Prevalence, prognosis, and factors associated with left ventricular diastolic dysfunction in systemic sclerosis

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ABSTRACT

Objectives. To determine the frequency, associated clinical factors, and prognostic significance of left ventricular (LV) diastolic dysfunction in systemic sclerosis (SSc).

Methods. We studied 153 consecutive patients with SSc and divided the study sample into those with and without LV diastolic dysfunction using established age-based normal cut-offs for lateral tissue Doppler early mitral annular (E') velocity, a marker of impaired relaxation and diastolic dysfunction. We compared clinical characteristics, laboratory tests, pulmonary function tests, and echocardiographic data between those with and without LV diastolic dysfunction. We used multivariable linear regression analyses to determine the factors most associated with lateral tissue Doppler E' velocity. We also performed multivariable Cox regression analyses to determine whether or not tissue Doppler E' velocity was independently associated with mortality.

Results. LV diastolic dysfunction was present in 23% of the subjects, whereas LV systolic dysfunction was present in 5.2% of subjects. Factors independently associated with LV diastolic dysfunction on multivariable analysis included SSc disease duration, age, coronary artery disease, and systemic hypertension. During a mean follow-up of 1.9±1.3 years, LV diastolic dysfunction was independently associated with increased risk of death (hazard ratio [HR] 3.2, 95% confidence interval [CI] 1.1–9.5, p=0.034 per each standard deviation decrease in tissue Doppler E' velocity).

Conclusions. LV diastolic dysfunction in SSc is independently associated with disease duration and is a marker of increased risk of death.

Introduction

Although cardiac involvement in systemic sclerosis (SSc) has long been recognised as a common and clinically important complication (1-7), and the incidence of reduced left ventricular (LV) ejection fraction recently well documented (8), there are fewer available data on the incidence, risk factors for development, and clinical importance of LV diastolic dysfunction. Prior studies in patients with SSc used novel echocardiographic techniques to compare relatively small numbers of patients with SSc to those without SSc. These studies found that LV diastolic dysfunction is more prevalent in SSc compared to healthy controls (9-14).

The largest published study to date on the prevalence of LV diastolic dysfunction in SSc used Doppler (which evaluates blood flow only) but did not use tissue Doppler imaging (which evaluates myocardial function directly) (15). Doppler parameters alone do not provide optimal insight into impaired LV relaxation, and therefore may incorrectly estimate the frequency of diastolic dysfunction in SSc. Furthermore, Doppler parameters can be abnormal in the setting of constrictive pericarditis without myocardial involvement, and it can be difficult to distinguish normal diastolic function from "pseudonormal" (moderate) diastolic dysfunction if only Doppler parameters are used (16). Tissue Doppler imaging is therefore critical for the comprehensive evaluation of diastolic function (16). Another limitation of prior studies of LV diastolic dysfunction in SSc is the lack of accounting for the influence of age, which is one of the most important determinants of impaired LV relaxation and overall diastolic dysfunction (16). Finally, no prior study has explored the association between LV diastolic dysfunction and death in SSc.

Given the importance of myocardial disease in SSc and uncertainties regarding the clinical significance of LV diastolic dysfunction in SSc, evaluation of LV diastolic dysfunction with tissue Doppler imaging in SSc (and adjusting

diastolic parameters for age) is critical to improving our understanding of prevalence and prognosis of direct myocardial involvement in SSc. Using comprehensive echocardiography, including Doppler and tissue Doppler imaging, we therefore sought to evaluate LV diastolic function in a large cohort of well-characterised patients with SSc. We hypothesised that reduced tissue Doppler E' velocity, an early marker of impaired relaxation and LV diastolic dysfunction, is common in SSc; it is associated with longer disease duration (independent of age), and it predicts mortality.

Methods
Patients
Consecutive patients who were referred to the Northwestern Scleroderma Program (Northwestern University, Chicago, IL) from 2005–2009 and met American College of Rheumatology criteria for systemic sclerosis were studied (17). The study sample consisted of patients with limited cutaneous SSc (lcSSc) or diffuse cutaneous SSc (dcSSc) based upon the LeRoy criteria (18). Patients who met American College of Rheumatology criteria for rheumatoid arthritis, inflammatory myopathies such as dermatomyositis and polymyositis, and/or systemic lupus erythematosus in addition to SSc were excluded from the study (19-23). Patients diagnosed with scleroderma mimics (nephrogenic systemic fibrosis, eosinophilia-myalgia sydrome, paraneoplastic syndromes, scleredema, scleromyxedema) and localised scleroderma (including morphea) were also excluded.

Some, but not all patients were entered prospectively into the study because clinical enrollment of patients in the Northwestern Scleroderma Programme began before initiation of a prospective SSc registry (78 [51%] of the 153 patients in the present study were participants in our prospective SSc registry; all other patients were studied retrospectively). Study of patients in the Northwestern Scleroderma Program was approved by the Northwestern University Institutional Review Board, and patients who were entered prospectively into the study provided written,

informed consent according to the Declaration of Helsinki.
All subjects were evaluated by one of two rheumatologists upon initial intake into the Northwestern Scleroderma Program. A detailed, standardised medical history was taken to evaluate SSc disease duration, defined as time between the onset of the first non-Raynaud symptom of SSc and the initial clinic visit; comorbidities including diabetes mellitus, systemic hypertension, coronary artery disease, cancer, thyroid disease, and smoking; SSc complications, including interstitial lung disease, pulmonary arterial hypertension (PAH), renal crisis, myositis, and erectile dysfunction; SSc-specific medications; and cardiovascular medications. Data on medications were obtained from the initial SSc clinic visit.
Systemic hypertension was defined as a resting systolic blood pressure >135 mmHg or resting diastolic blood pressure >85 mmHg (at the time of initial clinic visit); or documentation in the medical record of prior history of physician-diagnosed systemic hypertension. Coronary artery disease was defined as documented history of coronary angiography with coronary stenosis >50%, percutaneous coronary intervention, coronary artery bypass surgery, or myocardial infarction.
Manual chart review was conducted to determine the presence of interstitial lung disease and PAH. Interstitial lung disease was defined as the presence of any ground glass opacities, honeycombing, or fibrosis on high resolution computed tomography of the chest and a forced vital capacity <65% of predicted on pulmonary function testing. All patients were screened for pulmonary hypertension with Doppler echocardiography and pulmonary function testing. Any patient with unexplained dyspnea, signs and symptoms of right-sided heart failure, elevated pulmonary artery systolic pressure (PASP) on echocardiography, or isolated decrease in diffusing capacity of carbon monoxide (DLCO) was referred for further evaluation by a pulmonary hypertension specialist, and cardiac catheterisation was performed to determine if PAH was present. PAH

was recorded as present if the patient carried a diagnosis of PAH at baseline (based on prior testing) or if PAH was diagnosed during initial clinical evaluation. The diagnosis of PAH required invasively documented mean pulmonary artery pressure >25 mmHg, pulmonary capillary wedge pressure <15 mmHg, and pulmonary vascular resistance >3 Wood units (24, 25).
All patients underwent complete physical examination including documentation of digital ulceration; and modified Rodnan skin score (mRSS). Laboratory evaluation included testing for anti-topoisomerase I (Scl-70) and anti-centromere antibodies, complete blood count, albumin, sodium, blood urea nitrogen, creatinine, and B-type natriuretic peptide (BNP). Pulmonary function test results were also documented.

Echocardiography
All subjects underwent echocardiography as part of their initial clinical evaluation (within 1 month of initial clinic visit). Echocardiograms were performed by sonographers blinded to all clinical and laboratory data. Systolic, diastolic, and pulse pressure were measured and documented at the time of echocardiography. Patients underwent comprehensive two-dimensional echocardiography with Doppler and tissue Doppler imaging according to published guidelines (16, 26) using a Philips ie33 or Sonos 7500 echocardiographic machine. For the purposes of this study, a single experienced echocardiographer, also blinded to clinical and laboratory data, made quantitative measurements on all echocardiograms according to a systematic, pre-established research protocol.
PASP was calculated from tricuspid regurgitant (TR) jet peak velocity (to determine TR gradient) with the addition of estimated right atrial pressure (26). LV ejection fraction was calculated from the biplane method of discs. LV mass was calculated from the 2D area-length method and left atrial volume was calculated by the biplane method of discs (26). Right ventricular (RV) measurements, including RV maximal diameter, RV fractional area change, and tricuspid annular plane systolic

excursion (TAPSE), were obtained as described previously (27). LV systolic dysfunction was defined as LV ejection fraction <55%.

Diastolic dysfunction

Age-based cut-offs of tissue Doppler E' velocities at the lateral mitral annulus, derived from a population-based study and used in a large clinical trial of diastolic dysfunction, were used to define LV diastolic dysfunction. LV diastolic dysfunction was defined as present if lateral E' <10 cm/s if age <55 years, E' <9 cm/s if age 55–65 years, and E' <8 cm/s if age >65 years (28). The septal mitral annulus E' was not used to categorise patients since abnormal RV function, which may occur in SSc patients, can result in a reduced septal E' velocity. For patients with abnormal lateral E' velocity, grades of LV diastolic dysfunction were defined as follows: impaired relaxation was defined as E/A ratio <1. Moderate or severe diastolic dysfunction was defined as E/A ratio >1.

Mortality

All subjects were evaluated clinically every 3–4 months after enrollment into the Northwestern Scleroderma Program (*i.e.* the time of baseline echocardiography and enrollment into the present study) by one of two rheumatologists who specialise in SSc. Vital status, determined from chart review and from analysis of the Social Security Index, was available on all patients. Cause of death was determined by chart review. Survival time was defined as the date of last follow-up or contact with the patient (or date of death if applicable) minus date of baseline echocardiogram.

Statistical analysis

Patients were stratified by presence or absence of diastolic dysfunction (normal *vs.* abnormal E' velocity using age-based reference values). We compared demographic, clinical, laboratory, pulmonary function testing, and echocardiographic characteristics between patients with normal *vs.* abnormal LV diastolic function. Continuous variables were summarised by mean ± standard deviation and compared using *t*-tests

Table I. Clinical and demographic characteristics by absence or presence of diastolic dysfunction.

Characteristic	Diastolic dysfunction		*p*-value
	Absent (n=118)	Present (n=35)	
Age, years	49 ± 13	57 ± 11	0.0002
Female, n (%)	100 (85)	31 (89)	0.57
Race, n (%)			0.002
• White	70 (59)	27 (77)	
• Black	12 (10)	7 (20)	
• Other	36 (30)	1 (3)	
Disease duration, n (%)			0.022*
• <4 years	60 (52)	9 (26)	
• 4–8 years	27 (23)	14 (40)	
• >8 years	29 (25)	12 (34)	
Time from onset of Raynaud's phenomenon, years (median [25th–75th precentile])†	2.5 (1.1–8.2)	9 (3.7–15.1)	0.014
Scleroderma diagnosis, n (%)			0.71
• Limited cutaneous SSc	70 (59)	22 (63)	
• Diffuse cutaneous SSc	48 (41)	13 (37)	
Modified Rodnan skin score	12 ± 12	9 ± 11	0.18
Digital ulcerations, n (%)	85 (72)	28 (80)	0.35
Comorbidities, n (%)			
• Diabetes mellitus	3 (3)	2 (6)	0.32
• Systemic hypertension	21 (18)	15 (43)	0.002*
• Coronary artery disease	2 (2)	3 (9)	0.079*
• Cancer	10 (8)	7 (20)	0.057
• Thyroid disease	22 (18)	7 (20)	0.86
• Smoking history			0.47
No history of smoking	74 (63)	19 (54)	
Past smoker	35 (29)	11 (31)	
Current smoker	9 (8)	5 (14)	
SSc complications, n (%)			
• Interstitial lung disease	35 (30)	14 (40)	0.25
• Pulmonary arterial hypertension	11 (9)	6 (17)	0.20
• Renal crisis	2 (2)	0 (0)	0.99
• Myositis	5 (4)	1 (3)	0.99
• Erectile dysfunction	6 (5)	1 (3)	0.99
SSc-specific medications, n (%)			
• Penicillamine	6 (5)	1 (3)	0.99
• Cyclophosphamide	3 (3)	0 (0)	0.99
• Mycophenalate	7 (6)	3 (9)	0.70
• Azathioprine	1 (1)	1 (3)	0.41
• Prednisone	24 (20)	7 (20)	0.97
• Plaquenil	8 (7)	1 (3)	0.69
• Methotrexate	14 (12)	3 (9)	0.76
Cardiovascular medications, n (%)			
• ACE-inhibitor	13 (11)	9 (25)	0.03
• Angiotensin receptor blocker	12 (10)	3 (9)	0.99
• Beta-blocker	6 (5)	4 (11)	0.24
• Diuretic	11 (9)	7 (20)	0.09
• Calcium channel blocker	44 (36)	13 (37)	0.99
• Statin	14 (12)	9 (25)	0.044
• Anticoagulant	20 (17)	10 (29)	0.13
• Sildenafil	11 (9)	3 (9)	0.99
• Bosentan	4 (3)	3 (9)	0.20
Height, m	1.7 ± 0.1	1.6 ± 0.1	0.50
Weight, kg	70 ± 14	70 ± 18	0.91
Body mass index, kg/m²	26 ± 5	26 ± 7	0.89
Systolic blood pressure, mmHg	119 ± 15	125 ± 16	0.08
Diastolic blood pressure, mmHg	71 ± 7	73 ± 9	0.22
Pulse pressure, mmHg	48 ± 12	51 ± 11	0.14
Heart rate, bpm	84 ± 13	80 ± 10	0.06

For continuous variables, values represent mean ± standard deviation.
*$p<0.05$ after adjustment for age; †Time from onset of Raynaud's phenomenon to presentation was right-skewed, so median and 25th–75th percentile values are presented and groups were compared by the Wilcoxon rank-sum test.

(or non-parametric equivalent when appropriate). Categorical variables were compared using the chi-squared statistic (or Fisher's exact test when appropriate). Since reduced E' velocities (LV diastolic dysfunction) and aging are closely associated, we performed simple age-adjustment for all comparisons to evaluate the possibility of confounding by age.

Our regression analyses were planned to answer two fundamental questions: (1) which demographic, clinical, laboratory, and echocardiographic parameters are independently associated with diastolic dysfunction? and (2) is diastolic dysfunction independently associated with death in SSc? For the first part of our regression analysis, we performed univariable and multivariable linear regression analyses to determine which variables were most closely associated with LV diastolic dysfunction. Variables with $p<0.05$ on simple age-adjusted linear regression analyses (using lateral E' velocity as the dependent variable) were included in multivariable linear regression analyses. We performed our multivariable analysis in 2 phases: Model 1 included only SSc disease duration and age to demonstrate that SSc disease duration was independently associated with reduced E' velocity even after adjusting for age; Model 2 included the only 2 other clinical variables which were associated with reduced E' velocity after age adjustment (hypertension and coronary artery disease).

For the second part of our regression analysis, we constructed Cox proportional hazard models to determine whether reduced tissue Doppler E' velocity was independently associated with death. We performed our Cox modeling of E' velocity in 3 phases: Model 1 included only E' velocity and age (since age is highly associated with LV diastolic dysfunction); Model 2 additionally adjusted for female gender and SSc disease duration (since SSc disease duration was independently associated with LV diastolic dysfunction); and Model 3 additionally adjusted for the 2 main causes of death in SSc (interstitial lung disease and PAH), which are not thought to be related to LV diastolic dysfunction.

Table II. Laboratory and pulmonary function data by absence or presence of diastolic dysfunction.

Laboratory test	Diastolic dysfunction		p-value[‡]
	Absent (n=118)	Present (n=35)	
Anti-Scl70 antibody positivity, n (%)	40 (34)	6 (17)	0.051
Anticentromere antibody positivity, n (%)	17 (19)	11 (39)	0.027
Anti-U1 RNP antibody positivity [n=150], n (%)	4 (3)	1 (3)	0.99
Antinuclear antibody (nucleolar) positivity [n=142], n (%)	50 (46)	11 (33)	0.20
Anti-RNA polymerase antibody positivity [n=30], n (%)*	6 (24)	0 (0)	0.55
White blood cell count, k/μL	7.6 ± 2.7	8.1 ± 3.8	0.43
Haemoglobin, g/dl	12.7 ± 2.0	12.9 ± 1.4	0.56
Sodium, mEq/L	139 ± 3	141 ± 11	0.094
Albumin, g/dl	3.7 ± 0.4	3.6 ± 0.5	0.13
Blood urea nitrogen, mg/dl	13 ± 7.6	16 ± 6.8	0.17
Serum creatinine, mg/dl	0.91 ± 0.56	0.93 ± 0.20	0.83
B-type natriuretic peptide, pg/ml*	38 (21-73)	62 (41-177)	0.006[†]
Forced expiratory volume in 1 second (FEV$_1$), % predicted	77 ± 20	76 ± 15	0.63
Forced vital capacity (FVC), % predicted	73 ± 20	72 ± 15	0.78
FEV$_1$/FVC ratio, %	84 ± 7	81 ± 6	0.05
Total lung capacity, % predicted	84 ± 19	82 ± 17	0.58
Carbon monoxide diffusing capacity (DLCO), % predicted	85 ± 18	80 ± 23	0.05

For continuous variables, values represent mean ± standard deviation except where noted.
*Values are median (IQR) for B-type natriuretic peptide because of a right-skewed distribution.
[†]Wilcoxon Rank-Sum test [‡]None of the linear regression p-values remained significant at $p<0.05$ after adjustment for age.

For all analyses, a two-sided p-value <0.05 was considered statistically significant. Covariates were kept to a minimum in our multivariable regression models in order to retain statistical power by keeping models as parsimonious as possible. For all regression models, we studied E' velocity as a continuous variable in order to preserve statistical power. Stata version 10.1 (College Station, TX) was used for all statistical analyses.

Results

One hundred and fifty-three consecutive patients referred to the Northwestern Scleroderma Programme were included in the study; the majority of the patients (130/153, 85%) were female and mean age was 51±13 years. Of the 153 patients, 92 (60%) had lcSSc and 61 (40%) had dcSSc. LV systolic dysfunction was present in 8/153 (5.2%) of subjects, whereas LV diastolic dysfunction was present in 35/153 (23% [95% confidence interval 16–30%]) of the subjects.

Tables I–II show the clinical, demographic, laboratory, and pulmonary function test results for patients with and without LV diastolic dysfunction. The duration of SSc, defined as time between onset of first non-Raynaud symptom and time of first SSc clinic visit, was associated with diastolic dysfunction independent of age ($p=0.022$ after adjustment for age). Table III displays echocardiographic factors associated with LV diastolic dysfunction. Interestingly, RV fractional area change (a measure of RV systolic function) and tissue Doppler S' velocities (a measure of longitudinal LV systolic function and an early indicator of LV systolic dysfunction) were both independently associated with LV diastolic dysfunction and tissue Doppler E' velocities. In addition, increasing SSc disease duration was also independently associated with decreased tissue Doppler S' velocity (even after age adjustment) suggesting that longitudinal myocardial fiber dysfunction occurs in both systole and diastole simultaneously in SSc and may worsen with a more prolonged disease course. An alternate, expanded definition of disease duration (time from onset of Raynaud's phenomenon to first SSc clinic visit) was associated with diastolic dysfunction

Table III. Echocardiographic parameters by absence or presence of diastolic dysfunction.

Parameters	Diastolic dysfunction		p-value
	Absent (n=118)	Present (n=35)	
LV structure/function:			
• LV end-diastolic volume index, ml/m^2	38 ± 7	40 ± 12	0.24
• LV end-systolic volume index, ml/m^2	18 ± 4	19 ± 8	0.10
• LV ejection fraction, %	60 ± 6	59 ± 8	0.39
• LV mass index, g/m^2	76 ± 21	95 ± 27	<0.0001*
RV structure/function:			
• RV maximal diameter, cm	3.3 ± 0.6	3.3 ± 0.6	0.74
• TAPSE, mm	1.9 ± 0.7	1.5 ± 0.7	0.02
• RV fractional area change, %	44 ± 10	37 ± 11	0.005*
• Pulmonary artery systolic pressure, mmHg	31 ± 15	33 ± 11	0.62
LV diastolic parameters:			
• Transmitral E velocity, cm/s	98 ± 20	92 ± 18	0.12
• Transmitral A velocity, cm/s	81 ± 20	91 ± 27	0.02
• E/A ratio	1.4 ± 1.6	1.3 ± 1.5	0.66
• E deceleration time, ms	240 ± 13	237 ± 7	0.87
• Pulmonary venous systolic:diastolic ratio	1.2 ± 0.2	1.2 ± 0.3	0.50
• Left atrial volume index (ml/m^2)	22 ± 6	24 ± 7	0.31
Tissue Doppler parameters:			
• Septal E' velocity, cm/s	10 ± 2.7	6.6 ± 1.7	<0.0001*
• Lateral E' velocity, cm/s	13 ± 3.1	7.4 ± 1.3	<0.0001
• Septal S' velocity, cm/s	7.9 ± 1.6	7.0 ± 1.6	0.0070*
• Lateral S' velocity, cm/s	9.2 ± 2.1	7.4 ± 2.7	0.0001*
• Lateral E/E' ratio	8 ± 2	13 ± 4	<0.0001*
LV diastolic function grade:			<0.0001*
• Normal diastolic function	118 (100)	0 (0)	
• Mild (Grade I) diastolic dysfunction	0 (0)	16 (46)	
• Moderate or severe (Grade II or III) diastolic dysfunction	0 (0)	19 (54)	

For continuous variables, values represent mean ± standard deviation.
LV: left ventricular; RV: right ventricular; TAPSE: tricuspid annular plane systolic excursion; E: early diastolic; A: late (atrial) diastolic; E': early diastolic mitral annular velocity; S': systolic mitral annular velocity.
*p<0.05 after adjustment for age.

Table IV. Multivariable linear regression analysis of tissue Doppler E' velocity.

Predictor variable	Model 1		Model 2	
	β-coefficient (95% CI)	p-value	β-coefficient (95% CI)	p-value
SSc disease duration*	-0.7 (-1.3, -0.1)	0.022	-0.7 (-1.2, -0.1)	0.021
Age†	-1.6 (-2.0, -1.2)	<0.0001	-1.3 (-1.7, -0.9)	<0.0001
Hypertension	–	–	-1.7 (-2.9, -0.4)	0.008
Coronary artery disease	–	–	-2.9 (-5.7, -0.2)	0.036

*Per 4-year increase in disease duration. †Per decade increase in age.

(p=0.014), but this association did not persist after multivariable adjustment (p=0.055). Regardless of definition of disease duration, those with lcSSc had longer disease duration than those patients with dcSSc (p<0.01 for both definitions of disease duration).

Despite using age-based cut-offs for lateral tissue Doppler E' velocity, reduced E' was still strongly associated with age, and most clinical factors as-sociated with E' velocity on univariate analysis were no longer associated with E' after simple age-adjustment. The following factors were independently associated with reduced tissue Doppler E' velocity on multivariable analysis (Table IV): SSc disease duration, age, history of coronary artery disease, and systemic hypertension. Notably, neither type of SSc (limited or diffuse cutaneous) nor severity of skin involvement (as judged by mRSS) were associated with LV diastolic dysfunction. Use of SSc-specific medications was not associated with diastolic dysfunction. There appeared to be a correlation between anticentromere antibody status and LV diastolic dysfunction; however, closer investigation revealed that, since patients with anticentromere antibodies were older and those with anti-Scl70 younger, the association between antibody status and diastolic dysfunction was confounded by age (indeed, after age-adjustment, there was no longer an association between antibody status and LV diastolic dysfunction). None of the other autoantibodies tested were significantly different when those with and without diastolic dysfunction were compared (Table I). Figure 1 demonstrates that as SSc disease duration increases, the E/E' ratio (a marker of increased LV filling pressures) increases (age-adjusted p<0.0001 for the trend). During a mean follow-up of 1.9±1.3 years, 9/153 (5.9%) of the patients died. Causes of death included PAH (n=2), interstitial lung disease with associated pulmonary hypertension (n=2), pneumonia after stem cell transplantation (n=2), left-sided heart failure due to myocardial infarction with LV systolic dysfunction (n=1), oropharyngeal cancer (n=1), and rapidly progressive cancer (of unknown primary site) in the setting of significant PAH (n=1). On Cox proportional hazards analysis (Table V), baseline tissue Doppler E' velocity was independently associated with increased risk of death (univariate HR 3.5, 95% CI 1.2–10.1, p=0.019; multivariate HR 3.2, 95% CI 1.1–9.5, p=0.034 per standard deviation decrease in E' velocity). The association between tissue Doppler E' velocity and death persisted after excluding the 3 patients who died of non-SSc-related causes (univariate HR 4.7, 95% CI 1.3–16.7, p=0.015 per standard deviation decrease in E' velocity).

The presence of PAH at baseline was also associated with increased risk of death (HR 9.5, 95% CI 2.0–45.5; p=0.005). Adjustment for PAH did not eliminate the association between E' velocity and death, and there was no interaction between E' velocity and PAH
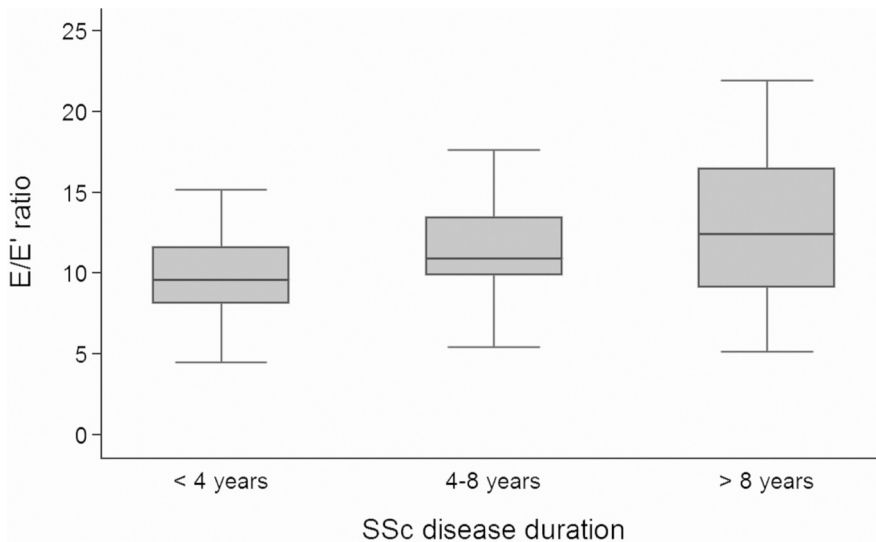
Fig. 1. Box and whisker plot of echocardiographic E/E' ratio *versus* systemic sclerosis disease duration. Increasing disease duration is associated with increased E/E' ratio, a marker of LV filling pressures (age-adjusted $p<0.0001$ for the trend).

as predictors of death (p=0.97 for interaction). Finally, we conducted additional analyses to explore the possibility that medications may have an effect on the relationship between diastolic dysfunction and death. We found that no medications were independently associated with death, and none of the medications had an effect on the association between E' velocity and death.

Discussion

Several studies have used Doppler echocardiography (29, 30) and tissue Doppler echocardiography (13-15, 31) to study LV diastolic dysfunction in SSc. Although these studies have demonstrated an increased frequency of LV diastolic dysfunction compared to healthy controls, ours is the first study to comprehensively study LV diastolic dysfunction with tissue Doppler imaging in a consecutive sample of SSc patients (n=153). We were therefore able to determine which clinical factors are associated with LV diastolic dysfunction in SSc, and we were able to demonstrate a possible association between reduced tissue Doppler E' velocity and increased risk of death, a novel observation.

Our finding that 5.2% of patients with SSc had reduced LV ejection fraction is almost identical to the 5.6% frequency found in the EULAR database (8). Similar to Meune *et al*. (12), we found that LV diastolic dysfunction is 4–5 times as common as LV systolic dysfunction in SSc and may be an early marker of cardiac fibrosis. In our study, LV diastolic dysfunction was associated with subtle abnormalities in longitudinal LV systolic function and RV systolic function. These findings indicate that reduced tissue Doppler E' velocities may

be a marker of generalised myocardial involvement in SSc.

We showed that increased SSc disease duration (time from first non-Raynaud's symptom to initial clinic visit) is associated with worse LV diastolic dysfunction. Patients with longer SSc disease duration were more likely to have LV diastolic dysfunction, and E/E' ratio (a marker of LV filling pressures) increased with increasing SSc disease duration (Fig. 1). Rosato *et al*. (14) previously found an association between SSc disease duration and LV diastolic dysfunction, although the association was not adjusted for age. Importantly, their definition of LV diastolic dysfunction (E'/A' <1 on tissue Doppler imaging) can be seen in normal older individuals (16). The latter may explain the much higher prevalence of diastolic abnormalities in their study (61% *vs*. only 23% in our study). The finding of an independent association between SSc disease duration and LV diastolic dysfunction suggests, but does not prove, a possible causal link between SSc and LV diastolic dysfunction. Of note, time from onset of Raynaud's phenomenon to enrollment in the study (expanded disease duration definition) was association with diastolic dysfunction on univariate (p=0.014), but not multivariable analysis (p=0.055). This may have been due to less accuracy in recalling onset of Raynaud's phenomenon *versus* recalling onset of first non-Raynaud's phenomenon symptom, or it may signify the closer association between non-Raynaud's phenomenon symptoms with diastolic dysfunction.

We found no association between extent of skin involvement (or autoanti-

Table V. Cox Proportional Hazards Analysis.

Predictor variable	Model 1		Model 2		Model 3	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Tissue Doppler E' velocity*	3.5 (1.2, 10.1)	0.019	3.6 (1.2, 10.8)	0.023	3.2 (1.1, 9.5)	0.034
Age†	0.9 (0.4, 1.7)	0.67	0.9 (0.4, 1.7)	0.67	0.9 (0.5, 1.7)	0.79
Female gender	–	–	0.88 (0.11, 7.23)	0.90	0.67 (0.07, 6.4)	0.73
SSc disease duration‡	–	–	0.93 (0.40, 2.14)	0.86	0.70 (0.26, 1.89)	0.48
Interstitial lung disease	–	–	–	–	1.42 (0.22, 9.21)	0.71
Pulmonary arterial hypertension	–	–	–	–	9.49 (1.98, 45.52)	0.005

*Per standard deviation decrease; †Per decade increase in age; ‡Per 4-year increase in disease duration.

body status) and degree of LV diastolic dysfunction in SSc. This was surprising given prior reports that identified a higher prevalence of all cardiac manifestations of SSc in patients with diffuse skin involvement (32). Many of the clinical factors associated with LV diastolic dysfunction (including medications, autoantibodies, and BNP) were no longer associated after simply adjusting for age. These findings indicate that aging is a primary determinant of LV diastolic dysfunction; thus, when studying the determinants of LV diastolic dysfunction in SSc, accounting for the confounding effects of age is essential. The factors that were independently associated with LV diastolic dysfunction (after adjustment for age) included SSc disease duration and cardiovascular comorbidities (systemic hypertension and coronary artery disease). The finding that epicardial (atherosclerotic) coronary artery disease is associated with LV diastolic dysfunction is interesting given the high frequency of microvascular cardiac ischaemia in SSc found in prior studies using thallium nuclear imaging (4). A prior study found that there is no increase in angiographically proven epicardial coronary artery disease in patients with SSc (33). Therefore, whether the association between coronary artery disease and LV diastolic dysfunction is similar to patients without SSc (in which this association is quite common [34]) or whether there are unique interactions between atherosclerotic coronary artery disease and microvascular ischaemia in SSc will require further exploration.

Importantly, we demonstrate that LV diastolic dysfunction may be associated with increased mortality. For each standard deviation decrease in E' velocity, the hazard ratio of death increased by 3.2-fold. On the basis of this finding, measurement of tissue Doppler E' could add to risk prediction in SSc and provide insight into possible subclinical cardiovascular disease. However, it remains to be seen whether or not reduced tissue Doppler E' and LV diastolic dysfunction truly predispose SSc patients to adverse events, whether these indices are indicative of worse vascular or fibrotic disease in SSc, or whether these markers are simply epiphenomenon associated with but not causing morbidity or mortality.

Several limitations should be considered when interpreting the results of our study. Although we have data on vital status and cause of death for all patients in our study, our findings are limited by lack of data on non-fatal outcomes such as worsening SSc symptoms, progression of cardiac disease (including development of LV systolic dysfunction or heart failure), or development of PAH. In addition, we lacked the statistical power to determine whether reduced tissue Doppler E' velocities were associated with specific causes of death. We also did not systematically evaluate for coronary artery disease using myocardial perfusion imaging or coronary angiography; thus, the relationship between myocardial ischaemia, myocardial fibrosis, and reduced tissue Doppler E' velocities should be investigated further. Future investigation into LV diastolic dysfunction in SSc should also determine whether tissue Doppler indices such as E' and S' deteriorate over time in some SSc patients and whether or not such deterioration is associated with progression to LV systolic dysfunction, heart failure, or worse outcomes. Finally, the cross-sectional nature of the first part of our study precludes establishing a cause-and-effect relationship between SSc disease duration and diastolic dysfunction, our study is limited by the lack of a control group (which could have provided further insight into the relationship between diastolic dysfunction and death), and our survival analyses should be viewed as preliminary given the low number of deaths and relatively short follow-up duration.

Conclusion
In summary, advanced age, duration of SSc, and cardiovascular comorbidities (systemic hypertension and coronary artery disease) are associated with LV diastolic dysfunction in patients with SSc. Reduced tissue Doppler E' velocity, a marker of LV diastolic dysfunction, may be independently associated with death and should be evaluated further in larger studies.

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