

EXTENDED REPORTS

Right ventricular diastolic abnormalities in systemic sclerosis. Relation to left ventricular involvement and pulmonary hypertension

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Abstract

Objectives—To investigate right ventricular diastolic function in systemic sclerosis (SSc) and its relation to clinical features of the disease.

Methods—Seventy seven unselected SSc patients and 33 healthy subjects were submitted to echocardiography and echo Doppler study to assess left and right systolic as well diastolic function and to estimate maximal arterial systolic pulmonary pressure (PAP). In addition, the patients were investigated to define the SSc subset and the extent of skin and internal organ involvement.

Results—An abnormal right ventricular filling, as expressed by an inverted tricuspidal (Tr) E/A ratio (Tr E/A ratio <1), was detected in 31 of the 77 SSc patients (40%) and in 0 of the 36 controls ($p < 0.001$). All the 31 patients with an inverted Tr E/A ratio were found to have a PAP > 30 mm Hg. Twenty resulted to have an inverted mitral (Mit) E/A ratio (Mit E/A ratio <1), indicating an abnormal left ventricular filling. In multiple regression analysis, Tr E/A ratio resulted to be independently correlated to both PAP ($r = -0.35; p < 0.003$) and Mit E/A ratio ($r = 0.39; p < 0.001$).

Conclusions—This study points out an impaired right ventricular filling in a significant percentage of SSc patients whatever the subset. This alteration is independently correlated to both PAP and left ventricular filling abnormalities.

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Systemic sclerosis (SSc) is a multisystem disorder of connective tissue characterised by widespread vascular lesions and fibrosis of the skin and distinct internal organs.^{1,2}

Some authors^{3,4} and we ourselves⁵ have pointed out an impaired left ventricular filling in a significant percentage of SSc patients in whom no other cause of altered diastolic function had been detected. Diastolic abnormalities in SSc are likely to depend on either myocardial fibrosis or myocardial ischaemia, or both.^{3–6} As myocardial fibrosis as well as small intramy-

cardial coronary vessel involvement are known to affect both left and right ventricles in SSc,^{7,8} an altered right ventricular filling is likely to occur in this disease. Nevertheless, such aspect has received little attention so far. In this study, we have investigated right ventricular diastolic function in SSc and its relation to clinical features of the disease.

Methods

PATIENTS

Seventy seven unselected SSc patients (74 women and three men, aged from 24 to 79 years, median 56, mean (SD) 53.4 (11.6)) admitted to the Institute of Clinical Medicine and Rheumatology of the 2nd University of Naples were studied. All of them were investigated by history, clinical examination and instrumental investigations to define the disease duration, the subset according to Giordano *et al*⁹ and the severity of various disease manifestations (that is, general conditions, peripheral vascular involvement, skin sclerosis, joint/tendons, muscle, gut, lung, heart and kidney involvement), which were scored from 0 (absent) to 4 (end stage) according to the scleroderma severity index developed by Medsger *et al*.¹⁰

CONTROLS

Thirty six subjects (33 women, three men), (aged from 28 to 75 years, median age 50, mean (SD) 49.6 (10.3)) without any past or present evidence of heart and/or lung disease acted as controls.

ECHOCARDIOGRAPHY AND ECHO DOPPLER STUDY

All examinations were obtained with a phased array system (HP), with a 2.5 or 3.5 MHz transducer. Complete 2D echocardiography as well as pulsed and continuous Doppler examination were performed in a standard manner.^{11,12}

The left ventricular ejection fraction (LVEF) was used as an index of left ventricular systolic pump function and was calculated by a modification of the method of Quinones *et al*.¹³ The percentage of shortening in right ventricle (RV) area during the systole (per cent fractional area shortening) (FAS%) was used as an index of RV systolic function and was calculated, in

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both subcostal and apical views, by means of the formula: end diastolic area–end systolic area/end diastolic area \times 100.¹⁴

RV inflow velocities were assessed by the parasternal short axis view at the level of the tricuspid valve with the sampling window placed at the tricuspid annulus. We chose this validated¹⁵ approach because most of our SSc patients are thin women in whom keeping the transducer in good contact with the skin at the apical window is hampered by the narrow intercostal spaces. According to Nishimura *et al*,¹² the following diastolic parameters were measured: tricuspidal (Tr) peak early inflow velocity (Tr peak E), peak late velocity (Tr Peak A), their ratio (Tr E/A) and deceleration time (Tr DT). As the RV diastolic filling is affected by respiration, measurement of beats was timed with respiration. In particular, at least three beats from the end inspiration and three beats from the end expiration were recorded, and their values were averaged.

LV inflow velocities were measured from the apical four chamber views, with the sample volume placed at the level of the leaflets tips of the mitral valve.¹² The following LV filling parameters were measured: mitral (Mit) peak E, Mit peak A velocities, Mit E/A ratio and Mit DT. Moreover, isovolumic relaxation time of the left ventricle (LV-IVRT) was also assessed as the time interval elapsing from the aortic valve closure to the mitral valve opening. Each value was obtained as the mean of the measures detected during at least three cardiac cycles.

Systolic pulmonary arterial pressure (PAP) was estimated when a tricuspidal regurgitation was detected by continuous wave Doppler echocardiogram. It was calculated by measuring the peak systolic pressure gradient across the tricuspid valve (peak regurgitant velocity) and adding the estimated right atrial pressure (10 mm Hg). In absence of a tricuspidal regurgitation, PAP was considered normal.

STATISTICAL ANALYSIS

Unpaired Student's *t* test, χ^2 with Yates's correction, Fisher's exact test, Spearman's correlation and multiple regression analysis were used when appropriate. All data were expressed as mean (SD); a *p* value <0.05 was considered statistically significant.

Results

Of the 77 patients, 23 were affected with limited cutaneous SSc (lc SSc), 38 with intermediate cutaneous SSc (ic SSc), 16 with diffuse cutaneous SSc (dc SSc). The disease duration ranged from 1 to 48 years, median 18, mean (SD) 17.3 (9.0).

The above mentioned Scleroderma Severity Index considers nine items: any alteration of each of them (score 1–4) was detected in the following percentages: peripheral vascular system (77 of 77, 100%); skin sclerosis (77 of 77; 100%); joint/tendons (18 of 77; 23%); muscles (6 of 77; 7%); gastrointestinal tract (65 of 77; 84%); lung (51 of 77; 66%); heart (17 of 77; 22%); kidney (2 of 77; 2%); general conditions (12 of 77; 15%). It is worth noting, that heart involvement scoring in this index is only evalu-

Table 1 Echographic and echo Doppler indices (mean (SD)) of right and left systolic and diastolic function in 77 SSc patients and 36 controls

	Patients (n=77)	Controls (n=36)	<i>p</i> Value
FAS (%)	40.3 (3.8)	41.2 (2.5)	NS
Tr peakE (cm/s)	41.4 (14.1)	45.1 (8.5)	NS
Tr peakA (cm/s)	37.9 (15.2)	36.5 (9.7)	NS
Tr E/A	1.2 (0.4)	1.2 (0.2)	NS
Tr DT (ms)	190.5 (37.0)	185.3 (14.1)	NS
LVEF (%)	59.9 (4.0)	60.0 (3.6)	NS
Mit peakE (cm/s)	65.7 (17.0)	70.0 (8.5)	NS
Mit peakA (cm/s)	57.7 (17.4)	46.6 (8.8)	<0.05
Mit E/A	1.2 (0.5)	1.5 (0.1)	<0.05
Mit DT (ms)	172.4 (28.7)	159.4 (10.0)	<0.05
LV-IVRT (ms)	78.5 (1.3)	59.3 (0.9)	<0.001

FAS = per cent fractional area shortening of the right ventricle; Tr peak E = tricuspidal peak early inflow velocity; Tr peak A = tricuspidal late velocity; Tr E/A = tricuspidal E/A ratio; Tr DT = tricuspidal deceleration time; LVEF = left ventricular ejection fraction; Mit peak E = mitral peak early inflow velocity; Mit peak A = mitral flow late velocity; Mit E/A = mitral E/A ratio; Mit DT = mitral deceleration time; LV-IVRT = left ventricle isovolumic relaxation time.

ated on the basis of clinically evident cardiac manifestations, including arrhythmias and congestive heart failure, ECG, conduction defects, and LVEF.

No significant difference was detected between SSc patients and controls in any anatomical parameter of the right and the left ventricle as measured at the peak of ECG R wave (data not shown)—that is, left ventricular posterior wall thickness, left ventricular internal diameter in diastole, interventricular septal thickness, right ventricular free wall thickness and right ventricular internal diameter in diastole. Therefore, no chamber was found to present a significantly increased wall thickness. It is worth noting that eight SSc patients only had presented with mild systemic arterial hypertension, which was controlled by calcium channel blockers and/or ACE inhibitors.

Table 1 shows right and left echocardiographic and echo Doppler indices of systolic and diastolic function in SSc patients and controls. No significant difference was detected between patients and controls in any index of systolic function. However, two patients were found to have a LVEF <50% and three patients were found to have a FAS <30%—that is, below the lower normal values.

No difference was detected in Tr E/A ratio between patients and controls, neither was any difference detected in Tr peak E, Tr peak A and Tr DT. Nevertheless, an inverted Tr E/A ratio (to be considered as an index of abnormal right ventricular relaxation) was found in 31 of the 77 SSc patients (40%) and in none of the 36 controls (*p* <0.001). Mit E/A ratio was significantly lower in SSc patients than in controls (*p* <0.05). Actually, an inverted left ventricular E/A ratio was detected in 25 of 77 SSc patients (32%) and in four of the 36 controls (11%) (*p* <0.03). The inversion of Mit E/A ratio seemed to mainly depend on a significant increase of Mit peak A associated with a slight but not statistically significant decrease of Mit peak E. Consistent with an abnormal left ventricular filling, SSc patients were found to present statistically significant longer Mit DT and IVRT.

Table 2 Echo Doppler parameters of left and right ventricular filling (mean (SD)) in controls and in SSc patients with (group I) and without (group II) an inverted tricuspidal E/A ratio

	Group I (n=31)	Group II (n=46)	Controls (n=36)
Tr peakE (cm/s)	37.0 (12.4)§*	43.9 (14.6)	45.1 (8.5)
Tr peakA (cm/s)	48.1 (17.0)†***	31.1 (8.7)	36.5 (9.7)
Tr E/A	0.8 (0.1)†***	1.4 (0.3)	1.2 (0.2)
Tr DT (ms)	188.2 (34.0)	188.8 (36.5)	185.3 (14.1)
Mit peakE (cm/s)	59.9 (17.2)*§	69.7 (15.9)	70.0 (8.5)
Mit peakA (cm/s)	63.6 (18.2)**	52.3 (14.1)§	46.6 (8.8)
Mit E/A	1.0 (0.3)†***	1.4 (0.5)	1.5 (0.1)
Mit DT (ms)	173.5 (30.5)§	170.5 (27.1)§	159.4 (10.0)
IVRT (ms)	82.5 (13.5)*§	76.5 (10.1)§	59.3 (5.9)
PAP (mm Hg)	43.8 (9.8)†*** (n=31)‡	32.9 (5.3) (n=39)‡	26.0 (5.3) (n=24)‡

‡Number of patients in whom pulmonary artery pressure could be estimated. *p<0.05 versus group II, †p<0.001 versus group II, **p<0.01 versus group II patients, ***p<0.001 versus controls, §p<0.05 versus controls, || p<0.01 versus controls. IVRT = isovolumic relaxation time; PAP = systolic pulmonary arterial pressure. Other abbreviations as Table 1.

Table 2 shows echo Doppler parameters of right and left ventricular filling and estimated PAP values in the 31 patients with an inverted Tr E/A ratio (group I) (women 29; men 2 aged 24 to 79, mean (SD) 58.3 (10.8) with a disease duration ranging from 1 to 48 years, median 18, mean (SD) 16.5 (10.1) in comparison with those detected in the 46 patients with a normal Tr E/A ratio (group II) (women 45; men 1 aged 26 to 74, mean (SD) 50.2 (0.9) with a disease duration ranging from 4 to 33 years, median 17, mean (SD) 18 (8.6)). In group I, as expected, a significantly lower Tr E/A ratio was observed with respect to both group II patients and controls (0.8 (0.1) versus 1.4 (0.3) and 1.2 (0.2) respectively; p<0.001). This result was accounted for by both a significantly higher Tr peak A velocity (48.1 (17.0) cm/s in group I versus 31.1 (8.7) cm/s in group II and 36.5 (9.7) cm/s in controls; p<0.05) and a significantly lower Tr peak E (37.0 (12.4) cm/s in group I versus 43.9 (14.6) cm/s in group II and 45.1 (8.5) cm/s in controls; p<0.05). In addition, group I patients were found to present a lower Mit peak E, a greater Mit peak A, a lower Mit E/A ratio and a longer IVRT with respect to both group II patients and controls. Group II patients differed from controls only in a greater Mit peak A and a longer IVRT (p<0.05). In detail, a left ventricular diastolic dysfunction, as expressed by a Mit E/A ratio <1, was found in 20 of 31 (64%) group I patients compared with 5 of 46 (11%) group II patients, (p<0.001) and four of the 36 controls (11%).

PAP could be valued (that is, a tricuspidal incontinence had been detected) in 70 of 77 patients and in 24 of 36 controls. In the seven patients in whom no tricuspidal incontinence was detected, PAP was considered normal.

Pulmonary hypertension (that is, an estimated maximal PAP >30 mm Hg) was detected in 31 of 31 (100%) of group I patients and in 18 of 46 (39%) group II patients (p<0.0001) and in 0 of 36 controls (p<0.0001). The prevalence of pulmonary hypertension was also statistically greater in group II patients than in controls (p<0.0001). Moreover, a PAP ≥40 mm Hg was found in 17 of 31 group I and five of 46 group II patients (p<0.0001) and a PAP ≥50 mmHg was

detected in 14 of 31 group I and one of 46 group II patients (p<0.0001).

Tr E/A ratio (dependent variable) was found to be inversely correlated to PAP (n=70; r=-0.41; p<0.0001) and positively correlated to Mit E/A ratio (n=77; r=0.44; p<0.0001). These correlations were then investigated in multiple regression analysis in the 70 SSc patients in whom PAP could have been valued. TrE/A ratio resulted to be independently correlated to both Mit E/A ratio (r=0.39; p<0.001) and PAP (r=-0.35; p<0.003). No correlation was found between Mit E/A ratio and PAP.

Of the 31 patients with an inverted Tr E/A ratio, all presented a PAP >30 mm Hg and 17 also impaired left ventricular filling (that is, a Mit E/A ratio <1).

No correlation was found between altered right ventricular filling and any epidemiological (sex, age, disease duration), or clinical parameters of the disease—that is, either the presence or the severity score of the nine organ system considered. In particular, the Tr E/A ratio did not correlate with either forced vital capacity or diffusing lung capacity for CO (r=0.151, p=0.278; r=0.058, p=0.736, respectively). Moreover, no difference was detected in the prevalence of an abnormal right ventricular filling in patients belonging to different SSc subsets. As a matter of fact, a Tr E/A ratio <1 was detected in eight of 16 patients with dc SSc (50%); in 13 of the 38 patients with ic SSc (33%) and in 10 of the 23 patients with lc SSc (43%). Moreover, no difference was detected in the mean Tr E/A ratio among the three subsets: 1.1 (0.4) in dc SSc; 1.2 (0.4) in ic SSc; 1.1 (0.4) in lc SSc respectively (p>0.05).

Our series is characterised by a very low number of men (n=3). As the exclusion of the three male patients did not affect the results, we chose to include them in the analysis.

Discussion

We have investigated right ventricular diastolic function in SSc and its relation to clinical and epidemiological features of the disease. We discovered an abnormal right ventricular filling in 40% of SSc patients. Such alteration was detected in many patients without clinically evident cardiac disease and resulted to be correlated with both left ventricular diastolic abnormalities and pulmonary hypertension.

Scleroderma heart disease is historically subclassified into primary and secondary.⁷ Primary SSc cardiac disease depends on the involvement of myocardium and/or pericardium and/or small intramyocardial vessels by SSc heart disease itself; secondary cardiac involvement develops either in patients with systemic arterial hypertension mainly induced by renal scleroderma (left ventricular disease) or in those with vascular and/or interstitial lung disease (right ventricular disease).

The pathological hallmark of SSc heart disease is myocardial fibrosis.^{7,8,16} Myocardial fibrosis and myocardial ischaemia have long been known to affect ventricular filling.^{17,18} SSc myocardial fibrosis is different from that occurring in patients with coronary atherosclerosis.

Actually, SSc myocardial fibrosis is equally distributed throughout the right and left ventricles, does not involve the immediate subendocardial layers, is not related to the distribution of the epicardial coronary vessels and is not associated with haemosiderin deposits.^{7 19-21} The detection of left ventricular filling abnormalities in SSc patients^{5 6} led us to study right ventricular filling in this disease. Such an aspect has received little attention so far. In point of fact, no contribution has been made in that regard except for that by Candell-Riera *et al*,²² who detected a significantly low Tr E/A ratio in 63 patients with lc SSc.

In our study, we have found right diastolic abnormalities in 31 of 77 patients (40%), with no difference in either the prevalence of an inverted Tr E/A ratio or in the Tr E/A ratio values among patients belonging to different subsets.

In our SSc patients with an abnormal right ventricular filling, we detected a significant increase in Tr peak A, suggestive of abnormal relaxation.²³ This pattern is classically caused by ventricular hypertrophy (that is, secondary to hypertension or aortic stenosis, etc) in which prominent atrial contraction is important for ventricular filling. A similar pattern, however, has also been observed in patients with cardiac amyloidosis with no or little evidence of increased right ventricular free wall thickness. It was ascribed to early amyloid infiltration possibly interfering with the relaxation process.²⁴ In our SSc patients, we failed to find ventricular hypertrophy. In them, myocardial fibrosis might play a part in promoting right as well left ventricular filling abnormalities with a mechanism similar to amyloid infiltration. In fact, SSc myocardial fibrosis is known to be patchy, to be distributed throughout the myocardium in both left and right ventricle, and is associated with a normal wall thickness—that is, the normal muscle is destroyed and replaced by fibrosis without any increased collagen deposition.⁸ However, at present, it must be considered speculative to attribute diastolic abnormalities to myocardial fibrosis.

Our study has some limitations. The gold standard techniques devoted to assess diastolic function and pulmonary artery pressure are those based on invasive techniques.^{25 26} Nevertheless, a number of studies have pointed out that both right ventricular diastolic function and PAP levels can be accurately investigated by echo Doppler study.²⁷⁻³⁰ In addition, right atrial and ventricular function could have been better studied by measuring vena cava superior flow and hepatic vein flow.^{31 32} However, hepatic venous flow dynamics is known to be mainly related to mean right atrial pressure.³³⁻³⁶ As our SSc patients showed normal right atrium and inferior vena cava diameters, we did not investigate this topic. Likewise, we did not study vena cava superior flow.

A further limitation could arise from the low number of male patients in our series (3 of 77 (3.9%)). We must emphasise, however, that our series has long been characterised by such an epidemiological aspect. In fact, of 106 SSc patients recruited from 1965 to 1981,³⁷ only five (4.7%) were men. The same was true a few

years later, when of 164 patients recruited from 1965 to 1984, only 10 were men (6%).³⁸ We do not know why SSc in our unit is essentially a female disease. Nevertheless, the patient series reflect the general epidemiological features of our whole SSc series. Moreover, excluding three male patients from the analysis did not change the results.

In conclusion, we have found an impaired right ventricular filling in patients with SSc. Such alteration is detectable in patients without any clear cut evidence of cardiac disease. Nevertheless, its prognostic significance awaits to be defined.

- Black CM, Stephens SC. Systemic sclerosis (Scleroderma) and related disorders. In: Maddison PJ, Isenberg DA, Woo P. *Oxford textbook of rheumatology*. Oxford: Medical Publications, 1993:771-89.
- Le Roy EC. Systemic sclerosis (Scleroderma). In: Bennett JC, Plumm F, Glass DN, eds. *Cecil textbook of medicine*. Philadelphia: WB Saunders, 1996:1483-8.
- Kazzam E, Waldenstrom A, Landelius J, Hallgren R, Arvidsson A, Caidhal K. Non-invasive assessment of left ventricular diastolic function in patients with systemic sclerosis. *J Intern Med* 1990;228:183-92.
- Pace L, Capelli L, Bove E, Coppola N, Ciarmiello A, Sorrentino S, *et al*. Left ventricular diastolic function in systemic sclerosis: assessment by radionuclide angiography. *J Nucl Med* 1992;33:68-72.
- Maione S, Valentini G, Giunta A, Migliaresi S, Itri F, Picillo U, *et al*. Evaluation of cardiac structures and function in systemic sclerosis by Doppler echocardiography. *Cardiology* 1991;79:165-71.
- Valentini G, Vitale DF, Giunta A, Maione S, Gerundo G, Arnese MR, *et al*. Diastolic abnormalities in systemic sclerosis: evidence for associated defective cardiac functional reserve. *Ann Rheum Dis* 1996;55:455-60.
- Owens GR, Follansbee WP. Cardiopulmonary manifestations of systemic sclerosis. *Chest* 1987;91:118-27.
- Follansbee WP, Miller TR, Curtiss EI, Orié JE, Bernstein RL, Kiernan JM, *et al*. A controlled clinico-pathologic study of myocardial fibrosis in systemic sclerosis (scleroderma). *J Rheumatol* 1990;17:656-62.
- Giordano M, Valentini G, Migliaresi S, Picillo U, Vatti M. Different antibody patterns and different prognoses in patients with scleroderma with various extent of skin sclerosis. *J Rheumatol* 1986;13:911-16.
- Medsker TA, Silman AS, Steen VD, and International Scleroderma Study Group. Development of severity index for Systemic Sclerosis. *Arthritis Rheum* 1994;37(suppl 9): 260S.
- Tajik AJ, Seward JB, Hagler DJ, Mair DD, Lie JT. Two-dimensional real-time ultrasonic imaging of the heart and great vessels. Technique, image orientation, structure identification and validation. *Mayo Clin Proc* 1978;53: 271-303.
- 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.
- Quinones MA, Waggoner AD, Reduto LA, Nelson JG, Young JB, Winters WL Jr, *et al*. A new simplified and accurate method for determining ejection fraction with two-dimensional echocardiography. *Circulation* 1981;64: 744-53.
- Kaul S, Tei C, Hopkins JM, Shah PM. Assessment of right ventricular function using two-dimensional echocardiography. *Am Heart J* 1984;107:526-31.
- Yu CM, Sanderson JE, Chan S, Yeung L, Hung YT, Woo KS. Right ventricular diastolic dysfunction in heart failure. *Circulation* 1996;8:1509-14.
- D'Angelo WA, Fries JF, Masi AT, Shulman LE. Pathologic observations in systemic sclerosis (scleroderma). A study of fifty-eight autopsy cases and fifty-eight matched controls. *Am J Med* 1969;46:428-40.
- Labovitz AJ, Pearson AC. Evaluation of left ventricular diastolic function: clinical relevance and recent Doppler echocardiographic insights. *Am Heart J* 1987;114:836-51.
- Brutsaert DL, Sys SU, Gillebert TC. Diastolic failure: pathophysiology and therapeutic implications. *J Am Coll Cardiol* 1993;22:318-25.
- Weiss S, Stead E, Warren J, Bailey O. Scleroderma heart disease, with a consideration of certain other visceral manifestations of scleroderma. *Arch Intern Med* 1943;71:749-76.
- Sackner M, Heinz R, Steinberg A. The heart in scleroderma. *Am J Cardiol* 1966;17:542-59.
- Bulkley BH, Ridolfi R, Salyer W, Hutchins G. Myocardial lesions of progressive systemic sclerosis: a cause of cardiac dysfunction. *Circulation* 1976;53:483-90.
- Candell-Riera J, Armandans-Gil L, Simeon CP, Castell-Conesa J, Fonollosa-Pla V, Garcia-Del-Castillo H, *et al*. Comprehensive noninvasive assessment of cardiac involvement in limited systemic sclerosis. *Arthritis Rheum* 1996;39:1138-45.

- 23 Brutsaert DL, Rademakers FE, Sys SU, Gillebert TC, Housmans PR. Analysis of relaxation in the evaluation of ventricular function of the heart. *Prog Cardiovasc Dis* 1985;28:143-63.
- 24 Klein AL, Hatle LK, Burstow DJ, Taliencio CP, Seward JB, Kyle, et al. Comprehensive Doppler assessment of right ventricular diastolic function in cardiac amyloidosis. *J Am Coll Cardiol*. 1990;15:99-108.
- 25 Modersohn D, Walde T, Bruch L. Diastolic heart function: pathophysiology, characterization and therapeutic approaches. *Clin Cardiol* 1993;16:850-8.
- 26 McLaughlin VV, Genthner DE, Panella MM, Rich S. Reduction in pulmonary vascular resistance with long-term epoprostenol (prostacyclin) therapy in primary pulmonary hypertension. *N Engl J Med* 1998;338:273-7.
- 27 Pye MP, Pringle SD, Cobbe SM. Reference values and reproducibility of Doppler echocardiography in the assessment of the tricuspid valve and right ventricular diastolic function in normal subjects. *Am J Cardiol* 1991;67:269-73.
- 28 Appleton CP, Hatle LK, Popp RL. Cardiac tamponade and pericardial effusion: respiratory variation in transvalvular flow velocities studied by Doppler echocardiography. *J Am Coll Cardiol* 1988;11:1020-30.
- 29 Chan KL, Currie PJ, Seward JB, Hagler DJ, Mair DD, Tajik AJ. Comparison of three Doppler ultrasound methods in the prediction of pulmonary artery pressure. *J Am Coll Cardiol* 1987;9:549-54.
- 30 Graettinger WF, Greene ER, Voyles WF. Doppler predictions of pulmonary artery pressure, flow and resistance in adults. *Am Heart J* 1987;113:1426-37.
- 31 Appleton CP, Hatle LK, Popp RL. Superior vena cava and hepatic vein Doppler echocardiography in healthy adults. *J Am Coll Cardiol* 1987;10:1032-9.
- 32 Hatle LK, Appleton CP, Popp RL. Differentiation of constrictive pericarditis and restrictive cardiomyopathy by Doppler echocardiography. *Circulation* 1989;79:357-70.
- 33 Nagueh SF, Kopelen HA, Zoghbi WA. Relation of mean right atrial pressure to echocardiographic and Doppler parameters of right atrial and right ventricular function. *Circulation* 1996;93:1160-9.
- 34 Kircher BJ, Himelman RB, Schiller NB. Non-invasive estimation of right atrial pressure from the inspiratory collapse of the inferior vena cava. *Am J Cardiol* 1990;66:493-6.
- 35 Jue J, Chung W, Schiller NB. Does inferior vena cava size predict right atrial pressure in mechanically ventilated patients? *J Am Soc Echocardiogr* 1992;5:613-19.
- 36 Luca L, Mario P, Giansiro B, Maurizio F, Antonio M, Carlo M. Non invasive estimation of mean right atrial pressure utilizing the 2D-Echo transverse diameter of the left hepatic vein. *Int J Card Imaging* 1992;8:191-5.
- 37 Giordano M, Valentini G, Ara M, Tirri G, Capelli L, Vatti M. Epidemiology of progressive systemic sclerosis in Italy. In: Black CM, Myers AR, eds. *Current topics in rheumatology. Systemic sclerosis (scleroderma)*. London: Gower Medical, 1985:15:72-7.
- 38 Giordano M, Valentini G, Vatti M, Tirri G, Gualdieri L, Lupoli S. Epidemiology of systemic sclerosis in Italy (study of 164 cases). *Conn Tissue Dis* 1984;3:3-16.