Seminars in Arthritis and Rheumatism ▮ (2015) ▮▮▮–▮▮▮

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

A right ventricular diastolic impairment is common in systemic sclerosis and is associated with other target-organ damage

Christophe Meune, MD, PhD[a,b,c,*], Dinesh Khanna, MD[d], Jamil Aboulhosn, MD[e], Jérôme Avouac, MD, PhD[f,**], André Kahan, MD[f], Daniel E. Furst, MD[e], Yannick Allanore, MD, PhD[f]

[a] Department of Cardiology, Paris 13 University, Avicenne Hospital, AP-HP, 125 rue de Stalingrad, Bobigny 93000, France
[b] UMR S 942, Lariboisière Hospital, Paris, France
[c] Department of Cardiology, Paris-Descartes University, Cochin Hospital, AP-HP, Paris, France
[d] University of Michigan Scleroderma Program, Ann Arbor, MI
[e] Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA
[f] Department of Rheumatology A, Paris-Descartes University, Cochin Hospital, AP-HP, Paris, France

ARTICLE INFO

Keywords:
Systemic sclerosis
Cardiovascular
Echocardiography
Myocardial involvement
Diastolic dysfunction
Right ventricle

ABSTRACT

Objective: Heart involvement in systemic sclerosis (SSc) is a strong prognostic factor. Our aim was to examine left ventricle (LV) and right ventricle (RV) involvement.
Methods: We examined LV and RV, systolic and diastolic functions, using echocardiography and Tissue-Doppler echocardiography (TDE) indexes, in a cohort of 212 consecutive SSc patients seen during a 9-month period at 2 institutions (Paris, France and Los Angeles, USA). They were compared to 50 healthy controls.
Results: When compared to controls, SSc patients had consistently impaired RV indices that include reduced RV contractility ($p < 0.001$), larger right atrial area ($p = 0.027$) and overall RV diastolic dysfunction (25% of SSc patients versus 0% of controls; $p < 0.001$). Patients also exhibited alterations in LV contractility and diastolic function ($p < 0.001$ each). In multivariate analysis, RV contractility as expressed by the TDE S_T parameter was associated with $_T$DE LV contractility S_M ($p = 0.030$), DLCO ($p = 0.013$) whereas RV diastolic impairment was associated with systolic pulmonary artery pressure ($p = 0.015$). A subgroup of 27 patients had proven pulmonary arterial hypertension (PAH); comparison between SSc-PAH versus SSc free of PAH patients revealed reduced LV diastolic function (transmitral *E/A* ratio, $p = 0.045$ and $E_A < 10$ cm/s, $p = 0.029$), reduced overall RV contractility (21.5% versus 4.5%; $p = 0.03$) and reduced RV diastolic function (transtricuspid *E/A* ratio; $p = 0.014$ and 68% versus 29% with impaired function; $p = 0.001$).
Conclusions: Our data show that RV is commonly affected in SSc with predominant impaired diastolic function. Several factors, including primary heart, lung vascular disease and pulmonary hypertension, contribute to such impairment.

Introduction

Systemic sclerosis (SSc) is a connective tissue disease characterized by widespread vascular lesions and fibrosis of the skin and internal organs [1]. The prevalence of cardiac involvement varies dramatically between studies, ranging from 5% to near 100%, depending on the studied population, the study sample size and the tool used for assessment [1–5]. However, it is a poor prognostic factor according to a recent meta-analysis [6]. All cardiac tissues may be affected by SSc. In addition, secondary heart disease involvement due to severe internal organ damage, such as pulmonary arterial hypertension (PAH), severe interstitial lung disease or renal crisis, can occur [1,4,7–9].

Theoretically, the right ventricle (RV) might be affected very early in the course of the disease [10] as it might be involved in both primary myocardial involvement and/or lung vascular or lung interstitial disease, which are common in SSc [10–12]. While several studies reported possible RV alterations in SSc patients PAH [13–16], only a few, small series investigated RV function in unselected SSc patients [4,17–21]. The limitations of the sample

* Corresponding author at: Department of Cardiology, Paris 13 University, Avicenne Hospital, AP-HP, 125 rue de Stalingrad, 93009 Bobigny Cedex, France
** Corresponding author.
E-mail addresses: christophe.meune@avc.aphp.fr (C. Meune), javouac@me.com, jerome.avouac@cch.aphp.fr (J. Avouac).

http://dx.doi.org/10.1016/j.semarthrit.2015.07.002
0049-0172/

size and of the various tools used for the assessments in those studies did not permit a clear picture of the prevalence, impairment of diastolic function and risk factors.

RV function is a strong prognosticator in various conditions, including pulmonary hypertension (PH) [22,23] or heart failure [24], highlighting the critical need for its careful evaluation [4,13–18]. Furthermore, in the context of SSc, recent data suggested that intrinsic RV dysfunction might contribute to the poorer outcomes observed in SSc-PAH compared to idiopathic PAH [25]. The aim of the present study is to investigate RV systolic and diastolic function, in a large SSc cohort of unselected patients compared to a control group.

Methods

This cohort study enrolled consecutive patients with confirmed SSc, after informed consent, at 2 tertiary institutions that were highly skilled in the management of SSc patients (the Rheumatology A and Cardiology departments at Cochin Hospital, Paris, France and the Rheumatology and Pulmonary and Radiology departments at University of California at Los Angeles Hospital, CA). Disease duration was determined based on the first non-Raynaud symptom of the disease. The local ethics committees approved the protocol.

We carried out a complete evaluation of all these patients, laboratory testing including autoantibody determination (anti-topoisomerase-1 and anti-centromere antibodies), chest computed tomography scan and measurement of forced vital capacity (FVC) and the diffusing capacity for carbon monoxide (DLCO). Lung fibrosis was defined by 30% of lung parenchymal involvement on CT scan.

Patients with suspected PAH, based on (a) DLCO% $<55\%$ predicted without severe interstitial lung disease, or (b) an estimated systolic pulmonary arterial pressure ≥ 40 mm Hg on echocardiogram (see below), or (c) if they complained of unexplained dyspnea [7,26], underwent right heart catheterization (RHC). PAH was confirmed if pulmonary artery pressure (mPAP) $\geq$ 25 mm Hg and pulmonary capillary wedge pressure <15 mm Hg on RHC [27]. Patients with already known PAH were not included in the study, as well as those with previous coronary heart disease, heart failure and/or severe clinically lung disease (i.e., those treated with discontinued oxygen therapy).

The echocardiographic findings of the SSc patients were compared with those of age-sex matched controls chosen on a 4:1 ratio.

Echocardiographic Measurements

All patients underwent a complete echocardiographic study after they rested for 20 min at ambient room temperature, performed by senior cardiologists according to the recommendations of the American Society of Echocardiography. LV ejection fraction (EF) was based on the Simpson's method (LVEF $<$ 55% was defined as abnormal). Pulmonary arterial pressure (PAP) was calculated from the transtricuspid pressure gradient, after the addition of an estimated 5–10 mm Hg right atrial pressure based on inferior cava venous dimension and its collapsibility.

In addition, pulsed tissue-Doppler echocardiography (TDE) was used to measure systolic mitral annular velocity (S_M), lateral annulus early diastolic velocity (Ea), tricuspid systolic annular velocity (S_T) and tricuspid annular early diastolic velocity (E_T) [4,28]. The systolic movement of the base of the RV free wall was also measured by M-mode imaging from an apical 4-chamber view to determine the tricuspid anteroposterior systolic excursion (TAPSE), a strong measurement of RV longitudinal function [29].

RV reduced contractility was defined as the existence of a TAPSE $<$ 16 mm or $S_T < 10$ cm/s as suggested [28]. RV diastolic dysfunction was defined as impaired relaxation (tricuspid E/A ratio $<$ 0.8), pseudo-normal RV filling (tricuspid E/A ratio of 0.8–2.1 together with a tricuspid E/E_T ratio $>$ 6), or restrictive filling in case of tricuspid E/A ratio $>$ 2.1 [28].

Statistical analyses

The data are expressed as means $\pm$ standard deviation (SD) for Gaussian variables, median [25–75th percentile] for non-Gaussian continuous variables, and numbers and percentages for categorical variables. Patients with SSc were compared with controls, as well as SSc patients with versus without proven PAH and SSc patients with versus without severe lung involvement, using Mann–Whitney test for comparisons of continuous variables and chi-square or Fisher's exact test for differences in frequency as appropriate. Spearman correlations tests were performed to detect the presence of correlations between variables. The possible role played by selected variables in relationship to RV function was examined in univariable analysis using linear regression analyses. As RV contractility indexes are continuous variables with threshold values recommended by guidelines [28], we also examined the possible relation between different variables and RV contractility indexes expressed as categorical variables (below and under the cut-off value). Multivariable regression was then performed and included all variables that emerged from univariable analysis. $p < 0.05$ was defined as statistically significant. The STATA statistical software, version 10.1 (StataCorp LP, College Station, TX) was used for all data analysis.

Results

A total of 212 SSc patients were included (female 81%, age 55 $\pm$ 13 years) and compared to 50 controls (female 84%, age 53 $\pm$ 11 years). The baseline characteristics of the total cohort, the 107 patients from Cochin (Paris, France) and the 105 patients from Los Angeles (CA, USA) are presented in Table 1, while their main echocardiographic findings are listed in Table 2. Most of the characteristics of the patients from the 2 institutions were similar. Patients from the French center, when compared to the US center, had a lower prevalence of lung fibrosis ($p = 0.001$), lower erythrocyte sedimentation rate and CRP concentrations ($p = 0.006$ and $p < 0.001$ respectively), were more often treated with calcium channel antagonists ($p < 0.001$). To increase the power of the subsequent analyses, the 2 cohorts were combined for in-depth echocardiographic analyses, including SSc subsets comparisons.

Comparison of SSc patients versus controls

The mean age, sex distribution, and mean systolic and diastolic blood pressure of the patients with SSc and controls were similar (Table 3). The proportion of patients with cardiovascular risk factors was low (smokers 6.4%, diabetes 3.2%, known hypertension 27.3%) and did not differ when compared with controls. When compared to controls, SSc patients had increased heart rate, reduced LVEF (61 $\pm$ 7% versus 67 $\pm$ 3% in controls, $p < 0.001$) although only a small proportion had LVEF $<$ 55% (3.8% versus 0.0% respectively, $p = 0.361$). They also had reduced mitral Doppler E/A ratio. Similar results were obtained with TDE indexes ($S_M = 9.8 \pm 2.2$ cm/s versus 11.9 $\pm$ 2.7 cm/s, $p < 0.001$, 10.8 versus 0.0% having $S_M < 7.5$ cm/s, $p = 0.010$, $E_A < 10$ cm/s in 35.8% SSc patients versus 12.0% controls, $p < 0.001$); surprisingly left atrial areas were not different (Table 3).