High Prevalence of Right Ventricular Systolic Dysfunction in Early Systemic Sclerosis

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ABSTRACT. Objective. To assess right ventricular (RV) function in patients with early systemic sclerosis (SSc) and the acute effects of calcium channel blockers on RV ejection fraction (RVEF).

Methods. Forty-two consecutive patients with SSc with less than 5 years' disease duration and normal pulmonary arterial pressure (35 women, 7 men; mean age 54.3 ± 9.7 years; 16 with diffuse and 26 with limited cutaneous forms, systolic pulmonary arterial pressure 30.3 ± 5.4 mmHg) were prospectively evaluated. All underwent pulmonary function testing, echocardiography, and radionuclide ventriculography at rest and 2 hours after receiving 40 mg oral nicardipine, and were compared at baseline with 20 gender and age matched controls.

Results. None of the patients with SSc had clinical evidence of heart failure. At baseline, SSc patients had significantly lower LVEF ($68.5\% \pm 7.9$ vs $72.4\% \pm 5.0$, $p = 0.049$) and RVEF ($36.5\% \pm 7.0$ vs $45.8\% \pm 5.7$, $p < 0.0001$). Sixteen patients had reduced RVEF ($< 35\%$), 3 had reduced LVEF ($< 55\%$), and 10 had reduced peak filling rate (PFR). RVEF correlated to both LVEF and PFR ($r = 0.64$, $p < 0.0001$, and $r = 0.36$, $p = 0.0037$, respectively), whereas no correlation was found with pulmonary function impairment or pulmonary arterial pressure. Nicardipine resulted in a significant increase in RVEF (from $36.5\% \pm 7.0$ to $42.3\% \pm 8.4$, $p < 0.001$) whereas afterload indicated by mean arterial pressure did not differ significantly.

Conclusion. Reduced RVEF appears to be a common feature in early SSc; it may be due to intrinsic myocardial involvement and is acutely improved by nicardipine. (J Rheumatol 2004;31:1941–5)

Key Indexing Terms:
SYSTEMIC SCLEROSIS
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RIGHT VENTRICULAR FUNCTION
CALCIUM CHANNEL BLOCKERS

Systemic sclerosis (SSc) is a connective tissue disease characterized by widespread vascular lesions and fibrosis of skin and internal organs. Primary myocardial involvement is common in SSc[1-5], and when clinically evident is recognized as a poor prognostic factor[6-7].

SSc primarily affects the vascular system and is characterized by microcirculation impairment including vasospasm. Myocardial fibrosis is suspected to be a consequence of, at least in part, repeated focal ischemia resulting from abnormal vasoreactivity with or without structural associated arteriolar abnormalities. Indeed, some histopathologic examinations have revealed diffuse patchy fibrosis with contraction band necrosis unrelated to epicardial coronary arteries stenosis[2], while concentric intimal hypertrophy associated with fibrinoid necrosis of intramural

coronary arteries have been noticed in other studies[8]. Moreover, several clinical studies have suggested that spontaneous or induced functional abnormalities of small coronary arteries might contribute to myocardial damage[3-5,9-11], and that vasodilatators mitigate both myocardial perfusion and function abnormalities[3,12,13].

A few studies have addressed the possibility of combined altered right ventricular (RV) function[4,5,14,15]; however, RV systolic function has been investigated in limited series. The aim of our study was to assess baseline RV ejection fraction (EF), as well as systolic and diastolic left ventricular (LV) function, and the acute effects of the calcium channel blocker (CCB) nicardipine in SSc patients with early disease.

MATERIALS AND METHODS

Patients and controls. Consecutive SSc patients with less than 5 years' disease duration were prospectively studied after informed consent. All patients fulfilled SSc diagnosis criterion, and were separated in 2 categories according to skin involvement[16]. Onset of disease was defined as the time when skin became involved.

Patients with known atherosclerotic heart disease, renal failure determined by serum creatinine > 150 µmol/l, pulmonary artery hypertension (defined as ≥ 40 mmHg in systolic pulmonary arterial pressure determined by echocardiography), or contraindication to calcium channel antagonists were excluded. No patient was treated with vasoactive drugs, including CCB and angiotensin-converting enzyme inhibitors, or steroids at the time of the study. All patients underwent physical examination, laboratory

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testing [blood cell count, serum creatinine, creatine kinase (CPK), lactate-dehydrogenase (LDH), antinuclear, anti-centromere, anti-topoisomerase 1 antibodies], pulmonary high resolution computerized tomography scan (fibrosis was defined as the presence of honeycombing), pulmonary function testing (routine spirometry with forced vital capacity, forced volume in one second, and single breath diffusing capacity for carbon monoxide), echocardiography (ECHO), and radionuclide ventriculography at rest and 2 hours after 40 mg oral nicardipine.

Patients with SSc were compared to 20 gender and age-matched controls (17 females, 3 males, 53.9 ± 10.0 yrs) referred to our institution for cardiac status determination before adriamycin chemotherapy. The healthy cardiac status of the controls was confirmed by the absence of relevant cardiac medical history, normal cardiac examination, ECG, and ECHO.

Echocardiographic measurements. All ECHO were recorded by an experienced echocardiographer and then independently analyzed by blinded methods by 2 cardiologists unaware of other information. Ultrasound examinations were performed with an ATL HDI5000 system (ATL ultrasound, Bothell, Washington, DC, USA) equipped with second harmonic imaging technologies and a 2–3.5 Mhz phased array transducer. Conventional measurements, including LV wall thickness, wall thickening, fractional shortening, LV diameter, and mitral Doppler filling patterns were made according to the guidelines of the American Society of Echocardiography. RV systolic pressure was calculated from the transtricuspid pressure gradient after addition of 10 mmHg as an estimation of right atrial pressure.

Radionuclide ventriculography. Each patient underwent radionuclide ventriculography at rest and 2 hours after oral 40 mg nicardipine with a gamma camera (General Electric, Starport 400AT) interfaced with an ADAC computer (DPS 3300). After *in vitro* red cell labeling with 555 MBq technetium-99m, gated-blood pool images were obtained for 300,000 counts in each of the 16 frames. The best-left anterior oblique view was used to image the ventricles. LVEF and RVEF were determined by a 2-region-of-interest, with an automatic thresholding technique for background subtraction[17]. A LVEF ≥ 55% and a RVEF ≥ 35% were defined as normal.

To determine LV diastolic measures, LV regions of interest were drawn manually on each of the 16 frames, allowing determination of the time-activity curve. Peak filling rate (PFR) was computed as the maximum on the first derivate of the time-activity curve and normalized by the end-diastolic number of counts. A PFR value > 2.1 end-diastolic volume/second (EDV/s) was defined as normal[18]. All radionuclide measurements were performed independently by 2 experienced practitioners who were unaware of the patients' status.

Statistical analysis. Statistical analysis was performed using Statview software (Abacus concept, Berkeley, USA). Data are expressed as means ± standard deviation (SD). Patients with SSc were compared with controls using Student's t test for comparison of normally distributed continuous variables and chi-square analysis for differences in frequency. The effect of nicardipine was evaluated using Student's paired t test for normally distributed continuous variables and McNemar's chi-square analysis for differences in frequency. Subgroup analysis in SSc patients was performed using the Mann-Whitney test. Linear regression and Spearman correlation tests were used to determine the existence of correlations between variables. A p value < 0.05 was necessary for statistical significance in all comparisons.

RESULTS

Forty-four consecutive patients with less than 5 years' disease duration were screened. Of these, 2 were not included due to pulmonary hypertension in one patient and renal failure in the other. Results are therefore presented for 42 patients (35 women, 7 men). Clinical and biological characteristics of patients are summarized in Table 1. None of the SSc patients had moderate or severe dyspnea (15 were

Table 1. Clinical and biological characteristics of patients with SSc.

Variable	Patients with SSc, n = 42
Age, mean ± SD range, yrs	54.3 ± 9.7 (39–78)
Disease duration, mean ± SD, yrs	2.5 ± 1.4
Raynaud's syndrome	42
Cutaneous form of the disease, limited/diffuse	26/16
Pulmonary fibrosis, CT scan	18
% Forced vital capacity, mean ± SD	96.9 ± 19
Forced vital capacity < 70% normal value	2
% DLCO/mean Hb, mean ± SD	87.4 ± 16
DLCO/mean Hb < 70% normal value	5
CK > 145 UI/l	5
LDH > 290 UI/l	18
Hb, mean ± SD, g/dl	12.9 ± 1.2
Anti-topoisomerase-1 antibodies	11
Anti-centromere antibodies	5

CT: computerized tomography; DLCO: monoxyde carbon diffusing capacity; Hb: hemoglobin; CK: creatine kinase; LDH: lactate-dehydrogenase.

in class I, and 27 in class II subgroups according to the New York Heart Association) and none had clinical evidence of heart failure.

Results of radionuclide ventriculography at rest and ECHO for patients and control subjects are shown in Table 2.

Patients with SSc had lower RVEF and LVEF when compared to controls (36.5 ± 7.0% vs 45.8 ± 5.7%, p < 0.0001 and 68.5 ± 7.9% vs 72.4 ± 5.0, p = 0.049, respectively) whereas pulmonary arterial pressure did not differ significantly. Three patients had reduced LVEF (< 55%) as compared with none in controls (NS for difference), whereas 16 patients had reduced RVEF (< 35%) (including all patients with reduced LVEF) and none in controls (p = 0.0014). RVEF correlated with LVEF (r = 0.64, p < 0.0001) (Figure 1), PFR (r = 0.36, p = 0.0037), whereas no correlation was found with demographic criteria, cutaneous form of disease, or other SSc characteristics including pulmonary artery pressure and pulmonary function tests.
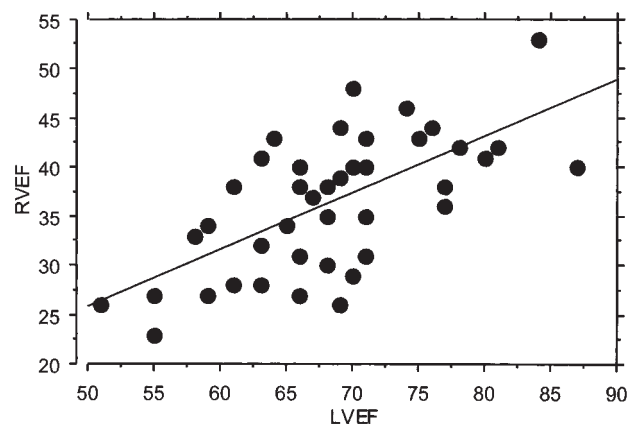

Figure 1. Correlation between right ventricular ejection fraction (RVEF) and left ventricular ejection fraction (LVEF) at rest (r = 0.64, p < 0.0001).

Table 2. Results of radionuclide ventriculography at rest and ECHO in SSc patients and controls. Results are expressed as mean ± SD.

	SSc Patients (42)	D form (16)	L form (26)	Controls (20)	SSc versus Controls, p	D versus L*
Systolic arterial pressure, mmHg	121.4 ± 21.7	111.6 ± 14.0	125.4 ± 23.5	133.3 ± 23.8	0.123	0.225
Diastolic arterial pressure, mmHg	68.0 ± 11.7	62.4 ± 13.5	70.3 ± 10.6	79.6 ± 12.2	0.006 §	0.343
Heart rate beats/min	69.7 ± 15.1	75.8 ± 17.2	66.4 ± 13.0	74.8 ± 12.7	0.222	0.173
% LVEF	68.5 ± 7.9	68.9 ± 6.0	68.3 ± 9.0	72.4 ± 5.0	0.049 §	0.669
% RVEF	36.5 ± 7.0	37.3 ± 5.5	36.0 ± 7.8	45.8 ± 5.7	< 0.0001 §	0.453
PFR, EDV/s	2.6 ± 0.6	2.7 ± 0.5	2.5 ± 0.6	2.8 ± 0.6	0.207	0.162
Posterior wall thickness, mm	8.9 ± 1.6	8.7 ± 1.3	9.0 ± 1.8	7.9 ± 1.4	0.043 §	0.486
Interventricular septum thickness, mm	9.2 ± 2.0	9.4 ± 2.1	9.0 ± 1.9	7.9 ± 1.6	0.022 §	0.460
LV end-diastolic diameter, mm	45.3 ± 4.5	46.1 ± 4.8	44.8 ± 4.3	43.2 ± 4.6	0.110	0.321
Transmitral E/A ratio	1.02 ± 0.36	0.95 ± 0.34	1.1 ± 0.37	1.24 ± 0.51	0.073	0.410
Systolic pulmonary arterial pressure, mmHg	30.3 ± 5.4	31.7 ± 5.8	29.5 ± 5.1	27.6 ± 3.8	0.078	0.234

D: diffuse cutaneous form; L: limited cutaneous form; PFR: peak filling rate; EDV: end-diastolic volume/s. * Mann-Whitney tests.

Diastolic LV function, assessed by PFR (determined by radionuclide ventriculography at rest) and E/A ratio (determined by ECHO) tended to be reduced in patients with SSc when compared to controls, although not significant (p = 0.073 for the E/A ratio). When regarding individuals, 10 SSc patients exhibited reduced diastolic LV function assessed by radionuclide ventriculography (defined as PFR < 2.1) in comparison with 2 controls (p = 0.17). Overall, 18 SSc patients (43%) had abnormal cardiac status, including 3 with reduced LVEF, 10 with altered LV diastolic function, and 16 with reduced RVEF.

SSc patients had increased posterior wall and interventricular septum thickness compared to controls whereas they had lower diastolic blood pressure and non-significantly different systolic blood pressure (Table 2). No SSc patient had significant pericardial effusion.

Patients with diffuse cutaneous forms had more severe pulmonary disease than patients with limited cutaneous disease (mean ± SD forced vital capacity in SSc patients with diffuse cutaneous disease = 87% ± 12 vs 103% ± 20 in SSc patients with limited cutaneous disease, p = 0.0061, pulmonary fibrosis 13/16 in diffuse SSc versus 5/26 in limited SSc, p < 0.0001), whereas LVEF and RVEF did not differ significantly between patients with diffuse or limited cutaneous form (Table 2).

After nicardipine, LVEF, RVEF, and PFR increased significantly (p < 0.0001 for each) whereas no statistically significant variation was seen in systolic, diastolic pressure, or systolic pressure-heart rate product (Table 3). In SSc patients with altered cardiac status, 2/3 patients normalized their LVEF (p = NS), 7/16 normalized their RVEF (p = 0.023), and 7/10 normalized their PFR (p= 0.023) after nicardipine. Individual data of the effects of nicardipine on RVEF are shown in Figure 2.

DISCUSSION
The main findings of our study are that 16 of the 42 SSc patients had reduced resting RVEF measured by radionu-clide ventriculography, and RVEF did not correlate with pulmonary involvement or with pulmonary arterial pressure. Overall cardiac dysfunction is frequent in SSc even in patients with early disease. Lastly oral nicardipine may mitigate cardiac abnormalities.

RVEF in SSc patients has been evaluated in a limited number of studies, and our study focused on RVEF in a large series of SSc patients with disease duration < 5 years. Some authors reported normal RVEF and LVEF values in patients with SSc[5], whereas others reported isolated reduced RVEF without LV impairment[14] or associated with LV myocardial involvement[4]. Indeed, in Follansbee, et al's[4] study of 26 SSc patients with diffuse cutaneous disease (disease duration 3 months–23 years) 4 patients had reduced LVEF and 7 reduced RVEF, including the 4 patients with reduced LVEF. Moreover, these patients with reduced RVEF had abnormal LV response to exercise (p < 0.002), and RVEF was lower in the patients with greater thallium-perfusion score defects (36 ± 12 vs 47 ± 7, p < 0.025)[4]. Our study confirms that SSc patients have reduced RVEF when compared to controls (p < 0.0001). Moreover, our patients exhibited a high prevalence of reduced RVEF defined by RVEF < 35% (16/42) when compared to reduced LVEF defined as LVEF < 55% (3/42), independent of cutaneous form of SSc. On the other hand, reduced RVEF often coexists with LV systolic or diastolic impairment (isolated RVEF impairment in 8 patients, RVEF impairment associated with LV diastolic function in 8, including the 3 patients with altered LVEF). Finally, RVEF correlated with LVEF (Figure 1) and PFR, whereas it did not correlate with arterial pressure and was not associated with pulmonary fibrosis. These results suggest that reduced RVEF is not due to pulmonary involvement. Furthermore, while both impairments of RV and LV are correlated, our study supports the hypothesis of intrinsic myocardial involvement[3-5,9-11]. Our findings of improvement in both LVEF and RVEF after oral nicardipine and a correlation between them (r = 0.48, p = 0.0013) may constitute further evidence for the same pathogenic pathway in both

Table 3. Pharmacodynamic effect of nicardipine in SSc patients. Results are expressed as mean ± SD.

	Rest Values	Post-Nicardipine Values	p
Heart rate, beats/min	69.7 ± 15.1	76.7 ± 15.8	< 0.0001
Systolic arterial pressure, mmHg	121.4 ± 21.7	114.3 ± 16.7	0.085
Diastolic arterial pressure, mmHg	68.0 ± 11.7	64.7 ± 10.4	0.359
Mean arterial pressure, mmHg	85.8 ± 14.0	81.2 ± 11.7	0.171
Systolic pressure-heart rate product	8535.3 ± 2557.9	8440.3 ± 1830.8	0.756
% LVEF	68.52 ± 7.88	73.97 ± 7.33	< 0.0001
% RVEF	36.52 ± 6.95	42.33 ± 8.37	< 0.0001
PFR, EDV/s	2.57 ± 0.56	3.10 ± 0.67	< 0.0001

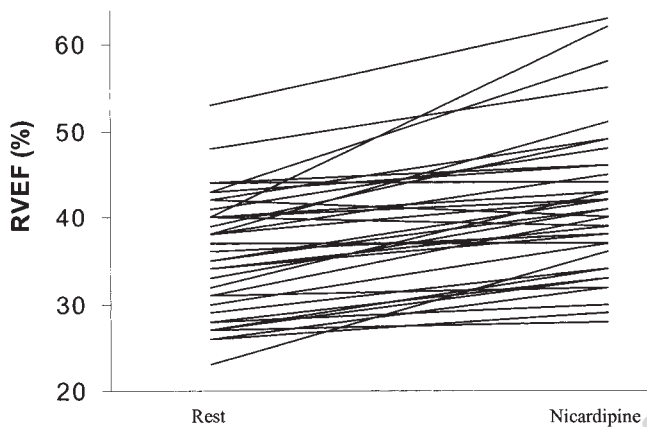LVEF: left ventricular; RVEF: right ventricular ejection fraction.

Figure 2. Right ventricular ejection fraction (RVEF) at rest and after nicardipine (40 mg).

impairments as global heart involvement. Differences between RV and LV involvement may be due to anatomical and physiological differences between both ventricles. RV is thinner than LV, and filling pressures are reduced in RV when compared to LV. As a consequence, RV dilatation may be more prone to develop after volume overload when compared to LV. Overall, RVEF might therefore be interpreted as an earlier marker and/or a more sensitive index of myocardial involvement than LVEF in SSc patients. This may suggest that RVEF should be investigated as a potential predictive factor, for example, for heart failure[19,20].

In our study, 10 out of 42 patients with SSc had an abnormal LV diastolic function. This is in accordance with echographic studies using mitral valve Doppler indices that have reported a high incidence (up to 40%) of relaxation abnormalities[5,21-24]. We found that PFR correlated with resting LVEF (r = 0.48, p < 0.001) and resting RVEF (r = 0.36, p = 0.0037), whereas no correlation was found with other criteria, including pulmonary involvement and arterial pressure. This suggests also that diastolic impairment is the result of intrinsic myocardial involvement, and may precede systolic dysfunction[24,25], and both myocardial fibrosis and myocardial ischemia may account for reduced ventricular filling[26].

Overall, we observed a high prevalence of myocardial dysfunction in SSc patients with short disease duration, both in the diffuse and limited cutaneous forms of the disease, which illustrates the striking cardiac involvement in this disease.

Skeletal myositis has also been shown to be associated with cardiac complications[27], but neither RVEF nor LVEF correlated to muscle involvement (defined as elevation of CK or LDH) in our study.

In this short term study, we also showed that nicardipine, a CCB, mitigates LV and RV alterations. CCB are potent vasodilatators that cause vascular smooth muscle relaxation and relief of arterial vasospasm. The exact mechanism by which nicardipine improved RVEF and both LVEF and LV diastolic measures cannot be determined from this study. These results are consistent with previous studies that found that nicardipine may improve thallium perfusion scores and LVEF[3,12], and we may hypothesize that improvement in diastolic measures and RVEF may be due to the same effects. On the other hand, CCB may decrease systolic blood pressure and result in an increase in sympathetic tone. Therefore, improvement in RVEF may be due to modifications in loading conditions, and we cannot affirm that our results are secondary to improvement in intrinsic myocardial function. This is an important limitation in the evaluation of the acute effects of CCB on LVEF or RVEF in our study and others[12]; techniques such as magnetic resonance imaging or tissue Doppler imaging may help clarify this issue.

In a recent study, we showed that oral nicardipine may reduce pulmonary arterial hypertension in patients with SSc[28]. Our results may therefore signify that patients with SSc have overall vascular reactivity and suggest early treatment with CCB in patients with either pulmonary arterial hypertension, reduced LVEF, and reduced RVEF, regardless of Raynaud's syndrome, in order to limit the progression of the disease. Longterm effects of such drugs remain to be determined.

In conclusion, we have shown that RV impairment is a common feature in SSc patients even at an early stage. RV

functional properties correlate with LV systolic and diastolic measures, but are independent of pulmonary artery pressure and pulmonary fibrosis, and thus may represent an early marker of intrinsic myocardial involvement. We also showed that the CCB, nicardipine, mitigates RV function abnormalities, as previously shown for LVEF. Study of the longterm significance of RV dysfunction and effects of calcium channel blockers is warranted.

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