Research Article

Pulmonary Circulation

Hemodynamic changes after acute fluid loading in patients with systemic sclerosis without pulmonary hypertension

Michele D'Alto[1], Emanuele Romeo[1], Paola Argiento[1], Agostino Mattera Iacono[1], Serena Vettori[2], Antonella Riccardi[2], Yannick Allanore[3], Antonello D'Andrea[4], Gaetano Rea[5], Eduardo Bossone[6], Gabriele Valentini[2], Robert Naeije[7] and Paolo Golino[1]

[1]Cardiology, University "L. Vanvitelli" – Monaldi Hospital, Naples, Italy; [2]Rheumatology, University "L. Vanvitelli" Naples, Italy; [3]Rheumatology, A department, Cochin Hospital, Paris Descartes University, Paris, France; [4]Cardiology, Umberto I Hospital, Nocera, Italy; [5]Radiology, Monaldi Hospital, Naples, Italy; [6]Cardiac Rehabilitation, Cardarelli Hospital, Naples, Italy; [7]Department of Cardiology, Erasme University Hospital, Brussels, Belgium

Abstract

A fluid challenge with a rapid infusion of saline helps to discriminate between pre- and post-capillary pulmonary hypertension (PH) and allows unmasking hidden post-capillary PH. Systemic sclerosis (SSc) patients may present with biventricular systolic and diastolic dysfunction. The aim of this study was to evaluate the hemodynamic changes of the pulmonary circulation in SSc patients without PH after a fluid challenge. Twenty-five SSc patients and 25 controls underwent right heart catheterization in basal conditions and after volume loading with saline infusion of 7 mL/kg over 5–10 min. At baseline, there was no difference in hemodynamics between SSc patients and controls. Rapid volume loading resulted in a significant increase in pressures and flows in both groups. Increases in right atrial pressure (3 ± 1 vs. 2 ± 1 mmHg, $P = 0.03$), mean pulmonary artery pressure (5 ± 1 vs. 3 ± 1 mmHg, $P < 0.001$), and pulmonary artery wedge pressure (PAWP; 5 ± 2 vs. 3 ± 1 mmHg, $P < 0.001$) were larger in SSc patients than in controls. Conversely, cardiac index (0.4 ± 0.2 vs. 0.6 ± 0.3 L/min/m^2, $P = 0.005$) increased less in SSc patients than in controls. Pulmonary vascular resistance did not differ between groups before and after volume loading. Four SSc patients and only one of the controls reached a PAWP > 18 mmHg suggesting latent left heart failure. Even if differences are small and not diagnostic for heart failure, SSc patients without PH have a larger increase in pulmonary vascular pressures and a smaller increase in cardiac output than controls after an acute volume loading, probably due to subclinical left ventricular diastolic dysfunction.

Keywords

systemic sclerosis, fluid challenge, pulmonary hypertension

Date received: 17 September 2018; accepted: 7 November 2018

Pulmonary Circulation 2018; 9(1) 1–6
DOI: 10.1177/2045894018816089

Systemic sclerosis (SSc) is a multi-system autoimmune disorder characterized by widespread vascular lesions and fibrosis of the skin and internal organs[1] with a shortened survival rate mainly due to lung and heart disease related to heart failure. Heart involvement is reported in approximately 30% of SSc patients.[2] A large number of studies have investigated heart diseases in SSc patients using different non-invasive modalities, mainly echocardiography.[3–8]

Heart failure with preserved ejection fraction (HFpEF) due to diastolic dysfunction may be challenging to diagnose, even with invasive hemodynamic data.[9] For this reason, there is an increasing use of fluid challenge test (FCT) in the catheterization laboratory. In fact, acute volume loading increases left ventricular end-diastolic volume and filling pressures[10] and is useful for unmasking hidden post-capillary pulmonary hypertension (PH).[11]

The aim of this study was to evaluate the hemodynamic changes of the pulmonary circulation after a FCT in SSc patients without PH.

Corresponding author:
Michele D'Alto, Via Tino di Camaino, 6 - 80128 Naples, Italy.
Email: mic.dalto@tin.it

Methods

This was a prospective, single-center study. All consecutive patients with SSc meeting the 2013 American College of Rheumatology/European League against Rheumatism classification criteria (12) referred to the Pulmonary Hypertension Unit of Monaldi Hospital, Naples (Italy), to undergo right heart catheterization (RHC) for suspicion of PH, between 1 January 2014 and 31 December 2015, were considered.

All patients were assessed using the European Scleroderma Trials and Research Group minimal essential dataset.[13] Patients were divided into two subsets (diffuse or limited cutaneous SSc) according to the classification of LeRoy et al.[14] Autoantibody profile and capillaroscopic abnormalities were investigated as previously described.[15] Disease duration was calculated from the onset of Raynaud's phenomenon. Disease activity was assessed with the European Scleroderma Study Group activity index,[16,17] and disease extent and severity were assessed with the revised Medsger scale;[18] a score ≥ 1 was considered indicative of each organ/system involvement (i.e. for cardiac disease, at least the presence of a conduction defect and/or a left ventricular ejection fraction <50%; and for lung disease, at least the presence of a lung diffusion for carbon monoxide and/or a forced vital capacity <80% of the respective predicted values, the presence of bibasilar crackles at lung auscultation, bibasilar fibrosis at standard chest X-ray).

The patients underwent a step-by-step diagnostic work-up according to current guidelines on PH,[19] thus including clinical evaluation, lung function tests, echocardiography, chest high-resolution computed tomography scan and ventilation/perfusion scan.

The non-invasive score, named H_2FPEF,[20] has been used to better characterize the patients and estimate the probability of HFpEF.

An invasive evaluation was decided only if thought to be clinically relevant.

RHC without sedation was performed by two experienced cardiologists (MD and ER). Measurements of right atrial pressure (RAP), right ventricular (RV) pressure, systolic, mean and diastolic pulmonary pressures (sPAP, mPAP, and dPAP, respectively), and pulmonary artery wedge pressure (PAWP) were taken at end-expiration. Cardiac output (CO) was measured by thermodilution using an average of at least three measurements. Pulmonary vascular resistance (PVR) was calculated as mPAP minus PAWP (transpulmonary pressure gradient [TPG]) divided by CO. The diastolic pressure gradient (DPG) was calculated as dPAP minus PAWP.

FCT was performed as previously described[11] by intravenous administration of 7 mL/kg saline over 5–10 min during RHC. All hemodynamic measurements were repeated immediately after the end of the saline administration.

All SSc patients not satisfying the criteria for PH diagnosis (mPAP < 25 mmHg) and age- and sex-matched controls were enrolled in this study. The presence of atrial fibrillation or flutter was considered exclusion criteria.

All patients gave written informed consent and the study was approved by the Institutional Review Board at Monaldi Hospital, Naples (Italy).

Results are reported as mean ± standard deviation unless otherwise noted. In between-group differences, continuous variables were compared by Kruskal–Wallis tests, whereas categorical variables were compared by Student–Newman–Keuls test.

Statistical analysis was performed using MedCalc, version 16.4.3 (MedCalc Software, Ostend, Belgium).

Results

SSc group

The SSc study group consisted of 25 patients (23 women; mean age = 66 ± 9 years; median disease duration = 14 years; range = 1–50 years).

Data on clinical, serological characteristics, organ involvement, and therapies are available for 21/25 patients and are listed in Table 1.

All patients were treated with low-dose aspirin, nifedipine (20–60 mg), and proton pump inhibitors. In addition, 12/21 (57%) patients were also treated with either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for systemic hypertension, 16/21 (76%) received low-dose corticosteroids (≤10 mg prednisone equivalent) and vitamin D supplementation, 11/21 (52%) received low-dose pulse cyclophosphamide (500 mg up to a cumulative dose of 10 g) administered for either active alveolitis or early diffuse disease and followed by either azathioprine or mycophenolate mofetil, and 1/21 (5%) received intercurrent iloprost infusion for ischemic ulcers developed despite treatment with calcium channel blockers. No patient was under diuretic treatment.

Of 21 SSc patients, two (10%) had diabetes, three (14%) had coronary artery disease, four (19%) had hyperlipidemia, and one (5%) had severe obesity (body mass index [BMI] > 30 kg/m^2). The mean H_2FPEF score was 1.3 ± 0.8.

Controls

A total of 25 sex-, age-, weight-, and body surface area-matched controls (23 women; mean age = 65 ± 9 years) admitted to the Cardiology Unit of Monaldi Hospital, Naples (Italy), to undergo clinically indicated RHC and that showed normal pulmonary pressure (mPAP <25 mmHg) were selected for comparison.

Of 25 controls, 13 (52%) had hypertension and were on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, three (12%) had diabetes, (16%) four had coronary artery disease, four (16%) had hyperlipidemia, and one (4%) had severe obesity (BMI > 30 kg/m^2). The mean H_2FPEF score was 1.2 ± 0.8.

No patient was under diuretic treatment.

Table 1. Clinical, serological characteristics, organ involvement, and therapies at baseline of the 21/25 patients with systemic sclerosis.

Characteristics	
Disease subtype and clinical manifestations	
lcSSc	17/21 (81)
dcSSc	4/21 (19)
Years from RP (median, range)	14 (1–50)
RP	20/21 (95.2)
Scleroderma	1/21 (4.8)
Median modified Rodnan skin score (median, range)	1.5 (0–10)
Telangiectasia	18/21 (85.7)
History of and/or active DU and/or pitting scars	13/21 (61.9)
Sinovytis	1/21 (4.8)
Muscle weakness and/or CK elevation	9/21 (42.8)
Melanoderma	1/21 (4.8)
Gastrointestinal involvement	17/21 (81)
History of renal crisis	0
Autoantibodies	
ANA	21/21 (100)
ACA	9/21 (42.9)
ATA	10/21 (47.6)
RNA pol III	0
PM-Scl	0
Fibrillarin	0
Negative SSc-marker autoantibodies	0
Features of lung involvement	
FVC $<$ 80% predicted	7/21 (33.3)
DLCO $<$ 80% predicted	16/21 (76.2)
ILD on HRCT of the lungs	10/21 (47.6)
EScSG-AI (median, range)	1.75 (0–3)
EScSG-AI $\geq$ 3	3/21 (14.3)
Therapies	
Proton pump inhibitors	21/21 (100)
Low-dose aspirin	21/21 (100)
Calcium channel blockers	21/21 (100)
Glucocorticoids + vitamin D	16/21 (76)
Immunosuppressants	11/21 (52)
ACE-I/ARB	12/21 (57)
Prostanoids	1/21 (5)

Values are expressed as n (%), except where otherwise indicated.
ACA, anticentromere antibodies; ACE-I, angiotensin-converting enzyme inhibitors; ANA, antinuclear antibodies; ARB, angiotensin receptor blockers; ATA, anti-topoisomerase I antibodies; dcSSc, diffuse cutaneous systemic sclerosis; DLCO, diffusing lung capacity for carbon monoxide expressed as a percentage of the predicted value; DU, digital ulcers; EScSG-AI, European Scleroderma Study Group-Activity Index; FVC, forced vital capacity expressed as a percentage of the predicted value; HRCT, high resolution computed tomography; ILD, interstitial lung disease; lcSSc, limited cutaneous systemic sclerosis; RNA pol III, anti-RNA polymerase III; RP, Raynaud's phenomenon; SD, standard deviation; SSc, systemic sclerosis.

Table 2. Demographic, clinical, and echocardiographic features.

	Control (n = 25)	SSc (n = 25)	*P* value
Female sex (%)	23 (92%)	23 (92%)	1.0
BSA (m^2)	1.7 ± 0.2	1.6 ± 0.1	0.67
Age (years)	65 ± 9	66 ± 9	0.60
WHO FC			
I	20 (80%)	17 (68%)	
II	5 (20%)	8 (32%)	
III	0 (0%)	0 (0%)	
IV	0 (0%)	0 (0%)	
Systolic BP (mmHg)	126 ± 14	130 ± 15	0.39
Diastolic BP (mmHg)	69 ± 6	69 ± 7	0.92
Heart rate (bpm)	77 ± 9	79 ± 10	0.42
H_2FPEF score	1.3 ± 0.8	1.2 ± 0.8	0.48
Echocardiography			
LAVI (mL/m^2)	23 ± 7	25 ± 6	0.11
LVEDd (mm)	45 ± 5	47 ± 6	0.28
LVESd (mm)	28 ± 5	29 ± 4	0.15
IVS (mm)	10 ± 3	10 ± 4	0.79
PW (mm)	9 ± 4	8 ± 4	0.26
LVEF (%)	60 ± 5	62 ± 4	0.18
TAPSE (mm)	24 ± 5	22 ± 4	0.29
IVC (mm)	14 ± 6	13 ± 8	0.32
E/A	1.4 ± 0.5	1.2 ± 0.4	0.15
E/e′	5.8 ± 2.0	7.2 ± 2.7	0.02

Continuous variables are expressed as mean ± standard deviation.
A, A wave; BP, blood pressure; bpm: beats per minute; BSA, body surface area; E, E wave; e', E wave at mitral annulus; H_2FPEF, clinical and echocardiographic score for calculating the probability of heart failure with preserved ejection fraction; ICV, inferior cava vein; LAVI, left atrium volume index; IVS, interventricular septum; LVEDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESd, left ventricular end-systolic diameter; PW, posterior wall; TAPSE, tricuspid annulus plane systolic excursion; WHO FC, World Health Organization functional class.

Hemodynamics

Demographics, clinical, and echocardiographic features of SSc patients and controls are shown in Table 2. Baseline hemodynamics are shown in Table 3.

A higher E/e′ in SSc than in controls (7.2 ± 2.7 vs. 5.8 ± 2.0; $P = 0.02$) was the only difference between the two groups at echocardiographic evaluation.

Blood pressure, heart rate, and all hemodynamics did not differ between groups.

Notably, 9/25 SSc patients (36%) and 6/25 controls (24%) showed mPAP in the range of 21–24 mmHg and 4/25 SSc patients (16%) and 2/25 controls (8%) showed PAWP in the range of 12–15 mmHg.

FCT was well tolerated and no patient in both groups developed significant side effects.

Hemodynamics after fluid challenge are shown in Table 4, with changes in Table 5. CO, RAP, RV pressure, sPAP, mPAP, dPAP, and PAWP increased in both groups.

Table 3. Baseline hemodynamics.

	Control (n = 25)	SSc (n = 25)	*P* value
RAP (mmHg)	4 ± 1	4 ± 2	0.49
RV systolic pressure (mmHg)	28 ± 6	30 ± 6	0.27
Systolic PAP (mmHg)	27 ± 6	29 ± 6	0.15
Mean PAP (mmHg)	18 ± 3	19 ± 3	0.10
Diastolic PAP (mmHg)	11 ± 2	12 ± 3	0.6
PAWP (mmHg)	8 ± 2	9 ± 3	0.58
PAWP–RAP (mmHg)	4 ± 2	4 ± 2	0.90
Cardiac index (L/min·m^2)	3.3 ± 0.5	3.3 ± 0.5	0.83
PVR (Wood Units)	1.8 ± 0.7	2.0 ± 0.9	0.23
TPG (mmHg)	9 ± 3	11 ± 3	0.21
DPG (mmHg)	3 ± 2	3 ± 3	0.21

Continuous variables are expressed as mean ± standard deviation.
$P < 0.05$ vs. Control.
DPG, diastolic pressure gradient; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RV, right ventricular; SSc, systemic sclerosis; TPG, transpulmonary pressure gradient.

Table 4. Hemodynamics after fluid challenge.

	Control (n = 25)	SSc (n = 25)	*P* value
RAP (mmHg)	6 ± 1	7 ± 2	0.03
RV systolic pressure (mmHg)	31 ± 6	35 ± 6	0.04
Systolic PAP (mmHg)	30 ± 6	34 ± 6	0.04
Mean PAP (mmHg)	21 ± 3	24 ± 3	0.0002
Diastolic PAP (mmHg)	14 ± 2	17 ± 3	0.0001
PAWP (mmHg)	12 ± 3	14 ± 3	0.005
PAWP–RAP (mmHg)	5 ± 2	7 ± 3	0.077
Cardiac index (L/min·m^2)	4.0 ± 0.5	3.7 ± 0.6	0.13
PVR (Wood Units)	1.4 ± 0.6	1.7 ± 0.7	0.10
TPG (mmHg)	9 ± 3	10 ± 3	0.25
DPG (mmHg)	2 ± 1	3 ± 3	0.41

Values are expressed as mean ± standard deviation.
$P < 0.05$ vs. Control.
DPG, diastolic pressure gradient; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RV, right ventricular; SSc, systemic sclerosis; TPG, transpulmonary pressure gradient.

The increase in pressure values was proportionally larger and the increase in CO lower in SSc patients compared to controls. PVR, TPG, and DPG did not significantly change after FCT in both groups.

Four out of 25 SSc patients (16%) and 1/25 controls (4%) showed a PAWP ≥ 18 mmHg after fluid challenge. During a three-year follow-up, two patients developed HFpEF, both with SSc and a PAWP ≥ 18 mmHg after fluid challenge.

Table 5. Fluid challenge-induced changes in hemodynamics.

	Control (n = 25)	SSc (n = 25)	*P* value
Δ RA systolic pressure (mmHg)	2 ± 1	3 ± 1	0.03
Δ RV systolic pressure (mmHg)	3 ± 1	4 ± 2	0.001
Δ Systolic PAP (mmHg)	3 ± 1	4 ± 2	0.026
Δ Mean PAP (mmHg)	3 ± 1	5 ± 1	<0.001
Δ Diastolic PAP (mmHg)	3 ± 1	5 ± 1	<0.001
Δ PAWP (mmHg)	3 ± 1	5 ± 2	<0.001
Δ PAWP-RAP (mmHg)	1 ± 2	2 ± 2	0.02
Δ Cardiac index (L/min·m^2)	0.6 ± 0.3	0.4 ± 0.2	0.004
Δ PVR (Wood Units)	−0.4 ± 0.4	−0.3 ± 0.5	0.87
Δ TPG (mmHg)	0 ± 1	−1 ± 2	0.87
Δ DPG (mmHg)	0 ± 1	−1 ± 2	0.44

Values are expressed as mean ± standard deviation.
$P < 0.05$ vs. Control.
Δ: difference between before and after fluid challenge.
DPG, diastolic pressure gradient; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RV, right ventricular; SSc, systemic sclerosis; TPG, transpulmonary pressure gradient.

Discussion

The main finding of the present study is that fluid challenge with a rapid infusion of 7 mL/kg saline over 5–10 min at RHC induces a larger increase of pulmonary pressures and a smaller increase of flow in SSc patients without PH compared to controls.

Recently, a scoring system based on clinical and echocardiographic findings aimed to discriminate HFpEF from non-cardiac causes of dyspnea has been developed by Reddy et al.[20] and then validated in a separate test cohort. This score, named H_2FPEF, is based on the presence of six features: obesity; hypertension; atrial fibrillation; pulmonary hypertension; age > 60 years; and E/e′ > 9. The author found that the H_2FPEF score might be used to rule out the HFpEF among patients with low scores (e.g. 0 or 1) and to establish the diagnosis of HFpEF with reasonably high confidence at higher scores (e.g. 6–9). They suggest using additional tests for patients with intermediate scores (e.g. 2–5).

Among the four individuals showing a PAWP ≥ 18 mmHg after fluid challenge, three (two SSc patients and one control) had a H_2FPEF score of 2 and one (SSc patients) had a H_2FPEF score of 3.

HFpEF due to diastolic dysfunction may be challenging to diagnose, even with invasive hemodynamic data. These data underscore a different response to the fluid loading in SSc patients compared to controls and allows a more comprehensive decision-making process in patients with intermediate probability of HFpEF.

The diagnosis of post-capillary PH is based on a mPAP ≥ 25 mmHg and a PAWP > 15 mmHg.[19] Moreover, current guidelines on PH[19] recommend interpreting invasive

hemodynamics in the context of the clinical picture and imaging. In fact, PAWP in PH due to left heart diseases may be found below the threshold of 15 mmHg in the resting state in patients with optimal therapy and volume depletion on diuretic intake. Based on this pathophysiological observation, an acute fluid loading has been increasingly used in daily practice as an adjunctive tool to discriminate between pre- and post-capillary PH.

Previous studies[21,22] showed that the upper limit of normal for PAWP after rapid infusion of 500 mL saline would be 18 mmHg. Recently, our group[11] investigated the clinical relevance of a FCT systematically added to standard RHC in patients referred for suspicion or evaluation of PH. Prediction bands calculated from quadratic fits of the PAWP changes in pooled controls confirmed 18 mmHg as a valid cut-off value for diagnosing post-capillary PH. This cut-off value, together with other clinical and non-invasive tools such as echocardiography, allows reclassification of 6–8% of patients with pre-capillary PH or normal hemodynamics at baseline.

Lack of data exists so far for SSc patients. Fox et al.[23] reported on left- and right-sided heart catheterization in 107 patients with SSc. Based on mPAP and PAWP, 29 out of 107 patients received a diagnosis of pulmonary arterial hypertension (PAH) and 24 a diagnosis of post-capillary PH after baseline RHC. Eleven out of 29 patients with PAH (58%) were reclassified as post-capillary PH on the basis of a left ventricular end-diastolic pressure >15 mmHg at baseline (n = 5) or after fluid challenge with 500 mL of saline over 5–10 min (n = 6). Thus, fluid challenge helped reclassify 22% of the patients otherwise thought to have PAH. Nevertheless, based on previous studies,[11,21,22] the threshold of 15 mmHg after fluid loading seems too low for identifying patients with post-capillary PH.

This was at the time the first study evaluating the hemodynamic changes after acute fluid loading in patients with SSc without PH. The data of the present study show that patients with SSc have a larger increase of PAWP probably due to their well-known left ventricular diastolic dysfunction. The increase in left ventricular filling pressure is backward transmitted and provokes a similar larger increase in pulmonary pressures compared to controls. These data may be particularly relevant because fluid loading is going to be standardized for the differential diagnosis between pre- and post-capillary PH, which remains challenging in older, overweight patients and individuals with cardiovascular risk factors showing ambiguous PAWP at baseline RHC. In addition, a larger increase of PAWP may also be considered a possible cause of otherwise unexplained effort dyspnea.

Our study also points out a larger increase of pulmonary vascular pressures after FCT in SSc patients than in controls. This finding is likely related to the "fixed" vascular system that is characteristic of SSc vasculature.[24] In fact, pulmonary vessels as well as vessels from other body districts are unable to undergo a vasodilatation similar to that occurring in normal controls.[25] This hypothesis appears to be supported by the concomitant smaller cardiac index increase after FCT compared to controls, which might reflect a reduced "preload reserve" of the ventricles. Moreover, because fluid challenge transiently increases systemic venous return, it may test the capacity of the right ventricle to adapt to a sudden increase in preload. Analogously, a reduced "contractile reserve" has been previously detected in SSc patients without PH by non-invasive study[26] using physical effort. Taken together, these data reflect an impaired capability of the right ventricle to cope with an increased volume or pressure in SSc patients.

Finally, it has recently been demonstrated that a cardiac index $<2.8\ L/min/m^2$ after a fluid challenge is an independent predictor of clinical worsening in idiopathic PAH.[27] Therefore, we may speculate that an intrinsic reduction of the preload reserve in patients with SSc can play a role in the poorer prognosis of SSc patients when developing PAH.

Limitations

This study has some limitations.

The main limitation is the small sample size, which not allows sub-group comparisons.

Both groups, SSc patients and controls, required an invasive evaluation for suspicion of PH; for this reason, at baseline 36% of SSc patients and 24% of controls showed a mPAP of 21–24 mmHg and 16% of SSc patients and 8% of controls showed a PAWP in the range of 12–15 mmHg. Therefore, it could be that SSc patients with no clinical indication to RHC and perfectly healthy controls would have a lower PAWP after a 7 mL/kg fluid challenge. Moreover, as we mainly looked for PAH, it is not known the response to FCT in patients with severe chronic lung diseases or hypoxia with and without SSc that did not undergo RHC because not clinically indicated.

Conclusions

In summary, SSc patients without PH have a larger increase of pulmonary pressures and a lower increase of flow compared to controls after an acute volume loading. This is probably due to subclinical left ventricular diastolic dysfunction and suggests a reduced preload reserve. This may have clinical relevance in identifying the limits of normal of hemodynamics in SSc patients undergoing FCT. Further larger studies are needed to confirm these findings.

Conflict of interest

The author(s) declare that there is no conflict of interest.

Funding

This research received no grant from any funding agency in the public, commercial, or not-for-profit sectors.

ORCID iD

Michele D'Alto http://orcid.org/0000-0001-5729-1038

References

1. Varga J. Systemic Sclerosis (Scleroderma). In: Goldman L and Schaffer AI (eds) *Goldman's Cecil Medicine*, 24th ed. Philadelphia: Elsevier Saunders, 2012, pp.1705–1713.
2. Elhai M, Meune C, Avouac J, et al. Trends in mortality in patients with systemic sclerosis over 40 years: a systematic review and meta-analysis of cohort studies. *Rheumatology* 2012; 51: 1017–1026.
3. Maione S, Valentini G, Giunta A, et al. Evaluation of cardiac structures and function in systemic sclerosis by Doppler echocardiography. *Cardiology* 1991; 79: 165–171.
4. Valentini G, Vitale DF, Giunta A, et al. Diastolic abnormalities in systemic sclerosis: evidence for associated defective cardiac functional reserve. *Ann Rheum Dis* 1996; 55: 455–460.
5. Giunta A, Tirri E, Maione S, et al. Right ventricular diastolic abnormalities in systemic sclerosis. Relation to left ventricular involvement and pulmonary hypertension. *Ann Rheum Dis* 2000; 59: 94–98.
6. De Groote P, Gressin V, Hachulla E, et al. Evaluation of cardiac abnormalities by Doppler echocardiography in a large nationwide multicentric cohort of patients with systemic sclerosis. *Ann Rheum Dis* 2008; 67: 31–36.
7. D'Andrea A, Stisi S, Bellissimo S, et al. Early impairment of myocardial function in systemic sclerosis: non-invasive assessment by Doppler myocardial and strain rate imaging. *Eur J Echocardiogr* 2005; 6: 407–18.
8. D'Alto M, Cuomo G, Romeo E, et al. Tissue Doppler imaging in systemic sclerosis: a 3-year longitudinal study. *Semin Arthritis Rheum* 2014; 43: 673–680.
9. Borlaug BA and Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. *Eur Heart J* 2011; 32: 670–679.
10. Courtois M, Mechem CJ, Barzilai B, et al. Delineation of determinants of left ventricular early filling. Saline versus blood infusion. *Circulation* 1994; 90: 2041–2050.
11. D'Alto M, Romeo E, Argiento P, et al. Clinical relevance of fluid challenge in patients evaluated for pulmonary hypertension. *Chest* 2017; 151: 119–126.
12. van den Hoogen F1, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. *Arthritis Rheum* 2013; 65: 2737–2747.
13. Valentini G, Medsger TA Jr, Silman AJ, et al. Conclusion and identification of the core set of variables to be used in clinical investigations. *Clin Exp Rheumatol* 2003; 21(3 suppl 29): 47–48.
14. LeRoy EC, Black C, Fleischmajer R, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol* 1988; 15: 202–205.
15. Valentini G, Cuomo G, Abignano G, et al. Early systemic sclerosis: assessment of clinical and pre- clinical organ involvement in patients with different disease features. *Rheumatology* 2011; 50: 317–323.
16. Valentini G, Della Rossa A, Bombardieri S, et al. European multicenter study to define disease activity criteria for systemic sclerosis. II. Identification of disease activity variables and development of preliminary activity indexes. *Ann Rheum Dis* 2001; 60: 592–598.
17. Valentini G, D'Angelo S, Della Rossa A, et al. European Scleroderma Study Group to define disease activity criteria for systemic sclerosis IV. Assessment of skin thickening by modified Rodnan skin score. *Ann Rheum Dis* 2003; 62: 904–905.
18. Medsger TA Jr, Bombardieri S, Czirjak L, et al. Assessment of disease severity and prognosis. *Clin Exp Rheumatol* 2003; 21(3 suppl 29): S42–46.
19. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2016; 37: 67–119.
20. Reddy YNV, Carter RE, Obokata M, et al. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. *Circulation* 2018; 138: 861–870.
21. Fujimoto N, Borlaug BA, Lewis GD, et al. Hemodynamic responses to rapid saline loading: the impact of age, sex, and heart failure. *Circulation* 2013; 127: 55–62.
22. Borlaug BA. Invasive assessment of pulmonary hypertension: time for a more fluid approach? *Circ Heart Fail* 2014; 7: 2–4.
23. Fox BD, Shimony A, Langleben D, et al. High prevalence of occult left heart disease in scleroderma-pulmonary hypertension. *Eur Respir J* 2013; 42: 1083–1091.
24. al-Sabbagh MR, Steen VD, Zee BC, et al. Pulmonary arterial histology and morphometry in systemic sclerosis: a case-control autopsy study. *J Rheumatol* 1989; 16: 1038–1042.
25. Wigley FM, Wise RA, Mikdashi J, et al. The post-occlusive hyperemic response in patients with systemic sclerosis. *Arthritis Rheum* 1990; 33: 1620–1625.
26. D'Alto M, Ghio S, D'Andrea A, et al. Inappropriate exercise-induced increase in pulmonary artery pressure in patients with systemic sclerosis. *Heart* 2011; 97: 112–117.
27. D'Alto M, Motoji Y, Romeo E, et al. Fluid challenge predicts clinical worsening in pulmonary arterial hypertension. *Int J Cardiol* 2018; 261: 167–171.