Seminars in Arthritis and Rheumatism 43 (2014) 673–680

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

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

Tissue Doppler imaging in systemic sclerosis: A 3-year longitudinal study

Michele D'Alto, MD, PhD[a], Giovanna Cuomo, MD[b], Emanuele Romeo, MD, PhD[a], Paola Argiento, MD, PhD[a], Michele Iudici, MD[b], Serena Vettori, MD, PhD[b], Maria Giovanna Russo, MD[a], Raffaele Calabrò, MD[a], Gabriele Valentini, MD[b,*]

[a] *Department of Cardiology, Second University of Naples, Monaldi Hospital, Naples, Italy*
[b] *Rheumatology Unit, Second University of Naples, II Policlinico, Via Pansini 5, Naples 80131, Italy*

ARTICLE INFO

Keywords:
Systemic sclerosis
Tissue Doppler imaging
Ventricular function
Pulmonary artery systolic pressure

ABSTRACT

Objectives: To investigate by standard echocardiography and pulsed-tissue Doppler imaging (TDI) the course of systemic sclerosis (SSc) heart disease and its correlation with epidemiological, clinical, and serological features of the disease and drug treatment.
Methods: A total of 74 consecutive patients (69 females, between the ages of 19 and 71 years, and disease duration 1–43 years) and 71 controls underwent cardiac assessment at baseline and at 3-year follow-up.
Results: At baseline, compared to controls, patients showed post-Bonferroni correction, impaired left (LV) and right ventricular (RV) diastolic function (E_m/A_m 0.85 ± 0.4 vs 1.5 ± 0.7, $p = 0.0003$; E_t/A_t 0.9 ± 0.3 vs 1.3 ± 0.4, $p = 0.0003$), subtle LV and RV systolic dysfunction (S_m 13.7 ± 2.7 vs 15.4 ± 3.2 cm/s, $p = 0.031$; $S_t < 11.5$ cm/s in 16/74 patients vs 0 controls, $p = 0.0031$), and higher pulmonary artery systolic pressure (sPAP) (26.1 ± 6.0 vs 24.1 ± 5.1, $p = 0.040$). At 3-year follow-up, SSc patients showed a further deterioration of biventricular diastolic and systolic function and a further sPAP increase. At multiple regression analysis of baseline data, $E_m/A_m < 1$ was detected in 55/74 patients vs 25/71 controls ($p < 0.0001$) and was associated with age ($p = 0.030$); $E_t/A_t < 1$ was detected in 16/74 patients vs 7/71 controls ($p < 0.0001$), was associated with NYHA class ≥ II ($p = 0.033$), late capillaroscopic pattern ($p = 0.029$), and a baseline cardiac Medsger severity score ≥ 1 ($p = 0.029$). TDI evidence of new abnormalities in RV and/or LV diastolic function was associated with a baseline cardiac Medsger severity score ≥ 1 ($p = 0.01$). Neither diastolic or systolic abnormalities nor sPAP changes correlated with treatment.
Conclusions: Our study confirms that SSc patients exhibit biventricular systolic and diastolic dysfunction and increased sPAP and reveals further deterioration at 3-year follow-up.

Introduction

Systemic sclerosis (SSc) is a clinically heterogeneous, multisystem autoimmune disorder characterized by widespread vascular lesions and fibrosis of the skin and internal organs [1] and a shortened survival rate due to SSc heart disease (HD) in approximately 30% of patients [2]. Formerly, the prevalence of HD in SSc patients estimated from autopsy studies [3] was higher than that detected by clinical examination and routine investigations [4]. However, subsequently, standard echocardiography (SE) [5–10], 24-h Holter electrocardiography [11], myocardial perfusion scintigraphy [12,13], and magnetic resonance imaging [14] have greatly improved the diagnostic accuracy of SSc-HD, so that its prevalence in the clinical setting now approximates that reported in autopsy studies [3,15]. Cross-sectional studies based on SE have repeatedly shown a high prevalence of left and right relaxation abnormalities and a very low frequency of depressed systolic function [5–10]. Tissue Doppler imaging (TDI) is a widely available, non-invasive technique that detects left and right diastolic and systolic functional abnormalities with a higher sensitivity and specificity than SE [16,17]. Various cross-sectional studies have investigated SSc-HD using TDI [18–24].

In a previous retrospective analysis of 77 prospectively enrolled SSc patients undergoing 2 or more SE examinations, we found that left ventricular (LV) filling dysfunction is progressive and precedes the occurrence of LV remodeling, and that systolic dysfunction, defined as LV ejection fraction <55%, is infrequent [25]. More recently, we used SE and pulsed TDI to evaluate pulmonary vascular response to exercise in consecutive SSc patients from 2 Italian centers (Naples and Pavia) to evaluate pulmonary vascular response to exercise [26]. In that study, SE and pulsed TDI were performed in all the SSc patients enrolled. Given the lack of

* Corresponding author.
E-mail address: gabriele.valentini@unina2.it (G. Valentini).

0049-0172/$ - see front matter © 2014 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.semarthrit.2013.10.004

longitudinal studies in SSc using TDI, we evaluated by both SE and TDI the Naples patients 3 years later to investigate the course of SSc-HD and look for correlations between SSc-HD and epidemiological, clinical, and serological features of the disease and drug treatment.

Methods

Patients

The study group consisted of 74 patients with SSc (69 females, 5 males; between the ages of 19 and 71 years, median = 54 years; with a disease duration between 1 and 43 years, median = 12 years), all of whom satisfied the 1980 ACR preliminary criteria for classification of the disease [27]. Of the original Naples series consisting of 87 patients, 13 were not reinvestigated at the end of follow-up. Of these 13 patients, 2 died (1 from lung cancer and 1 from sudden death), 1 suffered a myocardial infarction, 1 was undergoing hemodialysis after a scleroderma renal crisis, 1 became pregnant, 4 withdrew consent, and 4 moved out of Naples and declined to return for follow-up. However, these patients did not differ from the 74 patients included in the present study in terms of epidemiological, clinical, and serological features and SE and TDI parameters at baseline.

All patients were assessed using the EUSTAR Minimal Essential Data Set [28]. Patients were divided into 2 subsets (diffuse or limited cutaneous, dc- and lc-SSc) according to the classification of LeRoy et al. [29]. Autoantibody profile and capillaroscopic abnormalities were investigated as previously described [30]. Disease duration was calculated from the appearance of Raynaud's phenomenon. Disease activity was assessed with the EScSG activity index [31,32], and disease extent and severity were assessed with the revised Medsger scale [33]; a score ≥ 1 was considered indicative of each organ/system involvement (i.e., for cardiac disease, the presence of a conduction defect and/or a left ventricle ejection fraction less than 50%, and for lung disease, the presence of a lung diffusion for carbon monoxide and/or a forced vital capacity $<80\%$ of the respective predicted values). Of the 74 patients, 9 (12%) exhibited systemic arterial hypertension at baseline and after 3 years. Moreover, since diastolic and systolic right and left heart function might be affected by age, sex, body mass index, and blood pressure in both patients and controls and by disease duration and the severity of cardiac and lung disease in SSc patients, we evaluated the correlation among each of these features and SE and TDI parameters.

Medications

During the interval between the 2 observations, all patients were treated with low-dose aspirin, nifedipine (20–60 mg), and proton pump inhibitors. In addition, 11/74 (15%) patients were also treated with ACE inhibitors for systemic hypertension, 56/74 (76%) received low-dose corticosteroids ($\leq$10-mg prednisone equivalent) and vitamin D supplementation, 33/74 (45%) received low-dose pulse cyclophosphamide (500 mg upto a cumulative dose of 10 g) administered for either active alveolitis or early diffuse disease and followed by either azathioprine or mycophenolate mofetil, and 14/74 (19%) received intercurrent iloprost infusion for ischemic ulcers developed despite treatment with calcium channel blockers. Any medication affecting heart rate or vascular function (i.e., nifedipine and iloprost) was discontinued at least 7 days before SE and TDI examination. This washout period was chosen to ensure that heart rate was not influenced by these drugs, because heart rate can affect some SE and TDI parameters [34,35].

The epidemiological, clinical, and serological characteristics of SSc patients are listed in Table 1. This series mainly consisted of patients with lc-SSc (85%) with a disease duration >5 years (84%), a slow course (EScSG activity index <3 in 89% of cases), and a prevalence of HD, as determined by history, clinical examination, and ECG and ejection fraction assessment, as low as 22 out of 74 patients (29.7%).

Controls

A total of 71 patients' sex-, age-, weight-, and body surface area-matched controls (66 females, 5 males; between the ages of 18 and 72 years, median = 54 years) who were admitted to the cardiology unit for a cardiologic assessment before undergoing a minor surgical intervention and who agreed to participate in the study were selected for comparison. At the first evaluation, clinical examination, ECG, and chest X-ray were unremarkable. Of the 71 controls, 8 (11%) exhibited mild or moderate systemic arterial hypertension. Similar to SSc patients, any medication affecting heart rate or vascular function was discontinued at least 7 days before SE and TDI examination.

Echocardiography

Echocardiographic examination was performed by 2 highly trained, independent cardiologists (M.D. and P.A.), blinded to the clinical characteristics of the study population, using commercially available equipment with a phased array system (Philips iE33 ultrasound machine, Philips Medical Systems, Andover, MA) and a 2.5- or 3.5-MHz transducer. The procedure was performed in accordance with international recommendations [36,37]. Specific views included the parasternal long- and short-axis views (at the mitral valve and papillary muscle level); apical 4-, 2-, and 3-chamber views; and subcostal views, including respiratory motion of the inferior vena cava. Pulsed, continuous wave and color Doppler interrogation was performed on all 4 cardiac valves. Tissue Doppler imaging was performed to evaluate diastolic and systolic function of both the left and right ventricle from the 4-chamber view. Specific measurements were made by the average of 3–5 cardiac cycles.

M- and B-mode measurements

Left ventricular diastolic and systolic diameters, interventricular septum, and posterior wall thickness were assessed in the parasternal long-axis view with the patient in the left lateral position. Left ventricular ejection fraction was calculated with the biplane Simpson's rule in the apical 4- and 2-chamber views. Left atrial maximal volume was measured at the point of mitral valve opening using the biplane area–length method, and was corrected for body surface area [36]. Right ventricular (RV) end-diastolic chamber size was assessed accurately according to the American Society of Echocardiography guidelines for the echocardiographic assessment of the right heart in adults [38]. Right atrial (RA) measurements were obtained in the apical 4-chamber view. Right atrial area was estimated by planimetry at end systole (largest volume), tracing from the lateral aspect of the tricuspid annulus to the septal aspect, excluding the area between the leaflets and annulus, following the RA endocardium, excluding the inferior and superior vena cava and the RA appendage [38]. Tricuspid annular plane systolic excursion (TAPSE) was calculated as an index of RV longitudinal systolic function by placing an M-mode cursor through the tricuspid annulus in a standard apical 4-chamber window and measuring the difference between end-diastolic and end-systolic amount of longitudinal motion of the annulus.