

Left Ventricular Diastolic Function in Systemic Sclerosis

GIANCARLO AGUGLIA, ALESSANDRO SGRECCIA, MARIA LAURA BERNARDO, ENRICO CARMENINI, MANFREDI GIUSTI De MARLE, ALESSIA REALI, and SERGIO MORELLI

ABSTRACT. Objective. To assess left ventricular diastolic function in patients with systemic sclerosis (SSc) and to verify if a “primary” diastolic dysfunction might exist.

Methods. In total 124 patients and 41 healthy subjects underwent complete echocardiographic examination. The following pulsed wave Doppler variables were evaluated: peak velocity during early filling (E), peak velocity during late atrial filling (A), E/A ratio, and early filling deceleration time.

Results. Seventy-seven patients (62.1%) had conditions potentially affecting left ventricular diastolic function (Group A) and 47 patients (37.9%) formed a homogeneous group without cardiac involvement or other causes of abnormal diastolic function (i.e., systemic and/or pulmonary hypertension, ventricular hypertrophy, pericardial disease, systolic dysfunction, valvular heart disease, coronary artery disease) (Group B). The entire SSc population and Group A showed significant differences in the Doppler variables of diastolic function compared to the control group. No significant differences were found between Group B and controls.

Conclusion. In patients with SSc, left ventricular diastolic dysfunction was found only in patients with conditions potentially affecting left ventricular diastolic function. In patients without conditions potentially affecting left ventricular diastolic function no differences were seen in comparison with controls. SSc does not seem to cause “primary” diastolic abnormalities. (*J Rheumatol* 2001;28:1563–7)

Key Indexing Terms:

SYSTEMIC SCLEROSIS DIASTOLIC FUNCTION DOPPLER ECHOCARDIOGRAPHY

Systemic sclerosis (SSc) is a chronic disease of unknown etiology characterized by diffuse microangiopathy and excessive fibroblastic activity, with collagen deposition involving the skin and lungs, heart, kidneys, and gastrointestinal tract¹. In these patients, cardiac involvement affects survival, carrying a poor prognosis².

Autopsy studies have shown that cardiac involvement is far more common than clinically suspected³. This is the reason many investigators have looked for heart involvement in asymptomatic patients^{4–6}. The presence of fibrosis, probably due to coronary microcirculation involvement, is the pathological hallmark of myocardial disease in SSc, and this has led some investigators to hypothesize that impaired ventricular filling could represent the functional translation of this anatomical condition, occurring as an early finding in the natural history of scleroderma myocardial disease. Echocardiographic studies revealed diastolic function impairment in SSc, generally only in association with other

echocardiographic findings such as left ventricular hypertrophy or systolic dysfunction^{7,8}. Recently, investigators reported abnormal diastolic function variables in patients with SSc, despite normal systolic function and normal ventricular wall thickness^{9–11}.

Many conditions potentially affecting left ventricular diastolic function (systemic and/or pulmonary hypertension, ventricular hypertrophy, pericardial disease, systolic dysfunction) are common in SSc heart disease^{12–17}. It may be difficult to separate the influence of each single condition on diastolic function impairment. To assess the presence of “primary” diastolic dysfunction, we evaluated Doppler echocardiographic indices of left ventricular diastolic function in a large group of patients with SSc compared with healthy control subjects, and then performed a separate analysis on a selected group of SSc patients with no potential condition known to affect left ventricular diastolic function.

MATERIALS AND METHODS

From March 1993 to December 1998, we enrolled 124 patients (106 women, 18 men; mean age 51.99 ± 12.48 yrs; range 23–70). All patients satisfied the American Rheumatism Association preliminary criteria for definite SSc¹⁸; 57 patients had the diffuse form (dSSc) and 67 the limited form (lSSc) by location and extent of skin involvement¹⁹.

Forty-one healthy subjects (37 women, 4 men; mean age 52.59 ± 14.45 yrs, range 26–70) recruited by hospital staff and their relatives, with no evidence of any disease or family history of early cardiac death, were studied as controls.

From the Istituto di Clinica Medica I, Università La Sapienza, Rome, Italy.

Supported in part by a grant from Andrea Cesalpino Foundation.

G. Aguglia, MD, A. Sgreccia, MD, M.L. Bernardo, MD, E. Carmenini, MD, M. Giusti De Marle, MD, A. Reali, MD, S. Morelli, MD.

Address reprint requests to Dr. S. Morelli, Istituto di Clinica Medica I, Università “La Sapienza”, Policlinico Umberto I, Viale del Policlinico, 00161 Rome, Italy. E-mail: smorelli@uniroma1.it

Submitted July 24, 2000; revision accepted January 29, 2001.

Systemic hypertension was diagnosed in case of history of hypertension or values of systemic pressure > 140/90 mm Hg detected on at least 3 separate occasions.

All patients and controls underwent complete echocardiographic examination. Echocardiographic studies were performed using an instrument equipped with 2.25 and 3.5 MHz transducers (Ultramark 9, Advanced Technology Laboratories, Seattle, WA, USA) using the left parasternal and apical windows. All studies were recorded on videotape for offline analysis. Wall thicknesses, cavity sizes, and left ventricular ejection fraction were measured in M-mode tracings under 2 dimensional guide in the left parasternal long axis view, according to the criteria proposed by the American Society of Echocardiography²⁰. Left ventricular hypertrophy was diagnosed in presence of any wall thickness > 1.1 cm, while left ventricular dysfunction was defined as ejection fraction ≤ 50%. Left ventricular mass was estimated by the formula of Levy, *et al*²¹, and was divided by the body surface area to derive the left ventricular mass body index. Heart valve function was evaluated by 2D real-time pulsed wave and color Doppler imaging. Pulmonary artery systolic pressure was measured by continuous wave Doppler from the sum of systolic transvalvular tricuspid pressure gradient and right systolic atrial pressure estimated at 10 mm Hg²². Pulsed wave Doppler was employed for diastolic transmitral flow evaluation. At this point, optimal images from the apical 4 chamber view were obtained, and sample volume was located at the tips of the mitral valve leaflets within the left ventricular cavity. Doppler measurements were then traced with a handheld cursor and the following variables were evaluated: peak velocity during early filling (E), peak velocity during late atrial filling (A), and E/A ratio, early filling deceleration time.

Exclusion criteria for subjects included heart rate at rest > 90 beats/min, absence of sinus rhythm, and poor quality echocardiographic imaging.

Preload modifying drugs, such as nitrates or diuretics, were discontinued at least 24 h before echocardiographic examination.

Statistics. Results are reported as mean values ± standard deviation. Differences between groups were evaluated using Student's t test for quantitative variables, and Fisher's exact test or chi-squared test for discrete

variables, as appropriate. Differences were considered statistically significant with $p < 0.05$.

RESULTS

In this SSc population, 77 patients (62.1%) had conditions potentially affecting left ventricular diastolic function (Group A) (Table 1). Thus, 47 SSc subjects (37.9%) formed a homogeneous group of patients without cardiac involvement or other causes of altered diastolic function (Group B).

Tables 2–4 show general, clinical, and echocardiographic characteristics in patients and controls, also displayed for group and form of disease.

Group A showed significant differences in blood pressure, ejection fraction, left ventricular wall thickness, left ventricular mass index, and Doppler variables for diastolic function compared to the control group. The E/A ratio inversion was found in 6 controls, 47 patients in Group A ($p <$

Table 1. Conditions affecting left ventricular diastolic function in patients of Group A. Percentage value for all patients (Group A + Group B) shown in parentheses.

Pulmonary systolic pressure > 45 mm Hg	44 (35.5)
Left ventricular hypertrophy	39 (31.5)
Systemic arterial hypertension	33 (26.6)
Chronic renal insufficiency	15 (12.1)
Left ventricular systolic dysfunction	8 (6.5)
Moderate or severe pericardial effusion	6 (4.8)
Valvular heart disease	5 (4.0)
Coronary artery disease	4 (3.2)

Table 2. General, clinical, and echocardiographic characteristics in patients and controls. Data are mean value ± SD.

	All Patients (n = 124)	Group A (n = 77)	Group B (n = 47)	Controls (n = 41)
Age, yrs	51.99 ± 12.48	55.99 ± 10.13 [†]	45.45 ± 13.29*	52.59 ± 14.45
Disease duration, yrs	11.2 ± 8.0	10.8 ± 7.9	11.9 ± 8.2	
Resting heart rate, bpm	78.35 ± 6.81	78.31 ± 6.16	78.43 ± 7.82	76.70 ± 6.87
Systolic BP, mm Hg	124.15 ± 13.69	126.75 ± 15.08* [†]	119.89 ± 9.75	120.29 ± 9.37
Diastolic BP, mm Hg	77.18 ± 9.16*	79.42 ± 8.51* [†]	73.51 ± 9.08	73.14 ± 8.86
LVEDD, mm	44.80 ± 5.15	45.23 ± 5.76	44.10 ± 3.90	44.19 ± 4.03
Ejection fraction, %	61.85 ± 6.63	60.18 ± 6.77* [†]	64.57 ± 5.44	63.80 ± 7.14
IVS, mm	10.27 ± 1.76*	11.05 ± 1.59* [†]	8.99 ± 1.20	8.90 ± 1.14
PW, mm	9.74 ± 1.39*	10.23 ± 1.27* [†]	8.94 ± 1.21	8.90 ± 1.27
LVMI, g	99 ± 31*	110 ± 33* [†]	81 ± 15	84 ± 25
E, cm/s	66.60 ± 12.34	64.39 ± 10.95* [†]	70.23 ± 13.69	70.24 ± 10.24
A, cm/s	64.50 ± 18.70*	70.79 ± 19.01* [†]	54.19 ± 12.77	55.90 ± 14.23
E/A	1.14 ± 0.46	1.00 ± 0.39* [†]	1.38 ± 0.48	1.26 ± 0.20
DT, ms	185.04 ± 34.19	187.73 ± 37.61	180.64 ± 27.52	181.72 ± 25.32
PASP** mm Hg	43.93 ± 16.32	50.08 ± 17.70 [†]	33.91 ± 5.42	

* $p < 0.05$ vs controls. [†] $p \leq 0.01$ vs Group B.

**Three patients, 2 in Group A and 1 in Group B, were excluded from analysis because they had no tricuspid regurgitation; their pulmonary artery systolic pressure was considered normal.

A: late filling peak velocity; E: early filling peak velocity; E/A: early filling peak velocity to late filling peak velocity ratio; BP: blood pressure; DT: early filling deceleration time; IVS: end-diastolic interventricular septum thickness; LVEDD: left ventricular end-diastolic dimension; LVMI: left ventricular mass index; PASP: pulmonary artery systolic pressure; PW: end-diastolic posterior wall thickness.

Table 3. Characteristics of the patients by form of disease. Data are mean value \pm SD.

	Diffuse (n = 57)	Limited (n = 67)	Controls (n = 41)
Age, yrs	49.95 \pm 12.86	53.73 \pm 11.97	52.59 \pm 14.45
Disease duration, yrs	8.7 \pm 5.4 [†]	13.4 \pm 9.2	
Resting heart rate, bpm	77.79 \pm 6.62	78.84 \pm 6.98	76.70 \pm 6.87
Systolic BP, mm Hg	128.33 \pm 15.71 ^{*†}	120.60 \pm 10.57	120.29 \pm 9.37
Diastolic BP, mm Hg	78.95 \pm 9.20 [*]	75.67 \pm 8.91	73.14 \pm 8.86
LVEDD, mm	44.75 \pm 5.01	44.84 \pm 5.30	44.19 \pm 4.03
Ejection fraction, %	61.25 \pm 6.97	61.46 \pm 9.34	63.80 \pm 7.14
IVS, mm	10.62 \pm 1.91 [*]	10.01 \pm 1.61 [*]	8.90 \pm 1.14
PW, mm	10.08 \pm 1.45 [*]	9.46 \pm 1.29 [*]	8.90 \pm 1.27
LVMI, g	104 \pm 37 [*]	95 \pm 25 [*]	84 \pm 25
E, cm/s	66.88 \pm 12.64	66.37 \pm 12.18	70.24 \pm 10.24
A, cm/s	65.93 \pm 19.22 [*]	63.28 \pm 18.30 [*]	55.90 \pm 14.23
E/A	1.14 \pm 0.51	1.14 \pm 0.42	1.26 \pm 0.20
DT, ms	183.77 \pm 32.30	186.12 \pm 35.93	181.72 \pm 25.32
PASP**, mm Hg	50.08 \pm 17.70 [†]	33.91 \pm 5.42	

*p < 0.05 vs controls; [†]p \leq 0.01 vs limited form.

**Three patients, 2 with diffuse form and 1 limited form, were excluded from analysis because they had no tricuspid regurgitation; their pulmonary artery systolic pressure was considered normal.

Abbreviations as in Table 2.

Table 4. Characteristics of patients displayed by group and form of disease. Data are mean value \pm SD.

	Group A Diffuse (n = 39)	Group A Limited (n = 38)	Group B Diffuse (n = 18)	Group B Limited (n = 29)
Age, yrs	54.26 \pm 9.63	57.76 \pm 10.44 ^{††}	40.61 \pm 14.24	48.45 \pm 11.95 [*]
Disease duration, yrs	8.95 \pm 5.17 [*]	12.74 \pm 9.67	8.22 \pm 6.03 [†]	14.21 \pm 8.55
Resting heart rate, bpm	77.74 \pm 6.43	78.89 \pm 5.91	77.89 \pm 7.21	78.76 \pm 8.29
Systolic BP, mm Hg	131.54 \pm 17.25 [*]	121.84 \pm 10.62 ^{††}	121.39 \pm 8.54	118.97 \pm 10.47
Diastolic BP, mm Hg	80.90 \pm 9.10	77.89 \pm 7.68	74.72 \pm 8.13	72.76 \pm 9.69 [*]
LVEDD, mm	45.18 \pm 5.35	45.29 \pm 6.23	43.89 \pm 4.23	44.26 \pm 3.77
Ejection fraction, %	59.05 \pm 6.42	61.34 \pm 7.01 ^{††}	66.00 \pm 5.75	63.69 \pm 5.13
IVS, mm	11.46 \pm 1.68 [*]	10.66 \pm 1.37 ^{††}	8.75 \pm 1.02	9.03 \pm 1.25 [*]
PW, mm	10.60 \pm 1.26 [*]	9.86 \pm 1.17 ^{††}	8.89 \pm 1.20	8.93 \pm 1.26
LVMI, g	116 \pm 38	105 \pm 26 ^{††}	78 \pm 13	82 \pm 16 [*]
E, cm/s	63.05 \pm 9.33	65.76 \pm 12.38 ^{††}	75.17 \pm 15.01	67.17 \pm 12.08
A, cm/s	72.28 \pm 16.89	69.26 \pm 21.08 ^{††}	52.17 \pm 16.91	55.45 \pm 9.48 [*]
E/A	0/94 \pm 0.31	1.06 \pm 0.46 ^{††}	1.58 \pm 0.59 [†]	1.25 \pm 0.34
DT, ms	186.15 \pm 35.51	189.34 \pm 40.05	178.61 \pm 24.00	181.90 \pm 29.83
PASP**, mm Hg	53.58 \pm 19.12	46.32 \pm 15.66 ^{††}	35.24 \pm 5.47	33.14 \pm 5.34 [*]

*p < 0.05 vs Group A/limited form; [†]p < 0.05 vs Group B/limited form; ^{††}p < 0.05 vs Group B/diffuse form.

** Three patients, 2 with diffuse form (1 for each group) and 1 limited form (Group A), were excluded from analysis because they had no tricuspid regurgitation; their pulmonary artery systolic pressure was considered normal.

Abbreviations as in Table 2.

0.001 vs controls), and 8 patients in Group B. Six patients had left ventricular hypertrophy and normal systemic blood pressure. In this subset, mean Doppler measurements were similar to those of the entire group of 124 patients, and the E/A ratio inversion was present in only one case.

No significant differences in Doppler variables were found between Group B and controls.

DISCUSSION

We observed that in patients with SSc left ventricular diastolic function (evaluated by pulsed wave Doppler) was abnormal. However, this dysfunction was seen in patients with conditions known to affect left ventricular diastolic function (Group A), and not in patients with no features known to affect left ventricular diastolic function (Group B

and healthy controls). In this regard we accounted for age²³, heart rate²⁴, systolic dysfunction¹², valvulopathies²⁵, left ventricular hypertrophy¹³, pericardial effusion¹³, pulmonary hypertension¹⁴⁻¹⁷, and preload modifying drugs^{26,27}.

After the first description of scleroderma heart disease²⁸, many other studies proved that cardiac involvement in SSc is far more frequent than clinically suspected. Thus, the high prevalence of cardiac abnormalities in our group of patients (62.1%) is not surprising.

Many studies reported instrumental features of diastolic dysfunction in patients with SSc, using Doppler echocardiography or radionuclide angioventriculography^{7,8,29}. In most of them there were associated cardiovascular abnormalities, in particular left ventricular hypertrophy.

Our results contradict 3 recent studies⁹⁻¹¹ that reported abnormalities in Doppler variables of diastolic function in patients with SSc without left ventricular hypertrophy or systolic dysfunction. Valentini, *et al*⁹ observed E/A ratio inversion in 41% of 24 patients with SSc. Armstrong, *et al*¹⁰ showed a significantly prolonged mitral inflow deceleration time. Candell-Riera, *et al*¹¹ reported 63 ISSc patients with significantly prolonged A wave and E/A ratio inversion. The discrepancy between these reports and our results could be explained by differences in study populations, in particular the effect on left ventricular diastolic function by pulmonary arterial hypertension. About 35% of our patients had pulmonary hypertension of at least moderate degree. Reports²²⁻²⁵ have shown that, both in patients with primary pulmonary hypertension and in patients with chronic cor pulmonale, right ventricular pressure overload caused leftward displacement of the ventricular septum and compression of the left ventricle from end-systole throughout the early diastolic filling period. Since these studies reported a linear correlation between the severity of pulmonary hypertension and the degree of left ventricular diastolic function impairment, we excluded only patients with estimated pulmonary artery systolic pressure levels ≥ 45 mm Hg. In the past, the true prevalence of pulmonary hypertension might have been underestimated, although it is a well recognized abnormality in SSc³⁰. Indeed, based on clinical or radiographic criteria, previous studies reported this complication to be present in 5 to 9% of SSc patients^{30,31}. On the other hand, in the only invasive prospective study, Ungerer, *et al*³² estimated the overall prevalence of pulmonary hypertension in SSc to be as high as 33%. Our data are in agreement with Ungerer's results. In 38 patients with ISSc, Armstrong, *et al*¹⁰ identified only one subject with pulmonary hypertension. Candell-Riera, *et al*¹¹ found that this condition was present in only 14% of patients. Finally, in the study of Valentini, *et al*⁹ the potentially confounding effect of pulmonary hypertension on left ventricular diastolic function was not considered at all.

In patients with SSc, left ventricular diastolic dysfunction was found only in those with conditions potentially

affecting left ventricular diastolic function. In patients without conditions potentially affecting left ventricular diastolic function no differences were found in comparison with healthy controls. Thus, SSc does not seem to cause "primary" diastolic abnormalities.

REFERENCES

1. Seibold JR. Scleroderma. In: Kelley WN, Harris ED Jr, Ruddy S, Sledge CB, editors. Textbook of rheumatology. Philadelphia: WB Saunders; 1997:1133-62.
2. Medsger TA, Masi AT, Rodman GP, Benedek TG, Robinson H. Survival with systemic sclerosis (scleroderma): a life-table analysis of clinical and demographics factors in 309 patients. *Ann Intern Med* 1971;75:369-76.
3. Bulkley BH, Ridolfi RL, Salyer WR, Hutchins GM. Myocardial lesions in progressive systemic sclerosis. *Circulation* 1976;53:483-90.
4. Smith JW, Clements PJ, Levisman J, Furst D, Ross M. Echocardiographic features of progressive systemic sclerosis. Correlation with haemodynamic and post-mortem studies. *Am J Med* 1979;66:28-33.
5. Broussard GS, Dowd PM, Milne J, Dymond DS, Caplin J, Camm AJ. Non-invasive assessment of early cardiac involvement in systemic sclerosis. *Postgrad Med J* 1985;61:679-84.
6. Morelli S, Sgreccia A, De Marzio P, et al. Noninvasive assessment of myocardial involvement in patients with systemic sclerosis: role of signal averaged electrocardiography. *J Rheumatol* 1997;24:2358-63.
7. Kazzam E, Caidhal K, Lendelius J, Waldenstrom A. Non-invasive assessment of left ventricular diastolic function in patients with scleroderma. *J Intern Med* 1990;228:183-92.
8. Fujimoto S, Kagoshima T, Nakajima T, Dohi K. Doppler echocardiographic assessment of left ventricular diastolic function in patients with systemic sclerosis. *Cardiology* 1993;82:217-27.
9. Valentini G, Vitale DF, Giunta A, et al. Diastolic abnormalities in systemic sclerosis: evidence for associated defective cardiac functional reserve. *Ann Rheum Dis* 1996;55:455-60.
10. Armstrong GP, Whalley GA, Doughty RN, Gamble GD, Flett SM, Tan PL. Left ventricular function in scleroderma. *Br J Rheumatol* 1996;35:983-8.
11. Candell-Riera J, Armadans-Gil L, Simeon CP, Castell-Conesa V, Fonollosa-Pla V, Garcia-del Castillo H. Comprehensive noninvasive assessment of cardiac involvement in limited systemic sclerosis. *Arthritis Rheum* 1996;39:1138-45.
12. Xie GY, Berk MR, Smith MD, Gurley JC, DeMaria AN. Prognostic value of Doppler transmitral flow patterns in patients with congestive heart failure. *J Am Coll Cardiol* 1994;24:132-9.
13. Rittoo D, Monaghan M, Sadiq T, Nichols A, Richardson PJ. Echocardiographic and Doppler evaluation of left ventricular hypertrophy and diastolic function in black and white hypertensive patients. *J Human Hypertens* 1990;4:113-5.
14. Louie EK, Rich S, Levitsky S, Brundage BH. Doppler echocardiography demonstration of the differential effects of right ventricular pressure and volume overload on left ventricular geometry and filling. *J Am Coll Cardiol* 1992;19:84-90.
15. Nagaya N, Satoh T, Uematsu M, et al. Shortening of Doppler-derived deceleration time of early diastolic transmitral flow in the presence of pulmonary hypertension through ventricular interaction. *Am J Cardiol* 1997;79:1502-6.
16. Louie EK, Rich S, Brundage BH. Doppler echocardiographic assessment of impaired left ventricular filling in patients with right ventricular pressure overload due to primary pulmonary hypertension. *J Am Coll Cardiol* 1986;8:1298-306.

17. Tutar E, Kaya A, Gulec S, et al. Echocardiographic evaluation of left ventricular diastolic function in chronic cor pulmonale. *Am J Cardiol* 1999;83:1414-7.
18. Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). *Arthritis Rheum* 1980;23:581-90.
19. Le Roy EC, Black C, Fleishmajer R, et al. Scleroderma (systemic sclerosis). Classification, subset and pathogenesis. *J Rheumatol* 1988;15:202-5.
20. Sahn DJ, DeMaria A, Kisslo J, Weyman A, the Committee on M-mode Standardization of the American Society of Echocardiography. Recommendations regarding quantitation in M-mode echocardiographic measurements. *Circulation* 1978;58:1072-82.
21. Levy D, Savage DD, Garrison RJ, Anderson KM, Kannel WB, Castelli WP. Echocardiographic criteria for left ventricular hypertrophy: the Framingham Heart Study. *Am J Cardiol* 1987;59:956-60.
22. Yock PG, Popp RL. Non-invasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. *Circulation* 1984;70:657-62.
23. Spirito P, Maron BJ. Influence of aging on Doppler echocardiographic indices of left ventricular diastolic function. *Br Heart J* 1988;59:672-9.
24. Airaksinen KE, Ikaheimo MJ, Huikuri HV, et al. Effects of isometric exercise and heart rate on left ventricular filling pattern assessed by pulsed Doppler echocardiography. *J Intern Med* 1989;226:245-9.
25. Nishimura RA, Abel MD, Hatle LK, Tajik AJ. Assessment of diastolic function of the heart: background and current applications of Doppler echocardiography. Part II. Clinical studies. *Mayo Clin Proc* 1989;64:181-204.
26. Schneeweiss A, Marmor AT. Comparative evaluation of the effect of afterload- and preload-reducing drugs on diastolic cardiac function in hypertensive patients. *Cardiology* 1991;78:39-44.
27. Stoddard MF, Pearson AC, Kern MJ, Ratcliff J, Mrosek DG, Labovitz AJ. Influence of alteration in preload on the pattern of left ventricular diastolic filling as assessed by Doppler echocardiography in humans. *Circulation* 1989;79:1226-36.
28. Weiss S, Stead EA, Warren JV, Bailey OT. Scleroderma heart disease with consideration of certain other visceral manifestations of scleroderma. *Arch Intern Med* 1943;71:749-76.
29. Pace L, Capelli L, Bove E, et al. Left ventricular diastolic function: assessment by radionuclide angiography. *J Nucl Med* 1992;32:68-72.
30. Steen VD, Owens GR, Barnes EL, Fino GJ, Rodnan GP, Medsger TA Jr. Pulmonary involvement in systemic sclerosis (scleroderma). *Arthritis Rheum* 1985;28:759-67.
31. Stupi AM, Steen VD, Owens GR, Barnes EL, Rodnan GP, Medsger TA Jr. Pulmonary hypertension in the CREST syndrome variant of systemic sclerosis. *Arthritis Rheum* 1986;29:515-24.
32. Ungerer RG, Tashkin DP, Furst D, et al. Prevalence and clinical correlates of pulmonary arterial hypertension in progressive systemic sclerosis. *Am J Med* 1983;75:65-74.