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Mitral regurgitation and diastolic flow profile in systemic sclerosis

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To evaluate the left ventricular filling characteristics in systemic sclerosis, we examined 30 consecutive patients, 15 men and 15 women, and related the findings to those from 48 age- and sex-matched controls. All patients were investigated by pulsed and continuous wave mitral Doppler, and M mode echocardiography. We found the A wave of the mitral flow velocity as recorded by pulsed wave Doppler to be higher in patients (0.74 ± 0.07 vs 0.54 ± 0.02 m/sec, $P < 0.002$), while the E wave did not differ. The high A/E ratio indicating reduced distensibility, correlated to interventricular septal thickness ($r = 0.53$, $P < 0.001$), and atrial emptying index ($r = -0.55$, $P < 0.001$). Early filling was impaired, with a prolonged pressure half time (99 ± 6 vs 84 ± 4 msec, $P < 0.05$), and a reduced first third filling fraction (0.41 ± 0.02 vs 0.48 ± 0.01, $P < 0.001$). Mitral regurgitation was found in 67% of systemic sclerosis patients and in 15% of controls ($P < 0.001$). Doppler measures of left ventricular filling properties were not related to the presence of mitral regurgitation or systolic blood pressure.

We conclude that left ventricular distensibility and early filling properties are impaired in systemic sclerosis and not related to blood pressure, but rather to left ventricular wall thickness and therefore probably secondary to myocardial fibrosis. Mitral regurgitation is a common finding in systemic sclerosis.

Key words: Diastolic function; Doppler; Echocardiography; Left ventricle; Mitral regurgitation; Systemic sclerosis

Introduction

Diastolic dysfunction precedes systolic abnormalities in many clinical settings, and it has become evident that diastolic abnormalities may occur as a cause of congestive heart failure [1,2]. Assessment of diastolic properties is of particular importance with regards to therapy, since treat-

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ment directed at systolic performance may be of no benefit, or even detrimental, when diastolic dysfunction is isolated or dominating.

The characteristic manifestation of cardiac involvement in systemic sclerosis is myocardial fibrosis, and we were recently able to demonstrate that cold inducible vasospasm causes reversible myocardial perfusion defects in this disease [3]. Moreover, autopsy studies [4,5], and in the present study population echocardiography [6], have shown left ventricular hypertrophy to be a prevalent finding. Therefore, myocardial fibrosis, ischemia, and hypertrophy create an anticipation of diastolic dysfunction in systemic sclerosis. However, it appears that only preliminary, and somewhat contradictory, information on diastolic function in systemic sclerosis has been published [7–10]. In 2 of these studies the mitral valve closing velocity was used as the measure of the diastolic function [7,8]. One study showed abnormal response to exercise only [9], while in another investigation decreased coronary reserve but normal diastolic function was found in a group of seven patients [10].

During the last few years Doppler evaluation of mitral flow has appeared as a useful noninvasive technique for the evaluation of diastolic left ventricular function [11–14]. Since Doppler findings in systemic sclerosis have not been reported previously, we evaluated the mitral diastolic flow pattern by pulsed wave Doppler in a consecutive series of systemic sclerosis patients, and determined the presence of mitral regurgitation by pulsed and continuous wave Doppler. Findings were compared to those in age- and sex-matched controls, randomly selected from the population.

Materials and Methods

Subjects

Thirty consecutive patients (15 men and 15 females; age range 25–77 years, mean 54.5 years), with systemic sclerosis according to the American Rheumatism Association (ARA) criteria [15] were studied. The patients were referred from the Uppsala region to the Uppsala University Hospital between December 1986 and March 1988. Their disease had been recognized for 5.6 (range 0.5–23) years. None had left bundle branch block, while 1 patient had right bundle branch block.

For comparative purposes, age- and sex-matched control subjects were selected from the general population of Uppsala. A sample of 90 age- and sex-matched subjects (3 for each patient) was drawn from the population register kept by the County Census Bureau. All controls were informed about the investigation protocol, and 55 of them gave their consent to participate in the study. Controls were excluded if they were treated for hypertension ($n = 2$), if they had coronary ($n = 2$) or rheumatic ($n = 2$) heart disease according to clinical history or electrocardiogram. None of the controls had known renal or pulmonary disease or bundle branch block. One subject was excluded because of inadequate recordings. The remaining 48 subjects (26 men and 22 females, age range 25–77 years, mean 54.6 years) constituted a healthy control group.

Methods

A Doppler system (Alfred®, Vingmed A/S) equipped with a 2.0 MHz pulsed and continuous wave Doppler transducer (diameter 13.7 mm) was used to record the mitral flow spectrum at 50 mm/sec from the apical approach, while the subjects were in the left lateral position. Transducer placement and beam direction was guided by immediately preceding apical cross sectional echocardiography, and by the audiovisual continuous wave Doppler signal from the mitral flow and valve motion. Presence of mitral regurgitation was determined by pulsed and continuous wave Doppler. Pulsed wave Doppler signal was also recorded on strip charts (Honeywell 8100, dry silver paper) at 50 mm/sec, when the best spectral display was obtained from the mitral flow, sampling volume placed at the tip of the mitral leaflets.

M mode echocardiograms were obtained (Honeywell 8100, dry silver paper recorder, 50 mm/sec), guided by the two-dimensional short-axis view (Hewlett Packard ultrasound imaging system model 77020A), with the subjects in the left lateral position.

A 12-lead electrocardiogram was recorded, and

blood pressure was measured in the supine position after 15–30 minutes of rest.

Measurements

All measuring points were agreed upon by 2 observers (E.K. and K.C.). One investigator (E.K.) carried out all interpretations after the recordings had been coded and mixed by K.C. Only beats with acceptable or good quality were used for measurements. All measurements were obtained by means of digitizers (Summagraphics) connected to a PDP 11/34 or for the evaluation of Doppler signals to a PC-AT (IBM), utilizing locally developed software [16]. Five beats were measured. The means were used for further calculations. Doppler recordings suitable for digitization were obtained in 98%.

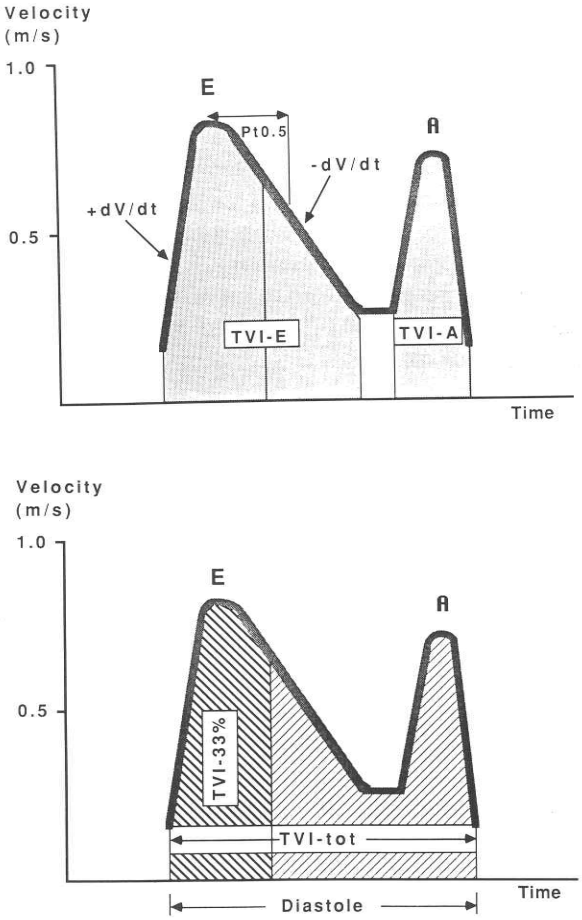

Fig. 1. The figure illustrates the measurements obtained from the mitral flow velocity profile. The upper panel shows the peak velocity of early filling (E) and the peak velocity of atrial contribution to left ventricular filling (A). Slopes ($+dV/dt$ and $-dV/dt$) and "pressure half time ($Pt0.5$) were calculated by the computer. The lower panel shows an approximation of "first-third filling fraction" by time velocity integral of first 33% of the left ventricular filling velocity curve (TVI-33%), and the total diastolic TVI (TVI-tot).

The following measurements were obtained from the Doppler spectral recording of the mitral flow profile (Fig. 1): (1) peak velocity of early (E) left ventricular filling; (2) peak velocity of atrial (A) contribution to left ventricular filling; (3) the ratios A/E, and E/A; (4) "pressure half time" or time from E to the time when velocity had decreased to $E/\sqrt{2}$; the positive and negative rate of change of early filling velocity; (5) the time velocity integrals of E, A, and the complete or total diastolic profile; (6) the time velocity integral of the first third (33%) of the diastolic profile; (7) the time velocity integral ratios A/total, E/total, and 33%/total.

Cardiac dimensions were measured from M-mode echocardiographic recordings according to the recommendations by the American Society of Echocardiography [17]. Left ventricular internal diameter and interventricular septal thickness were measured at the electrocardiographic Q-wave. Left ventricular dimension was measured also at end-systole (the shortest distance between the septum and the posterior wall). The cube formula was used to calculate ejection fraction.

Statistical analyses

Data are presented as mean ± standard error (SE) of the mean. Unpaired two-sided t-test was used to compare differences between patients and controls. P values < 0.05 were considered significant. Multiple regression analysis was used to elucidate whether diastolic abnormalities were secondary to heart rate or loading conditions.

Results

Mitral regurgitation was prevalent, 67.0%, among patients, vs 15.2% among controls ($P = 0.0001$). The spectral signals from a control sub-

ject and from a patient are shown in Fig. 2. Left ventricular early diastolic filling interpreted by pulsed Doppler showed no difference regarding the duration or rate of velocity increase ($+dV/dt$) (Table 1). The maximum rate of velocity decline ($-dV/dt$) of the E-wave only tended to be reduced, but "pressure half time" was prolonged. E and time velocity integral of E did not differ between groups, nor did time velocity integral ratio E/total. First third time velocity integral was not different between patients and controls, but the first-third filling fraction (33%/total time velocity integral) was markedly lower among patients.

In contrast to E, atrial contribution to left ventricular filling as measured by A was increased in patients compared to controls (0.74 ± 0.07 vs 0.54 ± 0.02 m/sec, $P < 0.002$). Not only the maximum velocity, but also time velocity integrals of A and A/total were increased.

The ratio A/E was increased in patients, and E/A was decreased. The situation was similar when using time velocity integrals of early filling and atrial contribution.

Ventricular septal thickness was selected as representative of left ventricular hypertrophy in the present study population [6]. Septal thickness was increased among patients (12.2 ± 0.5 cm, vs 9.9 ± 0.3. cm in controls, $P < 0.0001$). Blood pressure was not increased among patients, thus did not explain the increased septal thickness. A/E was not only the diastolic Doppler variable displaying the most significant difference between patients and controls, but it was also the variable most closely related to septal thickness ($r = 0.52$, $P < 0.01$). Not only A/E, but all measures of atrial contribution to left ventricular filling correlated significantly to septal thickness: time velocity integrals of A/E ($r = 0.45$, $P < 0.001$), A/total ($r = 0.32$, $P < 0.01$), and A ($r = 0.28$, $P < 0.05$), as well as the maximum velocity of A ($r = 0.32$, $P < 0.01$). Among measures expressing early filling properties, 33% time velocity integral/total ($r = 0.29$, $P < 0.05$) and E/total time velocity integral ($r = 0.27$, $P < 0.05$) were related to septal thickness, while pressure half time, maximum velocity of E, time velocity integral of E and 33% time velocity integral were not.

Within the control group, A/E was related to age ($r = 0.40$, $P < 0.01$), and to heart rate ($r = 0.30$, $P < 0.05$), while 33%/total time velocity integral was not. Multivariate analysis was performed to evaluate if the difference between patients and controls regarding A/E could be explained by different afterload (systolic blood pressure), heart rate, or preload (left ventricular end-

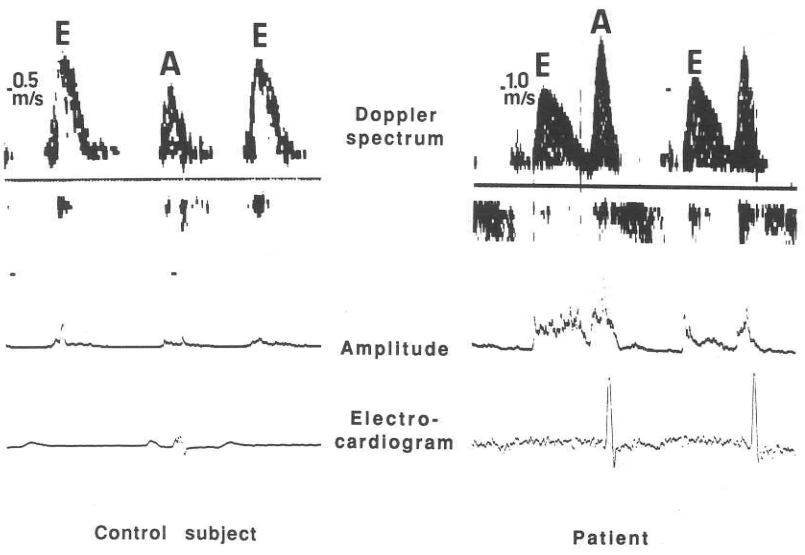

Fig. 2. The spectral Doppler signal of the left ventricular inflow is illustrated for a control subject and one of the patients.

TABLE 1

Pulsed wave mitral Doppler evaluation of left ventricular (LV) filling characteristics.

	Controls ($n = 43$)	Patients ($n = 30$)	P value
Early LV filling characteristics			
Mitral opening to E (msec)	69.4 ±3.2	72.7 ±3.3	NS
$+dV/dt$ of early filling (m/sec^2)	6.70±0.42	5.75±0.41	NS
$-dV/dt$ of early filling (m/sec^2)	2.86±0.25	2.68±0.22	NS
Pressure half time (msec)	83.6±3.6	99.2±5.5	< 0.02
E(m/sec)	0.69±0.03	0.72±0.07	NS
Time velocity integrals			
E(cm)	12.55±1.01	13.55±1.91	NS
E/total	0.64±0.01	0.61±0.01	NS
33% (cm)	9.53±0.8	8.99±1.2	NS
33%/total	0.48±0.01	0.41±0.02	< 0.001
Atrial contribution to LV filling			
A(m/sec)	0.54±0.02	0.74±0.07	< 0.002
Time velocity integrals			
A(cm)	4.77±0.26	6.81±0.83	< 0.01
A/total	0.27±0.02	0.32±0.02	< 0.05
Relation between early and late LV filling			
A/E	0.80±0.04	1.09±0.08	< 0.0005
E/A	1.35±0.06	1.09±0.01	< 0.05
Time velocity integrals			
A/E	0.41±0.02	0.54±0.04	< 0.005
E/A	2.86±0.24	2.15±0.16	< 0.05

A = peak velocity of atrial contribution to left ventricular (LV) filling; dV/dt = rate of change of mitral flow velocity; E = peak velocity of early LV filling; pressure half time = time to $E/\sqrt{2}$.

TABLE 2

Multiple regression analysis of possible confounding factors for A/E.

	β Coefficient	t value	P value
A/E	0.427	2.23	0.03
Systolic blood pressure	−0.003	0.89	NS
Heart rate	0.008	1.21	NS
End-diastolic dimension of left ventricle	−0.012	1.11	NS

A = peak velocity of atrial contribution to left ventricular filling; E = peak velocity of early left ventricular filling.

diastolic dimension) (Table 2). In this analysis, A/E was an independent predictor of reduced diastolic function. There was no correlation between A/E and ejection fraction ($r = -0.14$, NS). Doppler findings or other measures of diastolic function were not related to the duration of systemic sclerosis.

Discussion

In this study, we used Doppler echocardiography to evaluate left ventricular diastolic filling characteristics in patients with systemic sclerosis in comparison with age- and sex-matched controls selected from the general population. Age, which influences diastolic function, was identical in the 2 study groups. Furthermore, all controls and patients were evaluated by one and the same investigator. Great care was taken to ensure an objective evaluation of data, and bias was avoided by blinding identity of recordings to the interpreter. Therefore, our results, showing left ventricular inflow abnormalities to be a definite feature of systemic sclerosis, should be possible to generalize. Thus, we could not confirm the negative findings by Kahan et al. [10] who found no difference between controls and patients regarding left ventricular compliance when measured by invasive technique. Possible explanations of the differences in results could be differently chosen control material, different techniques, or that our patients had a more severe stage of the disease. Our findings indicating increased left ventricular passive stiffness and reduced early filling are consistent with the earlier studies by Smith et al. [8] and Gottdiener et al. [7] demonstrating echocardiographic evidence of decreased ventricular compliance.

Doppler echocardiography represents a relatively simple, reproducible method for noninvasive evaluation of left ventricular diastolic function, which correlates well with cineangiography [18], and radionuclide techniques [19]. Interpretable Doppler recordings can be obtained at a higher rate than left ventricular M-mode tracings suitable for endocardial digitization. However, the Doppler technique has certain limitations [12–14]. Dependence of mitral flow velocity upon movement of the sample volume location due to respiration

and the inherent cardiac motion [20] was considered in the present study by averaging several beats, and by taking great care to record the mitral spectral flow at the tip of the mitral leaflets. The normal waveform of the mitral Doppler spectrum shows a rapid increase in flow velocity in early diastole (E) concomitant with the rapid left ventricular filling. A period of diastasis follows, during which the flow velocity returns towards the zero baseline. Finally, the atrial contraction causes a second, normally less pronounced, increase in flow velocity (A). Our patients showed a different pattern, compatible with diastolic filling abnormalities. Early filling was reduced, with a low 33%/total time velocity integral, and a delayed downslope of E (prolonged "pressure half time"). Moreover, the atrial contribution to left ventricular filling was increased, with increased A and time velocity integral of A, as well as high A/E and A/total time velocity integral ratios. This shift in left ventricular filling towards late diastole indicates a decreased left ventricular distensibility. Thus, the Doppler pattern which we found in systemic sclerosis patients is in agreement with previous reports on Doppler findings of left ventricular filling abnormalities in various other diseases [11,12,19].

The prevalence of mitral regurgitation was similar among our controls (15%) as previously reported (19%) [21]. Our finding that mitral regurgitation was present in almost 2/3 of consecutive systemic sclerosis patients was unexpected, since mitral valve involvement has been reported to be infrequent in systemic sclerosis, and it has not been considered to be a component of the myocardial affection in this disease [22]. However, previous clinical studies reporting systolic murmurs in patients with systemic sclerosis have assumed the presence of mitral regurgitation, and in postmortem studies mild thickening and nodularity of mitral commissures have been described [4,5]. The high prevalence of mitral regurgitation in the present study compared to clinical reports is probably due to the high sensitivity of the Doppler method. The presence of mitral regurgitation may have tended to normalize the filling pattern in some patients [23]. Thus, group differences could have been somewhat more pronounced regarding early left ventricular filling if mitral regurgitation had been absent.

In our control group, E/total time velocity integral decreased with age and A/E increased, which is in accordance with previous reports [24], but the age matching of patients and controls in the present study precludes age as explanation of left ventricular filling abnormalities. Despite a relation between filling abnormalities and left ventricular hypertrophy as measured by septal thickness, blood pressure did not differ between groups. It is well recognized that the left ventricular filling velocity represents a spectrum of diastolic properties, and is influenced not only by intrinsic myocardial factors, but also by loading conditions and heart rate. However, the group difference regarding A/E ratio was not abolished when accounting for blood pressure, heart rate and preload (left ventricular end-diastolic dimension).

We conclude that diastolic mitral flow velocity measured by Doppler discloses left ventricular filling abnormalities in systemic sclerosis patients. These abnormalities may be due to left ventricular hypertrophy, left ventricular ischemia despite normal major coronary arteries, or the myocardial fibrotic process itself; all 3 entities being described in systemic sclerosis. Systemic sclerosis seems to be associated with a high prevalence of mitral regurgitation, which is usually not severe, and which may partly be caused by fibrotic degeneration of the mitral leaflets.

References

1 Hamilton Dougherty A, Naccarelli GV, Gray EL, Hicks CH, Goldstein RA. Congestive heart failure with normal systolic function. Am J Cardiol 1984;54:778–782.

2 Soufer R, Wohlgelernter D, Vita NA, et al. Intact systolic left ventricular function in clinical congestive heart failure. Am J Cardiol 1985;55:1032–1036.

3 Gustafsson R, Mannting F, Kazzam E, Waldenström A, Hällgren R. Cold-induced reversible myocardial ischaemia systemic sclerosis. Lancet 1989;ii:475–479.

4 D'Angelo WA, Fries JF, Masi AT, Shulman LE. Pathological observations in systemic sclerosis (scleroderma). A study of fifty-eight autopsy cases and fifty-eight matched controls. Am J Med 1969;46:428–440.

5 Bulkley BH, Klacsmann PG, Hutchins GM. Angina pectoris, myocardial infarction and sudden cardiac death with

normal coronary arteries: a clinopathologic study of 9 patients with progressive systemic sclerosis. Am Heart J 1978;95:563–569.
6 Kazzam E, Gustafsson R, Hällgren R, Landelius J, Waldenström A, Caidahl K. Noninvasive assessment of diastolic left ventricular function in patients with systemic sclerosis. J Int Med 1990;228:183–192.
7 Gottdiener JS, Moutsopoulos HM, Decker JL. Echocardiographic identification of cardiac abnormality in scleroderma and related disorders. Am J Med 1979;66:391–398.
8 Smith JW, Clements PJ, Levisman J, Furst D, Ross M. Echocardiographic features of progressive systemic sclerosis (PSS). Correlation with haemodynamic and postmortem studies. Am J Med 1979;66:28–33.
9 Montanes P, Lawless C, Black C, Oakley CM, Hughes G. The heart in scleroderma: noninvasive assessment. Clin Cardiol 1982;5:383–387.
10 Kahan A, Nitenberg A, Foult J-M, et al. Decreased coronary reserve in primary scleroderma myocardial disease. Arthrit Rheum 1985;28:637–646.
11 Snider AR, Gidding SS, Rocchini AP, et al. Doppler evaluation of left ventricular diastolic filling in children with systemic hypertension. Am J Cardiol 1985;56:921–926.
12 Appleton CP, Hatle L, Popp RL. Relation of transmitral flow velocity patterns to left ventricular diastolic function: new insights from a combined hemodynamic and Doppler echocardiographic study. J Am Coll Cardiol 1988;12:426–40.
13 Nishimura RA, Housmans PR, Hatle LK, Tajik AJ. Assessment of diastolic function of the heart: background and current applications of Doppler echocardiography. Part I. Physiologic and pathophysiologic features. Mayo Clin Proc 1989;64:71–81.
14 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.
15 Subcommittee for scleroderma criteria of American Rheumatism Association Diagnostic and therapeutic criteria committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthrit Rheum 1980;23: 581–590.
16 Caidahl K, Eriksson H, Hartford M, et al. Dyspnoea of cardiac origin in 67 year old men: (2) relation to diastolic left ventricular function and mass. The study of men born in 1913. Br Heart J 1988;59:329–338.
17 Sahn DJ, DeMaria A, Kisslo J, Weyman A. The committee on M-mode standardization of the American Society of Echocardiography: recommendation regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation 1978;58:1072–1078.
18 Rokey R, Kuo LC, Zoghbi WA, Limacher MC, Quinones MA. Determination of parameters of left ventricular diastolic filling with pulsed Doppler echocardiography: comparison with cineangiography. Circulation 1985;71:543–550.
19 Pearson AC, Goodgold H, Labovitz AJ, Ratcliff J. Comparison of pulsed Doppler echocardiography and radionuclide angiography in the assessment of left ventricular filling. Am J Cardiol 1988;61:446–454.
20 Gardin JM, Dabestani A, Takenaka K, et al. Effect of imaging view and sample volume location on evaluation of mitral flow velocity by pulsed Doppler echocardiography. Am J Cardiol 1986;57:1335–1339.
21 Choong CY, Abascal VM, Weyman J, et al. Prevalence of valvular regurgitation by Doppler echocardiography in patients with structurally normal hearts by two-dimensional echocardiography. Am Heart J 1989;117:636–642.
22 Follansbee WP. The cardiovascular manifestation of systemic sclerosis (scleroderma). Curr Probl Cardiol 1986;5:242–298.
23 Skaikh MA, Lavine SJ. Effect of mitral regurgitation on diastolic filling with left ventricular hypertrophy. Am J Cardiol 1988;61:590–594.
24 Miyatake K, Okamoto M, Kinoshita N, et al. Augmentation of atrial contribution to left ventricular inflow with aging as assessed by intracardiac Doppler flowmetry. Am J Cardiol 1984;53:586–598.