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Prevalence and factors associated with left ventricular dysfunction in the EULAR Scleroderma Trial and Research group (EUSTAR) database of patients with systemic sclerosis

Allanore, Y ; Meune, C ; Vonk, M C ; et al ; Distler, O ; Walker, U A

Abstract: **OBJECTIVES:** To measure the prevalence of, and factors associated with, left ventricular (LV) dysfunction in systemic sclerosis (SSc). **METHODS:** The EUSTAR database was first searched. A case-control study of a patient subset was then performed to further identify independent factors associated with LV dysfunction by simple and multiple regression. **RESULTS:** Of 7073 patients, 383 (5.4%) had an LV ejection fraction (EF) of <55%. By multiple regression analysis, age, sex, diffuse cutaneous disease, disease duration, digital ulcerations, renal and muscle involvement, disease activity score, pulmonary fibrosis and pulmonary arterial hypertension were associated with LV dysfunction. In the second phase, 129 patients with SSc with LVEF <55% were compared with 256 patients with SSc with normal LVEF. Male sex (OR 3.48; 95% CI 1.74 to 6.98), age (OR 1.03; 95% CI 1.01 to 1.06), digital ulcerations (OR 1.91; 95% CI 1.05 to 3.50), myositis (OR 2.88; 95% CI 1.15 to 7.19) and use of calcium channel blockers (OR 0.41; 95% CI 0.22 to 0.74) were independent factors associated with LV dysfunction. **CONCLUSION:** The prevalence of LV dysfunction in SSc is 5.4%. Age, male gender, digital ulcerations, myositis and lung involvement are independently associated with an increased prevalence of LV dysfunction. Conversely, the use of calcium channel blockers may be protective.

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Prevalence and factors associated with left ventricular dysfunction in the EULAR Scleroderma Trial and Research group (EUSTAR) database of systemic sclerosis patients

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Abbreviated title: left ventricular dysfunction in systemic sclerosis

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Abstract

Study objectives and methods To measure the prevalence of, and factors associated with, left ventricular (LV) dysfunction in SSc, we first queried the EUSTAR database. In a second phase, we performed a case-control study of a patient subset, to further identify independent factors associated with LV dysfunction by simple and multiple regression.

Results Among 7,073 patients, 383 (5.4%) had a LV ejection fraction (EF) <55%. By multiple regression analysis, age, sex, diffuse cutaneous disease, disease duration, digital ulcerations, renal and muscle involvement, disease activity score, pulmonary fibrosis and pulmonary arterial hypertension (PAH) were associated with LV dysfunction. In a second phase, 129 SSc patients with LVEF <55% were compared with 256 SSc patients with normal LVEF. Male sex (OR 3.48; 95% CI 1.74-6.98), age (OR 1.03; 95% CI 1.01-1.06), digital ulcerations (OR 1.91; 95% CI 1.05-3.50), myositis (OR 2.88; 95% CI 1.15-7.19), and calcium channel blockers (CCB) use (OR 0.41; 95% CI 0.22-0.74) were independent factors associated with LV dysfunction.

Conclusion The prevalence of LV dysfunction in SSc is 5.4%. Age, male gender, digital ulcerations, myositis and lung involvement are independently associated with increased prevalence of LV dysfunction. Conversely, CCB use may appear as protective.

Introduction

The prevalence of primary myocardial involvement by systemic sclerosis (SSc) has been subject to particular attention in recent years (1-3). It appears that once clinically apparent, cardiac involvement has a very poor prognosis (4-7). While the overall long-term prognosis of patients with SSc seems to have improved in recent years, the proportion of deaths due to heart disease has not changed significantly (7). The objective of this study was to precisely measure the prevalence of LV dysfunction ascertained by standard echocardiography, and to identify factors associated with a depressed LV ejection fraction (EF).

Patient population and methods

We first queried the EUSTAR database that has been described previously in details (8). LVEF was measured echocardiographically at each participating center, using Simpson's method: LVEF was classified as depressed if <55% or <50%. In a second phase, we performed a case-control study of a patient subset, to further identify independent factors associated with LV dysfunction by simple and multiple regression including parameters not registered in the EUSTAR database. Methods and statistical analysis details are available in supplemental file 1.

Results

By April 2008, 7,283 patients had been enrolled. Since neither LVEF nor the presence of LV dysfunction was recorded in 209, this analysis includes data collected in 7,073 patients (mean age 56 ± 14 years, 981 [13.9%] men). A total of 383 patients had a reduced LVEF corresponding to a 5.4% prevalence. The main characteristics of patients with versus those without LV dysfunction are shown in table 1.

Table 1: Characteristics of patients presenting with SSc and depressed versus normal left ventricular ejection fraction

	Left ventricular ejection fraction		P
	Depressed (n=383)	Normal (n=6,690)	
Age, y (means \pm SD)	61.3 \pm 13.4	56.1 \pm 13.7	<0.001
Men/women (%)	23/77	13/87	<0.001
Disease duration, y	12.0 \pm 9.7	9.6 \pm 7.8	<0.001
Cutaneous subtype;			
Diffuse (%)	47.5	32.0	<0.001
Friction rub (%)	19.2	10.8	<0.001
Synovitis (%)	23.3	16.2	<0.001
Raynaud' syndrome (%)	96.9	95.4	0.181
Digital ulceration (%)	52.4	30.5	<0.001
Muscle weakness (%)	47.9	25.9	<0.001
Pulmonary fibrosis (plain X-ray) (%)	56.9	35.5	<0.001
Elevated systolic pulmonary artery pressure (%)	50.7	18.7	<0.001
Palpitation (%)	48.9	23.1	<0.001
Conduction abnormality on electrocardiogram (%)	33.3	9.1	<0.001
Renal crisis (%)	8.2	1.9	<0.001
Positive anti-nuclear antibodies (%)	92.4	91.9	0.736
Positive anti-topoisomerase-1 antibodies (%)	37.5	32.1	0.030
Positive anti-centromere antibodies (%)	25.7	34.5	0.001
Elevated creatine-phosphokinase (%)	11.4	8.0	0.019
Elevation of acute phase reactants (%)	50.0	29.4	<0.001
Proteinuria (%)	15.3	5.45	<0.001
Active disease according to European score (%)	51.1	29.1	<0.001

Table 2 shows the ORs and 95% CI of associated factors with LV dysfunction.

Table 2: Factors significantly associated with a reduced left ventricular ejection fraction

	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
Age	1.02	1.04-10.2	<0.001	1.03	1.02-1.04	<0.001
Male gender	2.0	1.6-2.6	<0.001	1.98	1.46-2.68	<0.001
Disease duration, years	1.04	1.02-1.05	<0.001	1.03	1.02-1.04	<0.001
Diffuse cutaneous subtype	1.92	1.56-2.36	<0.001	1.38	1.06-1.81	0.018
Presence of friction rubs	1.96	1.50-2.55	<0.001			NS
Presence of synovitis	1.57	1.23-2.01	<0.003			NS
Presence of digital ulceration	2.51	2.03-3.01	<0.001	2.05	1.59-2.64	<0.001
Presence of muscle weakness	2.62	2.13-3.24	<0.001	1.86	1.44-2.39	<0.001
Pulmonary fibrosis	2.39	1.94-2.95	<0.001	1.33	1.02-1.72	0.034
Renal crisis	4.70	3.12-7.01	<0.001	3.60	2.14-6.07	<0.001
Positive anti-topoisomerase-1 antibodies	1.27	1.02-1.58	0.030			NS
Positive anti-centromere antibodies	0.66	0.52-0.83	<0.001			NS
Elevation of acute phase reactants	2.40	1.95-2.97	<0.001			NS
Active disease (European score)	2.55	2.06-316	<0.001	1.42	1.09-1.86	0.011
Elevated systolic pulmonary artery pressure				2.63	2.03-3.41	<0.001

It is noteworthy that men presenting with diffuse cutaneous SSc and active or past digital ulcerations, representing 203 patients (2.8%) in this study, were at particularly high risk of LV dysfunction (OR 3.2; 95% CI 2.1-4.9).

Case-control analysis

The second phase of the study included 385 patients including 129 with LVEF <55% and 256 controls. Diffuse cutaneous SSc was present in 145 patients, pulmonary fibrosis in 176, past or active digital ulcer in 204, and histories of renal crisis in 6 patients. Echocardiography revealed the presence of a systolic PAP >40 mmHg in 114 patients, of whom 34 had pre-capillary PAH confirmed by cardiac catheterization. Associated factors with reduced LVEF according to univariate and multivariate analyses are represented in table 3.

Table 3: Characteristics of SSc patients with and without abnormal left ventricular ejection fraction included in the nested case-control study.

	Left ventricular ejection fraction		P	Multivariate analysis (stepwise regression)		
	Reduced (n=129)	Normal (n=256)		OR	95% CI	P
Age, y	59.8±12.7	56.2±12.8	0.008	1.03	1.01-1.06	0.008
Men/women (%)	33 / 67	12 / 88	<0.001	3.48	1.74-6.98	<0.001
Disease duration, mo (1 st non-Raynaud symptom)	68.9±129.7	51.3±68.8	0.081			NS
Diffuse/limited cutaneous subtype (%)	45/55	34 / 66	0.036			NS
Smoking (past or present) (%)	21.1	11.1	0.009			NS
Systemic hypertension (%)	34.9	27.7	0.155			NS
Body mass index	23.6±4.6	24.7±4.4	0.031			NS
Diabetes (%)	5.5	4.3	0.615			NS
Presence of digital ulceration (%)	61.7	50	0.038	1.91	1.05-3.50	0.035
Presence of pulmonary fibrosis (%)	59.3	45.7	0.016			NS
Forced vital capacity	84.5±23.6	94.1±21.1	<0.001	0.98	0.96-0.99	0.001
Lung carbon monoxide diffusion; DLCO/VA	66.6±22.2	77.4±20.2	<0.001			NS
Echo sPAP	38.2±17.9	30.2±11.7	<0.001			NS
Pre-capillary PAH (%)	14.7	7.6	0.041			NS
Myositis (%)	12.7	5.4	0.013	2.88	1.15-7.19	0.024
Renal crisis (%)	5	2.5	0.227			NS
Positive anti-topoisomerase-1 antibodies (%)	31.2	37.8	0.206			NS
Positive anti-centromere antibodies (%)	30.2	31.4	0.802			NS
Use of CCB, past or present (%)	51.9	68.7	0.001	0.41	0.22-0.74	0.004
CCB for >12 months (%)	45.7	60.2	0.009			NA
Use of low dose prednisone (≤10 mg/d)	43.7	34.9	0.095			NS
Use of immunosuppressors (%)	48.1	42.6	0.313			NS
Use of endothelin antagonists (%)	16.3	9.8	0.065			NS

We conducted similar analyses for LVEF <45% (n=36) that confirmed the above results (supplemental file 1).

Discussion

The main observations made in this analysis were i) a 5.4% prevalence of LV dysfunction, ii) the identification of age, male gender, myositis, digital ulcers, lung involvement and absence of previous CCB treatment as associated factors with reduced LVEF.

Large studies that evaluate LV dysfunction are sparse. In a multicenter study of PAH, a *post hoc* analysis identified only 8 of 570 SSc patients (1.4%) with LVEF <45% (2). The EUSTAR database offers a unique opportunity to study the complications of SSc. The 5.4% prevalence of reduced LVEF measured in the first phase of our study is concordant with the 7.2% prevalence among patients with diffuse SSc, and 5% in patients with limited SSc, observed in the first report from EUSTAR (8). Therefore, a depressed LVEF stands among the 4 main manifestations of major organ involvement in SSc, together with PAH (9-11), renal crisis (12) and interstitial lung disease.

The second objective was the identification of factors associated with a reduced LVEF. We used a two-step strategy that included 1) an analysis of the entire EUSTAR database, allowing the inclusion of robust factors unequivocally pertinent considering the large number of patients included, and 2) a nested prospective case-control study of a subgroup, that includes more data, such as atherosclerosis risk factors, drug regimen and the presence of pre-capillary PAH. In order to limit the impact of disease duration, a typical contributor to organ dysfunction, we matched our two study groups for disease duration. Both analyses confirmed that male gender, age, muscle involvement, digital ulceration were independent associated factors with LV dysfunction. The association between digital ulcerations and cardiac dysfunction may be a manifestation of the diffuse microvascular lesions, which characterize the disease (1). The significant association between systolic PAP and reduced LVEF observed in the first part of the study should be interpreted with caution, since systolic PAP is influenced by LV function, and this is emphasized by the lack of independent association with pre-capillary PAH found in the second part of our study. In the nested study, except for male gender, typical cardiovascular risk factors were not associated with a reduced LVEF, an observation concordant with the prior demonstration of a predominant contribution of microangiopathy, versus the controversial results regarding that of atherosclerosis, in the development of primary myocardial involvement in SSc (1). Another important finding of the nested study was the markedly lower proportion of patients with reduced LVEF who had been previously treated with CCB. This is concordant with previous short-term studies (1). In addition, Steen et al. reported that patients presenting with PAH were significantly less often treated with CCB than patients without PAH (13) and, in another study, the development of digital ulcers was also delayed by vasodilator therapy (14). Altogether, these observations suggest that CCB may protect against microvascular complications. Pending the results of long-term prospective study, the broad use of CCB in patients with SSc, unless contraindicated, should be strongly considered. Our study is limited by its observational design and since we studied patients with a LVEF <55%, which has not been associated with an increased mortality in patients with SSc, our results do not apply to mortality. We expect the prospective follow-up that is ongoing to enable the identification of predictors of LV dysfunction and outcome in SSc patients with mildly decreased LVEF.

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METHODS

EUSTAR Registry

The European League Against Rheumatism (EULAR) Scleroderma Trials And Research (EUSTAR) MYOCARDIUM study is a two-phase program based on data collected in patients with SSc included in the EUSTAR registry. The structure and Minimal Essential Dataset (MEDS) of the EUSTAR database have been described previously in details (8). Briefly, since 2004, 150 participating medical centers entered consecutive patients in a registry, and all data in a specific database, which was locked for this study in April 2008. The registry includes demographic information, classification criteria, and a detailed clinical evaluation of SSc, that has been described elsewhere (8). Clinical variables include distinction of the cutaneous subset of the disease, disease duration, detection of antibodies and acute phase reactants, disease activity score, presence of active or past digital ulcerations, and the presence of renal, muscle, gastro-intestinal, pulmonary and cardiac involvement. Atherosclerotic risk factors and drug regimens were not recorded. LVEF was measured echocardiographically at each participating center, using Simpson's method. LVEF was classified as depressed if <55% or <50%, depending on the cut-off value adopted at each echocardiography laboratory. Baseline data collected during the first patient visit at a EUSTAR center were analyzed.

Case-control study

In a second 18-month phase, EUSTAR centers identified in the first step as having included patients with reduced LVEF were asked to include a) SSc patients identified as having echocardiographic LVEF <55% in the first phase and consecutively re-assessed in their respective center together with b) patients with SSc with normal LVEF (controls) who were enrolled in a 1:2 ratio in a nested case-control study, at the time of their next visit. Control patients 1) were entered in the registry either simultaneously or immediately after a patient with reduced LVEF, and 2) were matched for disease duration (± 1 year). The data collected included the items of the EUSTAR registry, atherosclerosis risk factors, detailed pulmonary function tests, and drug regimen, including corticosteroids, calcium channel blockers (CCB) and endothelin antagonists prescribed for >3 months. Angiotensin converting enzyme inhibitors were only considered if prescribed before the occurrence of LV dysfunction. When pulmonary arterial hypertension (PAH) was suspected, catheterization was recommended to 1) confirm its presence, defined as a mean pulmonary arterial pressure (PAP) >25mmHg, and 2) identify patients with pre-capillary PAH. Myositis was defined by any clinical symptom (myalgia with or without weakness) together with an elevation in creatine phosphokinases values in the absence of any other potential explanation.

All patients included in either database granted their informed consent to participate, and the research program was approved by all appropriate institutional ethics committees.

STATISTICAL ANALYSES

Data were expressed as means \pm standard deviation for continuous variables and numbers and percentages for categorical variables. From the EUSTAR registry, we first assessed the prevalence of LV dysfunction. To identify all potential factors associated with the existence of LV dysfunction, SSc patients with LV dysfunction were compared with SSc patients having normal LVEF using Student's *t*-test for

comparisons of normally distributed continuous variables, and chi-square test for differences in frequency. Odds ratio (OR) estimates and 95% confidence intervals from logistic regression were then calculated. Due to multiple tests, p-values between 0.01 and 0.05 should be interpreted with caution. In order to identify independent factors associated with LV dysfunction, all variables with $p < 0.10$ univariately, were entered as covariates in stepwise regression analysis. A similar protocol was used to identify associated factors with reduced LVEF in the second phase of the study (nested case-control). All analyses were performed with the STATA® statistical software, version 9.2 (StataCorp LP, College Station, TX). A p value < 0.05 was considered statistically significant.

RESULTS

Although not planned by the original study protocol, we conducted multivariate analyses for associated factors with LVEF $< 45\%$ ($n=36$) (4). Male gender (OR 2.62; 95% CI 1.17-5.89), diffuse SSc (OR 2.50; 95% CI 1.14-5.50) and absence of treatment with a CCB (OR 0.41; 95% CI 0.19-0.89) were associated by multiple variable analysis, and a trend was observed for digital ulcers (OR 2.06; 95% CI 0.89-4.79, $p=0.09$).

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Prevalence and factors associated with left ventricular dysfunction in the EULAR Scleroderma Trial and Research group (EUSTAR) database of systemic sclerosis patients

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