Original Article

Impairment of Right Ventricular Function in Patients with Systemic Sclerosis and Interstitial Lung Disease: Tissue Doppler Evaluation

Acometimento da Função Ventricular Direita em Pacientes com Esclerose Sistêmica e Doença Pulmonar Intersticial: Avaliação pelo Doppler Tecidual

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Abstract

Introduction: Systemic sclerosis (SSc) is an autoimmune tissue connective disease that courses with fibrosis and microvascular dysfunction. Involvement of the visceral organs, including the lungs and heart, is the main cause of death among patients with SSc. In this context, here we analyzed the relationship between right ventricle (RV) parameters assessed by tissue Doppler echocardiography and lung involvement in patients with SSc.

Methods: Patients fulfilling the 2013 SSc Classification Criteria underwent tissue Doppler echocardiography for the assessment of left ventricular (LV) systolic function (ejection fraction) and RV fractional area change (FAC), tissue Doppler s' (systolic) velocity, myocardial performance index, and tricuspid annular plane systolic excursion for the assessment of RV systolic function. Pulmonary systolic pressure was estimated using tricuspid regurgitation. Chest high-resolution computed tomography was used to evaluate the presence of pulmonary fibrosis. The patients were divided into two subgroups accordingly: Group I, patients with pulmonary fibrosis (n=26); and Group II, those without fibrosis (n=17).

Results: Among the 43 patients with SSc, most were female (86%), and the mean age was 51 ± 12 years. All patients had normal systolic ventricular function as evidenced by an LV ejection fraction > 55% and an RV FAC > 35%. No significant intergroup difference was noted in age or disease duration. Except for a decreased tissue Doppler s' velocity in patients with lung fibrosis, all indexes of RV performance were similar. Conclusion: In patients with SSc and pulmonary fibrosis, tissue Doppler identified early RV longitudinal myocardial involvement despite preserved RV radial systolic performance.

Keywords: Systemic Sclerosis; Tissue Doppler; Pulmonary Fibrosis.

Resumo

Introdução: *A esclerose sistêmica (ES) é uma doença autoimune do tecido conjuntivo que cursa com fibrose e disfunção microvascular. O envolvimento dos órgãos viscerais, incluindo os pulmões e o coração, é a principal causa de óbito na ES. Nesse contexto, analisamos a relação entre os parâmetros ventriculares direitos (VD) pela ecocardiografia com Doppler tecidual e o acometimento pulmonar em pacientes com ES.*

Métodos*: Os pacientes que preencheram os Critérios de Classificação da ES de 2013 foram submetidos à ecocardiografia com Doppler tecidual para avaliação da função sistólica (fração de ejeção) ventricular esquerda (VE), enquanto a função sistólica do VD foi avaliada por meio da fração de variação de área do VD (fractional area change — FAC), velocidade (sistólica) do Doppler tecidual, índice de desempenho miocárdico (IDM) e excursão sistólica do plano anular tricúspide (TAPSE). A pressão sistólica pulmonar foi estimada por insuficiência tricúspide. A tomografia computadorizada de alta resolução (TCAR) de tórax avaliou a presença de fibrose pulmonar. De acordo com os resultados da TCAR, os pacientes foram divididos em 2 subgrupos: Grupo I, incluindo pacientes com fibrose pulmonar (n=26), e Grupo II sem fibrose (n=17).*

Resultados: *Entre os 43 pacientes com ES, a maioria era do sexo feminino (86%) com idade de 51±12 anos. Todos os pacientes apresentavam função ventricular sistólica normal, avaliada pela FEVE>55% e FAC VD>35%. Não houve diferença significativa em termos de idade ou duração*

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da doença para os grupos. Exceto pela diminuição das velocidades do Doppler tecidual em pacientes com fibrose pulmonar, todos os índices de desempenho do VD foram semelhantes.

Conclusão: *Em pacientes com ES e fibrose pulmonar, o Doppler tecidual identifica acometimento miocárdico longitudinal precoce do VD, apesar do desempenho sistólico radial preservado do VD.*

Palavras-chave: *Esclerose Sistêmica; Doppler tecidual; Fibrose Pulmonar.*

Introduction

Systemic sclerosis (SSc) is an autoimmune connective tissue disease that courses with endothelial dysfunction, resulting in diffuse vascular lesions, excessive collagen production, and fibrosis of the skin and major organs, including the lungs, kidneys, and heart.[1] As the pulmonary fibrotic and vascular manifestations of SSc, including pulmonary hypertension and lung fibrosis, are the leading cause of death,[2] the early recognition of lung and heart involvement are essential for the proper management of these patients. Cardiac involvement includes right heart dysfunction due to pulmonary hypertension, myocardial fibrosis, and pericardial involvement and is usually associated with a poor prognosis.[3] It is unclear whether involvement of the right ventricle (RV) results directly from organ lesion or indirectly from lung disease (pulmonary hypertension and fibrosis). Thus, the noninvasive estimation of RV function with imaging is challenging due to the complex RV geometry. As tissue Doppler echocardiography has been adequately used to assess RV function and pulmonary pressures, here we analyzed the relationship between RV performance and lung involvement in patients with SSc.

Methods

Patients: Our population consisted of outpatients older than 18 years of both sexes who were diagnosed with SSc according to the 2013 Classification Criteria.[4] Only patients with a normal systolic left ventricular (LV) function (LV ejection fraction > 0.55) and preserved RV function (as assessed by a fractional area > 35%) were included in the study. Patients with suboptimal echocardiography windows were excluded. All patients provided written informed consent to participate. The study was approved by the local institutional ethics committee.

Echocardiography: A comprehensive echocardiography examination was performed of all patients by an experienced echocardiographer using commercially available equipment (Artida, Toshiba, Japan). LV diameters and systolic function (Teichholz formula) and mass were measured from bidimensional images obtained from the parasternal long-axis view. Left atrial volumes were obtained on two- and four-chamber views using the modified Simpson's biplane rule. Diastolic function was evaluated with transmitral Doppler, with the sample volume placed at the tips of the mitral valve on the apical four-chamber plane to obtain velocity recordings of early (E) and late (A) wave and E wave deceleration time. Tissue Doppler velocities were obtained from basal septal and lateral mitral annulus to record early (e') tissue Doppler myocardial velocities. Images were obtained at end expiration, and the average of three cycles was used in the analysis.

Assessment of RV function: RV performance was evaluated using RV fractional area change (FAC) defined as: (end-diastolic area − end-systolic area)/end-diastolic area × 100. From the apical four-chamber view, endocardial borders of the RV free wall and septum were traced to obtain end-diastolic area identified as the onset of the electrocardiography R wave from a simultaneously recorded electrocardiogram and end systole considered the smallest RV cavity size before tricuspid valve opening. Tissue Doppler myocardial systolic (s') velocity was obtained from the apical four-chamber view, with the sample volume placed at the lateral base of the tricuspid annulus. Myocardial performance index (MPI) was obtained from tissue Doppler recordings measured from the lateral RV wall and calculated as (a − b)/b, where (a) was the interval from the end of the late diastolic annular velocity to the onset of the early diastolic annular velocity and (b) was measured from the onset to the end of the systolic annular velocity. Tricuspid annular plane systolic excursion (TAPSE) was acquired by the placement of an M-mode cursor through the tricuspid annulus and the measurement of the distance of longitudinal movement of the annulus during systole. Pulmonary systolic pressure was measured from tricuspid regurgitation jet velocity and added to the right atrial pressure estimated as the inferior vena cava diameter at rest and after respiratory excursion. The diagnosis of pulmonary hypertension was considered when estimated pulmonary systolic pressure was >36 mmHg on Doppler echocardiography.

Chest high-resolution computed tomography (HRCT): Chest HRCT was performed within 1 month of the echocardiography to assess the presence of lung fibrosis. Fibrotic interstitial lung disease was considered present based on any of the following findings: reticular opacities, traction bronchiectasis, or honeycombing (isolated or in combination). According to the chest HRCT results, patients were divided into two groups: Group I, SSc patients with pulmonary fibrosis; and Group II, SSc patients without pulmonary fibrosis. Studies were reviewed to consensus by cardiothoracic radiologists with 1 (T.G.) and 6 years (F.K.) of experience with HRCT. (Figure 1)

Statistics: Continuous variables are expressed as mean ± standard deviation, while categorical variables are expressed as percentages. Continuous variables were compared using the two-sided Student's t test, whereas categorical variables were tested with the Chi squared or Fisher's exact test. Values of $p < 0.05$ were considered statistically significant.

Echocardiographic measurements of RV function (FAC, TAPSE, IPM, RV s') were repeated for 15 patients by two

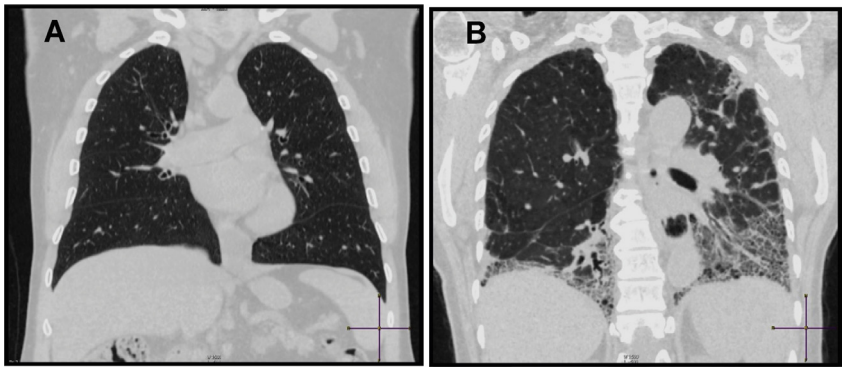

Figure 1 – *High-resolution chest computed tomography images of patients with systemic sclerosis showing (A) coronal reconstruction of a normal lung parenchyma; and (B) coronal reconstruction of fibrotic interstitial lung disease associated with systemic sclerosis showing reticular opacities, traction bronchiectasis, and honeycombing.*

readers (ACR and MR) for the assessment of intra- and interobserver variability. Variability was calculated as the difference between the two observations divided by the mean of the observations expressed as percentages.

Results

Among the 51 patients who underwent echocardiography, eight were excluded, five of them for not having undergone chest HRCT, two for having suboptimal echocardiographic images, and one for severe LV dysfunction; thus, the final group included 43 patients. Most patients were female (86%), with a mean age of 51 ± 12 years and a mean disease duration of 11.4 ± 8.7 years (median, 9.5 years). The mean LV ejection fraction was 0.63 ± 0.04, while the LV mass index was 92 ± 28 g/m^2. Regarding the RV assessment, the measurement of pulmonary artery systolic pressure from tricuspid regurgitation was feasible in 33 patients, with a mean value of 30 ± 14 mmHg. Pulmonary hypertension was uncommon in this group, with only five patients (15%) having a pulmonary systolic pressure > 36 mmHg. The other indices used to assess RV performance were normal as observed by TAPSE (22 ± 4 mm) and RV s' wave (12.7 ± 2.7 cm/s). The mean FAC was 47 ± 7%. The mean tissue Doppler RV MPI for the entire population was also within the normal range (0.47 ± 0.10).

Chest HRCT analysis: According to the HRCT results, there were 26 patients in Group I (lung fibrosis) and 17 patients in Group II (no lung fibrosis). There was no significant intergroup difference in age or sex, but disease duration was longer for patients with pulmonary fibrosis (12.9 ± 10 years vs. 8.1 ± 4.9 years, p < 0.03). LV systolic function and mass were also similar between groups. Regarding the assessment of RV function, except for the significant (p = 0.02) decrease in tissue Doppler s' velocities in patients with pulmonary fibrosis on chest CT, all indexes of RV performance were similar. (Table 1)

Discussion

As lung fibrosis and pulmonary hypertension are the leading causes of death in SSc,[5] the 2013 Classification Criteria defined visceral involvement as the lung only.[4] The early recognition of lung involvement is essential as *more than two-thirds of* patients will have interstitial abnormalities on chest HRCT,[6] which is well-established as an accurate and noninvasive tool for detecting and characterizing lung fibrosis.[7] The HRCT pattern in SSc patients is generally nonspecific interstitial pneumonia, with a greater proportion of ground-glass opacity and a lower proportion of coarse reticulation.[8] We studied two groups of patients with SSc with HRCT, one with lung fibrosis and the other without fibrosis, and showed that patients with SSc and lung fibrosis have significant lower tissue Doppler s' velocities than patients without fibrosis. A decrease in tissue Doppler velocities in patients with SSc, along with an increase in MPI, was already observed in association with a worse prognosis,[9] allowing the speculation that RV dysfunction could be related to RV fibrosis. Our findings are new because we showed the association between decreased longitudinal RV function and the presence of lung fibrosis. RV myocardial fibrosis reportedly occurred

Tabela 1 - Clinical and echocardiographic variables of patients with (Group I) and without (Group II) lung fibrosis.

	Group I (n=26)	Group II (n=17)	*p*
Age, years	53±11	51±12	NS
Female sex	23 (88%)	16 (94%)	NS
Disease duration, years	12.9±10	8.1±4.9	0,03
LV EF, %	62±2	64±4	NS
LV mass index, g/m2	92±18	89±34	NS
E/e' septal	11±4	11±3	NS
FAC, %	48±6	45±6	NS
RV s', cm/s	11.9±1.6	13.5±2.4	0,02
RV MPI	0.48±0.1	0.46±0.1	NS
TAPSE, mm	22.0±3.2	23.3±4.8	NS
PASP, mmHg	32±16	28±12	NS

EF, ejection fraction; FAC, fractional area change; LV, left ventricular; MPI, myocardial performance index; PASP, pulmonary artery systolic pressure; RV, right ventricular; s', systolic tissue Doppler wave; TAPSE, tricuspid annular plane systolic excursion. Values are shown as mean ± standard deviation or n (%).

concomitantly with lung fibrosis in pathological studies, so it is conceivable that RV dysfunction (assessed by RV s' velocity) results from RV fibrosis, particularly in this sample with a low prevalence of pulmonary hypertension (only five patients).

We acknowledge that this hypothesis is predominantly speculative, as endomyocardial biopsies were not performed to correlate histopathological findings with imaging techniques; however, these patients had no other right heart disease that would fully explain the decrease in tissue Doppler velocity. Furthermore, endomyocardial biopsy also has some disadvantages: myocardial fibrosis can be found in a patchy distribution throughout the myocardium, thus limiting biopsy accuracy, apart from being invasive and not without risk, in addition to a lack of studies with subclinical heart disease.

Histopathological studies comparing patients with SSc and idiopathic pulmonary hypertension showed a similar degree of RV myocardial fibrosis but greater inflammation in the former.[10] Tissue Doppler was able to identify incipient RV dysfunction better than other conventional parameters of RV performance. Tissue Doppler velocities are reduced in cardiomyopathies and have been used for the preclinical detection of several diseases. We also found no association with TAPSE, mainly due to pulmonary hypertension.[11]

The assessment of RV function is critical in these patients, as studies analyzing survival among patients with SSc have shown worse survival in patients with a high mean right atrial pressure and low cardiac index. A study comparing SSc patients with a control group using echocardiography with tissue Doppler observed a decrease in biventricular systolic and diastolic dysfunction; after a 3-year follow-up, the deterioration of these indices was also reported.[12]

The prevalence of PH in SSc is variable and depends on the method of detection and the population studied. Although cardiac catheterization is considered the gold standard for investigating PH, Doppler echocardiography is an important screening factor in daily rheumatologic practice.[13] Using transthoracic Doppler echocardiography, the prevalence of PAH is reportedly 13–35%.[14] This study had a low prevalence of PH, most likely due to the exclusion of patients with right and left myocardial dysfunction. Additionally, there was no significant difference in the presence of PH between subgroups.

Therefore, tissue Doppler s' velocity could be used as a potential predictor of RV dysfunction and possible pulmonary fibrosis in patients with SSc. Tissue Doppler has the advantage of being less dependent on load than usual indexes used to evaluate RV myocardial performance and could be used to serially monitor RV performance in patients with SSc. The RV s' velocity represents the integral of myocardial shortening velocity from base to apex; therefore, it provides information on global rather than regional ventricular function.

Limitations: As stated above, the presence of RV myocardial fibrosis can only be speculated since endomyocardial biopsies were not performed in this population. Moreover, delayed enhancement magnetic resonance imaging has been used to assess the presence of myocardial fibrosis in the LV,[15] so additional studies are necessary to identify the pattern and presence of RV fibrosis in association with lung fibrosis in patients with SSc.

In conclusion, this study showed that tissue Doppler systolic velocity may be an early indicator of myocardial RV involvement in patients with SSc and pulmonary fibrosis and could potentially be used to monitor RV performance in this population.

Authors' contributions

Each author contributed individually and significantly to the development of this article. Rodrigues ANT: conception and writing of the manuscript; Kay FU: CT assessment; Roque MCF and Becker D: performance of exams and measurements; Gripp TEH: tomography evaluation; Arruda AL: writing of the manuscript; Cerri GG and Sampaio-Barros PD; manuscript review.

Conflict of interest

The author declares that he has no conflict of interest

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