4.5	0.08
LVSF (%)	38.4±6	42.2±6.5	0.07
DIVST (mm)	8.6±1.1	7.9±0.8	0.02
LA area (cm2)	17.3±2.7	14.9±2.1	0.006
RA area (cm2)	13.9±2	12.5±1.5	0.02
Mitral E/A ratio	1.7±0.5	2.1±0.7	0.06
MDT (ms)	187±32	188±28	0,89
LV E/e	7±2.2	6.3±1.2	0.31
RV E/e	4.4±1.6	3.2±0.7	0.11
PASP (mmHg)	26.7±3.6	24.8±1.8	0.17

SLE: Systemic lupus erythematosus. LVDD: Left ventricular diastolic dimension. LVSD: Left ventricular systolic dimension. LVSF: Left ventricular shortening fraction. DIVST: Diastolic interventricular septal thickness. LA: Left atrial. RA: Right atrial. MDT: Mitral deceleration time. LV: Left ventricular. RV: Right ventricular. PASP: Pulmonary artery systolic pressure.

Table 3. Results of three-dimensional echocardiography assessment

	SLE group (n=37)	Control group (n=20)	p
Frame velocity (% HR)	484±128	492±68	0.82
End-diastolic volume (ml)	91±18	88.6±5.4	0.65
End-systolic volume (ml)	36.3±8.4	35.6±7.7	0.77
Stroke volume (ml)	54.9±11.9	53.2±9.1	0.77
Ejection fraction (%)	60±5.2	59.9±3.5	0.91
Sphericity index	0.37±0.06	0.36±0.07	0.36
End-diastolic mass (gr/m2)	69.6±7.7	69.6±6.8	0.99
LGS (%)	-19±2.7	-21.1±2.5	0.009
RGS (%)	50.7±8.7	56.5±5.6	0.02
CGS (%)	-17.6±2.9	-18.3±1.6	0.25
GSA (%)	-32.1±3.9	-34.7±2.1	0.004

SLE: Systemic lupus erythematosus. HR: Heart rate. LGS: Longitudinal global strain. RGS: Radial global strain. CGS: Circumferential global strain. GSA: Global strain area.

Table 4. Deformation according to systemic lupus erythematosus activity

	Group with active SLE	Group with inactive SLE	Control group	p
LGS (%)	-18 ± 2.5	-19.2 ± 2.7	0.01	0.01
RGS (%)	46.3 ± 6.1	51.2 ± 9.6	0.011	0.011
CGS (%)	-15.6 ± 1.7	-18.2 ± 3.1	0.037	0.037
GSA (%)	-30.3 ± 3.2	-32.3 ± 4.3	0.011	0.011

SLE: Systemic lupus erythematosus. LGS: Longitudinal global strain. RGS: Radial global strain. CGS: Circumferential global strain. GSA: Global strain area.

monary hypertension and valvular heart disease are among the various factors that can affect cardiac function. It has been reported that although myocarditis clinically affects between 5-10% of patients, subclinical involvement compromises more than 50% of patients with SLE, particularly those with some degree of disease activity. Myocardial injury suggests an immunological phenomenon, in which immune complex deposition is observed both in the wall of blood vessels and between myocytes. (12)

The risk of ischemic heart disease in patients with SLE is between 9 and 50 times higher than in the control population. (13) The participation of inflammation in the genesis and evolution of atherosclerotic lesions (factors that are also not included in the most commonly used risk scores) should be added to traditional risk factors such as age, sex, hypertension, dyslipidemia, diabetes, personal and family history of cardiovascular disease and smoking. In this sense, the presence of SLE increases the risk of suffering from cardiovascular disease once adjusted with the risk factors of the Framingham score. (14)

Regarding the drugs used in the treatment, the most frequent in our population were corticosteroids and hydroxychloroquine. With respect to corticosteroids, there is controversy as to whether they are responsible per se for increasing cardiovascular risk by negatively affecting some risk factors such as blood sugar levels, HTN, lipid profile and weight gain. However, it must be considered that the patients who receive the highest doses of these drugs are those who have the most active SLE (15). Hydroxychloroquine toxicity, although infrequent, can cause hypertrophy and severe myocardial dysfunction, altering cellular metabolism at the lysosomal level. (16)

In the only study performed with this technique in lupus patients, Huang et al (17) compared 3D deformation in 34 lupus patients and controls. The average age of the population was 31±8 years and 87% were women. Lupus activity was measured through the SLEDAI 2000 score (10.5±7.6 points). From a structural point of view, and unlike that observed in our work, lupus patients had greater ventricular mass and volume, which could be attributed to the higher blood pressure values of lupus patients. Ejection fraction was similar between both groups. The study of deformation revealed that patients with SLE had significantly lower values than the control population in all planes. The use of non-invasive techniques for the detection of subclinical disease has shown that patients with SLE have higher values of intima-media thickness, higher prevalence of atherosclerotic plaques in the carotid artery territory (18) and greater coronary calcification. (19) In addition, it has been demonstrated that the greater the atherosclerotic involvement in the carotid artery territory, the greater the possibility of cardiovascular events during follow-up. (20)

Several studies with MRI have shown significant differences in myocardial tissue characterization between patients with SLE and controls, even in disease remission periods and absence of cardiovascular disease symptoms, in different study sequences such as T1, T2 , early and late gadolinium enhancement (the latter less frequent) and recently T1 mapping. In general, myocardial involvement is usually diffuse, suggesting a pattern more compatible with inflammation (7, 21). Regarding echocardiographic studies, Yip et al. reported that compared with healthy people, patients with SLE had lower rates of myocardial contractility assessed by tissue Doppler and midwall shortening fraction, despite not showing differences in ejection fraction. (22) In a more recent publication, Buss et al. obtained similar results using strain and longitudinal strain rate by tissue Doppler. (5)

The study of myocardial deformation through the speckle tracking method is a semiautomatic technique of increasing use in the last decade and has proven its usefulness in different clinical scenarios, including another frequent rheumatological disease as rheumatoid arthritis. (23, 24). It allows analyzing regional function of all myocardial segments in different planes, independently of the ultrasound angle, because the analysis is based on 2D imaging (tracking of acoustic markers or speckles) and not on the Doppler effect. (25) Its limitation is the loss of tracking of these acoustic markers which, unlike 3D echocardiography, escape from the study plane (26).

Like any other method, 3D echocardiography has advantages and disadvantages. On the one hand, it allows the assessment of myocardial deformation in three orthogonal planes (longitudinal, radial and circumferential) simultaneously and in the same heartbeat. It also allows combining the information of longitudinal and circumferential plane deformation to calculate strain area. This parameter has shown better intra and interobserver correlation than its individual components separately, probably due to a decrease in speckle-tracking error and an improved

signal-to-noise ratio. As a disadvantage, 3D echocardiography requires optimal two-dimensional images, thus excluding between 10-20% of patients, and has a lower temporal resolution (27, 28). Several studies have shown its usefulness in the detection of early myocardial damage in different clinical scenarios such as patients with heart failure, valvular heart disease, ischemic heart disease and oncological treatment toxicity. (29-33)

Finally, based on the results of the present study, 3D echocardiography can be useful for the cardiological assessment of patients with SLE. It remains to be determined whether the differences found have any predictive value in symptom recurrence or cardiovascular events in the follow-up of these patients. Among the most important limitations of this work are those inherent to the technique used, such as its low temporal-spatial resolution, the need for optimal ultrasound windows and its low availability that prevent its more widespread use.

Conflicts of interests

None declared.

(See authors' conflicts of interest forms on the web/Supplementary material).

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