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ORIGINAL ARTICLE

Evaluation of right ventricular function performed by 3d-echocardiography in scleroderma patients

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SUMMARY

The impairment of the right ventricle (RV) in systemic sclerosis (SSc) is usually related to pulmonary arterial hypertension (PAH). New echocardiographic techniques, such as 3-dimensional echocardiography (3DE) and 2-dimensional speckle tracking (2DSTE), allow an accurate evaluation of the RV function. The aim of this study was to evaluate the RV function using 3DE and 2DSTE in SSc patients with no history of heart disease and no PAH.

Forty-five SSc patients, 42 females and 3 males, 28 with limited cutaneous SSc (lcSSc) and 17 with diffuse cutaneous SSc (dcSSc), were studied. Forty-three age- and gender-matched healthy subjects were enrolled as controls. All of them underwent a 3DE and 2DSTE ecocardiographic evaluation of the RV function. Systolic pulmonary arterial pressure (sPAP) and total pulmonary vascular resistance (tPVR) were also estimated by power doppler. RV echocardiographic parameters were compared in the different subsets of SSc patients. A statistical analysis was performed by t-test, ANOVA and multiple logistic regression.

RV areas in 2DSTE and volumes in 3DE were higher and RV function parameters were reduced in SSc patients compared with controls. Also sPAP and tVPR were higher, but they did not reach pathological values. Echocardiographic alterations were more pronounced in patients with lcSSc.

3DE and 2DSTE echocardiography allowed us to detect morphological and functional alterations of the RV in a group of SSc patients with no clinical signs of heart disease and no PAH. These patients had significantly higher sPAP and tPVR than healthy controls without reporting values compatible with PAH. These data suggest that RV alterations are related to a pressure overload rather than to an intrinsic myocardial involvement in SSc.

Key words: *Right ventricular function, 3d-echocardiography, Systemic sclerosis.*

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INTRODUCTION

Systemic sclerosis (SSc) is a connective tissue disease characterized by functional lesions and damage of the microcirculation, with alterations of the immune response and activation of fibroblast function, resulting in fibrosis in the skin and internal organs.

Pulmonary arterial hypertension (PAH) is one of the most severe visceral manifestations of SSc. It is a major cause of mortality in SSc patients, mainly in those affected by the limited cutaneous form (lcSSc) and with a long disease duration (1).

Before the introduction of specific treatment, the survival rate after 1 year from the diagnosis of PAH was approximately 45%, whereas it is estimated that the 3-year survival rate is around 60% (2).

The increase of pulmonary artery pressure (PAP) is due to an increase in pulmonary vascular resistance. The main pathogenetic mechanisms are dysregulation of endothelial cells, vasoconstriction, vascular wall remodelling and in situ thrombosis. Endothelial dysfunction is caused by both biochemical changes (hypoxia, acidosis, inflammatory mediators) and mechanical abnormalities (increased tension on the vessel walls) (3).

Another visceral manifestation in SSc patients is cardiac involvement, which is often clinically hidden. When it becomes clini-

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cally evident, it is regarded as a poor prognostic factor and actually causes about 20% of deaths attributed to this disease (4, 5).
It can involve all cardiac structures (endocardium, myocardium and pericardium) and may result in pericardial effusion, ventricular arrhythmias, conduction system defects, myocardial ischemia and heart failure. The functional and structural vascular impairment affecting the microcirculation seems to be the cause of repeated focal ischemia resulting into irreversible myocardial fibrosis (6).
Right ventricular (RV) involvement in SSc is usually related to the onset of pulmonary hypertension (PH). However it is still unclear whether SSc can directly affect the RV function in absence of PH.
Ventricular diastolic dysfunction is a sign of myocardial involvement in SSc (7). The methods generally used to detect cardiac involvement make it possible to identify myocardial abnormalities only at an advanced stage, when the organ damage has already occured.
Recently, the introduction of new more accurate echocardiographic techniques, such as 3-dimensional echocardiography (3DE) and 2-dimensional speckle tracking (2DSTE), has allowed a better assessment of the RV function and myocardial mechanics (8-10). In particular, the 3DE has proved to be accurate, sensitive and reproducible in the assessment of Vdx (11, 12).
The 2DSTE is an echocardiographic technique aimed to assess the systolic function of the left ventricle (LV). Recent studies have demonstrated its validity also in the assessment of the RV function (13).
The aim of this study was to use 3DE and 2DSTE in SSc patients to identify early echo markers of RV impairment, in the absence of PH.

MATERIALS AND METHODS

Forty-five patients attending the outpatient clinic of the Rheumatology Unit of Padova University Hospital were recruited. Inclusion criteria of this study consisted of a definite diagnosis of SSc according to the American College of Rheumatology/European League against Rheumatism (ACR/EULAR) classification (14), the absence of signs and symptoms of heart disease and no evidence of PAH in the standard echocardiography.
We enrolled forty-five SSc patients (42 female and 3 male) with a mean age of 56±13 years and mean SSc duration of 13.6±9.4 years.
Twenty-eight patients were affected by the limited form, while 17 by the diffuse cutaneous subset (dcSSc) of SSc. Antinuclear antibodies (ANA) were positive in all patients, with anti-centromere (ACA) specificity in 15 cases, anti-Scl-70 in 17 and without specific ANA in 13.
Forty-three age- and gender-matched healthy subjects were enrolled as controls.
All patients underwent transthoracic echocardiography with a Vivid E9 ultrasound scanner (GE Medical Systems, Horten, Norway) with MS5 and V4 probes. Images were captured both in the two-dimensional (2D) and Doppler modes using a M5S probe by parasternal, apical and subcostal approaches, and both volumetric 3D datasets of the four chambers of the heart with the apical approach in full-volume, the sum the partial volumes of 4-6 cycles consecutive cardiac, acquired in apnea.
For 2D images, three consecutive cardiac cycles were recorded in digital format and analyzed using the EchoPAC software (GE Medical Systems). 3D images were analyzed using the EchoPAC software (GE Medical Systems) and the 4D RV function (TomTec Imaging Systems, GmbH, Unterschleissheim, Germany). Particular attention was devoted to the assessment of the right ventricular 2DSTE. The longitudinal strain was measured in the apical section 4 rooms modified for Vdx. Both the global longitudinal strain, including the interventricular septum, and the longitudinal strain of the single free wall of Vdx were obtained.
All values observed were compared in the different cutaneous form of SSc and in the different antibody specificities.
A statistical analysis was performed using SPSS 18.0 for Windows (SPSS, Chi-

cago, IL, USA) and MedCalc for Windows 8.1.1.0 (Mariakerke, Belgium). Continuous variables with normal distribution were expressed as mean ± SD. The t-test, ANOVA and multiple logistic regression were used to compare patients and controls. A probability of less than 5% was considered significant.

RESULTS

The clinical and anthropometric characteristics of the SSc patients studied and the control subjects are summarized in Table I. Anthropometric data were similar, whereas the heart rate and the blood pressure showed a statistically significant difference, with higher values in the scleroderma patients.

The multiple logistic regression considered in the same model the three main variables measured in echocardiography and a correlation was found between SSc patients and control subjects: heart rate (P=0.0003), systolic blood pressure (P=0.002), diastolic blood pressure (P=0.048).

Table II reports the echocardiographic measurements of the RV.

Patients showed a significant increase of the RV size and a significant reduction of its contractile function as compared to controls in 2D-echocardiography. Longitudinal strain was similar in the two groups. A three-dimensional evaluation confirmed the increased size and reduced ejection fraction in patients with scleroderma. Doppler parameters showed higher values of systolic pulmonary pressure (sPAP) and pulmonary vascular resistance (tPVR) in scleroderma patients compared to healthy controls, despite they did not reach pathological values (Table II).

The comparison between the echocardiographic parameters in patients with different clinical subsets (Tab. III) showed an increase RV size in the dcSSc than the lcSSc, with a nonsignificant reduction of contractile function. The values of sPAP and

Table I - Anthropometric and clinical characteristics.

	Patients N=45	Controls N=43	P
Weight, kg	64±11	63±7	n.s.
Height, cm	163±7	164±7	n.s.
Heart rate/min	76±12	66±12	<0.0001
Systolic blood pressure, mmHg	134±21	120±21	0.002
Diastolic blood pressure, mmHg	78±9	74±7	0.035

n.s., not significant.

Table II - Echocardiographic parameters of right ventricle.

	Patients N=45	Controls N=43	P
Two-dimensional parameters			
End-diastolic area, cm^2	19±4	17±3	0.002
End-systolic area, cm^2	10±3.5	8±1.5	<0.0001
Fractional area change, %	47±8	52±6	0.002
TAPSE, mm	23±3	26±2	<0.0001
S Wave TDI, cm/s	12±2	15±3	<0.0001
Global longitudinal strain 2D, %	-24.8±4	-25.6±3	n.s.
Free wall longitudinal strain 2D, %	-30±5	-31.3±4	n.s.
Three-dimensional parameters			
End-diastolic volume 3D, mL	97±28	87±17	0.049
End-systolic volume 3D, mL	50±18	34±8	<0.0001
Ejection fraction 3D, %	49±6	61±6	<0.0001
Doppler parameters			
Pulmonary artery systolic pressure, mmHg	33±14	22±5	<0.0001
Pulmonary vascular resistance, WU	1.9±0.6	1.4±0.3	0.001

n.s., not significant.

Table III - Right ventricular echocardiographic parameters in different subsets of systemic sclerosis.

	lcSSc N=28	dcSSc N=17	P
Two-dimensional parameters			
End-diastolic area, cm^2	20.5±5	18±3	n.s.
End-systolic area, cm^2	11±3	9±3	0.045
Fractional area change, %	45±7	49±8	n.s.
TAPSE, mm	23±3	23±3	n.s.
S Wave TDI, cm/s	12±1	13±2	n.s.
Global longitudinal strain 2D, %	-25.5±3	-25.2±3	n.s.
Free wall longitudinal strain 2D, %	-29.6±4	-31±5	n.s.
Three-dimensional parameters			
End-diastolic volume 3D, mL	106±28	85±21	0.016
End-systolic volume 3D, mL	55±18	43±12	0.018
Ejection fraction 3D, %	48±7	50±5	n.s.
Doppler parameters			
Pulmonary artery systolic pressure, mmHg	33±10	30±11	n.s.
Pulmonary vascular resistance, WU	1.7±0.7	1.6±0.3	n.s.

lcSSc, limited cutaneous systemic sclerosis; dcSSc, diffuse cutaneous SSc; n.s., not significant.

tPVR were higher in patients affected with lcSSc, without reaching statistical significance. The echocardiographic parameters showed no significant difference in the patients with specific (ACA and Scl-70) and aspecific ANA.

DISCUSSION AND CONCLUSIONS

The study was conducted in a series of scleroderma patients with typical demographic characteristics: prevalence of females, average age of onset between 40 and 45 years, prevalent lcSSc, specific anticentromere antibody more frequently than the dcSSc.
We recruited patients with no symptoms or signs of heart disease or standard echocardiographic evidence of PAH.
The main aim of the study was an echocardiographic assessment of the RV.
We used highly sensitive methods capable of providing details of 2D images to evaluate the global longitudinal strain and the free wall of the RV. We took 3D images for a more accurate measurement of volumes and ejection fraction of the ventricle itself and power Doppler image to estimate sPAP and tPVR.
Our data showed that the RV in scleroderma patients had a higher end-diastolic and systolic volume and a reduced ejection fraction compared with healthy controls.
These morphological and functional alterations are not significant enough to cause clinical symptoms or signs, although conceivably stress tolerance is reduced. It should be emphasized that many scleroderma patients are not able to make any physical effort due to skin lesions, musculoskeletal disorders and frequent concomitant pulmonary fibrosis.
Power Doppler has shown that the sPAP values and tPVR were significantly higher in SSc patients than in healthy controls, although they did not reach values compatible with PAH. This observation may explain the alterations of the RV, probably secondary to the pressure overload and not to the damage caused by the intrinsic cardiomyopathy, because the strain values were comparable to those of healthy subjects.
Our data suggest that scleroderma patients without pulmonary hypertension have probably an obliterative vasculopathy which increases the resistance and pulmonary artery pressure.
These changes were more significant in the subset of patients with lcSSc. It is no coincidence that these subsets have developed PAH after many years.
In literature, only a few works have been published on the echocardiographic assessment of myocardial strain and 3D-echocardiography applied to SSc. Most of these were dedicated to a morphological and functional analysis of the LV.
These studies showed that the assessment of the myocardial function through the use of the echocardiographic speckle tracking strain was able to detect alterations in the function of Vsx in SSc patients, in the absence of symptoms related to myocardial dysfunction and with a preserved ejection fraction (15-18).
Only three authors studied the Vdx in SSc using the 2DSTE and their data are in line with those of our study (19-21). They showed how the systolic dysfunction of the Vdx may precede the onset of the increase in the sPAP values and reflect the adaptation of the myocardium to the obliterative vasculopathy that characterizes SSc.
The use of the 2DSTE echocardiographic method is useful to detect early functional changes in the Vdx in patients with SSc. It should be emphasized that a repeat echocardiogram with Doppler during the follow-up is very important to detect early myocardial alterations and to monitor the values of the pulmonary artery pressure (22, 23).

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