Left ventricular diastolic filling alterations in subjects with mitral valve prolapse: a Doppler echocardiographic study

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To assess left ventricular diastolic filling in mitral valve prolapse (MVP), we studied 22 patients with idiopathic MVP and 22 healthy controls matched for sex, age, body surface area and heart rate. A two-dimensional, M-mode and Doppler echocardiographic examination was performed to exclude any cardiac abnormalities. The two groups had similar diastolic and systolic left ventricular volumes, left ventricle mass and ejection fraction. Doppler measurements of mitral inflow were: E and A areas (the components of the total flow velocity-time integral in the early passive period of ventricular filling, E; and the late active period of atrial emptying, A), the peak E and A velocities (cm . s^{-1}), acceleration and deceleration half-times (ms) of early diastolic rapid inflow, acceleration time of early diastolic flow (AT), total diastolic filling time (DFT) (ms), and the deceleration of early diastolic flow (cm . s^{-2}). From these measurements were calculated: peak A/E ratio (A/E), E area/A area, the early filling fraction, the atrial filling fraction, AT/DFT ratio. All the Doppler measurements reported are the average of three cardiac cycles selected at end expiration. The mean peak A velocity, A/E velocity ratio, deceleration half time and atrial filling fraction were each significantly higher for subjects presenting a MVP (60 ± 12 cm . s^{-1} vs 49 ± 14, P < 0·008; 98 ± 13% vs 64 ± 12%, P < 0·0001; 120 ± 36 ms vs 92 ± 11, P < 0·002; 0·45 ± 0·14 vs 0·36 ± 0·08, P < 0·02). The opposite was found for the mean deceleration of early diastolic flow, which was significantly lower (290 ± 150 cm . s^{-2} vs 410 ± 122, P < 0·007). None of the remaining parameters was significantly different. In conclusion, we have documented a different pattern of ventricular filling in patients with MVP compared to healthy subjects. Other investigations are needed to clarify the significance and the causes of these observations.

Introduction

Mitral valve prolapse (MVP) is one of the most prevalent cardiac abnormalities[1]. The vast majority of patients with MVP are symptom free and many of the symptoms previously ascribed to the disorder are common in the general population[2]. Nevertheless, among patients with this condition, evidence suggests that mitral regurgitation and heart failure, as well as bacterial endocarditis, sudden death, and cerebral embolic events are increased in frequency[3–6]. MVP may be associated with diseases such as Marfan's syndrome[7], some of Ehlers-Danlos variants[8], and other conditions, but it may also be an idiopathic disorder[9].

Although several investigators have evaluated auscultatory or echocardiographic findings and the risk of complications in patients with MVP, none has performed Doppler echocardiographic studies to assess left ventricle (LV) diastolic properties in subjects with this disorder. Doppler echocardiography is being increasingly used to detect diastolic abnormalities, since it may provide an accurate non-invasive beat-to-beat evaluation of LV diastolic filling; some factors, however, may affect Doppler trans-mitral flow velocity measurements, i.e. mitral regurgitation, loading conditions and other cardiac or extra-cardiac disorders.

The purpose of our study was to assess LV diastolic properties in subjects with idiopathic MVP.

Table 1 Characteristics of the two patient groups. Values are mean ± standard deviation

	MVP group	Control group
Female	12	12
Male	10	10
Age (years)	23·5 ± 8 7	24·5 ± 9
Body surface area (m²)	1·67 ± 0·13	1·68 ± 0·13
Heart rate (beats . min⁻¹)	75 ± 5	75 ± 4

Methods

SUBJECT SELECTION AND STUDY PROCEDURES

We selected 22 subjects, aged between 15 and 43 years (average age ± 1 SD: 23·5 ± 8·7), on the basis of the following criteria: (1) presence of a mid-systolic click, (2) positive echocardiographic findings of mitral valve prolapse, (3) absence of mitral regurgitation at an accurate Echo-Doppler examination (4) absence of any other valvular cardiac chamber dimension and/or regional wall motion abnormality as determined by the two-dimensional M-mode and Doppler echocardiographic examination.

Each subject with MVP was matched with a healthy control for sex, age, body surface area and heart rate (Table 1). Control subjects were volunteers without any symptoms, signs and/or clinical findings of cardiac or extracardiac diseases. All were in sinus rhythm. All the subjects were informed of the purpose of the study and gave their consent.
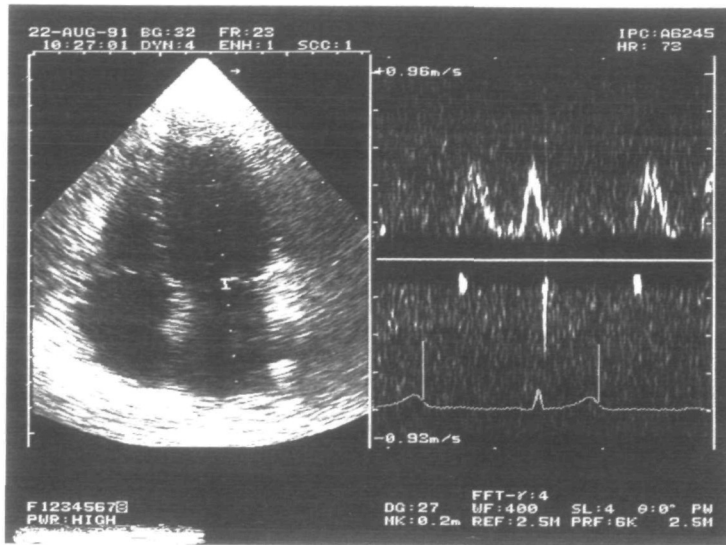
Figure 1   Pulsed Doppler examination of transmitral blood flow.

Subjects with symptoms and signs that may be associated with decreased blood volume, such as dizziness, syncope, orthostatic hypotension were not studied[10]. We also excluded all subjects with a history and/or clinical findings of rheumatic fever or rheumatic heart disease, coronary artery disease, arterial hypertension, arterial hypotension, diabetes mellitus, primary or secondary cardiomyopathy, congenital heart disease, connective tissue diseases (congenital or inflammatory) or hyperthyroidism.

ECHOCARDIOGRAPHIC EXAMINATION

Between 0800 and 1100 h, a standard two-dimensional, M-mode and Doppler echocardiographic examination was carried out on each subject in a partial left lateral recumbent position. An Esaote Biomedica computer-aided ultrasonoscope equipped with 2·5 and 3·5 MHz phased-array transducers was used; a standard VHS video format was used for recordings. Both transducers are capable of continuous Doppler activity, have pulsed Doppler capacity with a moveable Doppler cursor and an adjustable sample volume size. The sample volume size was set at 4 mm for this study.

Mitral valve prolapse was defined as systolic displacement of at least 3 mm behind the mitral valve ring of one or both mitral leaflets in the parasternal long-axis view on two-dimensional echocardiography[11]. Prolapse was confirmed by at least one orthogonal view.

Two-dimensional echocardiography included short-axis views at the level of the mitral valve and apical four- and two-chamber views to exclude regional wall motion abnormalities[12]

Standard M-mode echocardiographic examination, guided by two-dimensional echocardiography from the left parasternal window, was performed to exclude LV hypertrophy and LV mass differences between the two groups. Measurements were made according to the Penn convention. described by Devereux and Reichek[13]:

LV mass (g) = 1·04 [(LVID + VST + PWT)^3 − (LVID)^3] − 13·6; where LVID = diastolic LV internal diameter; VST = diastolic ventricular septal thickness, and PWT = diastolic posterior wall thickness. Measurement points were taken at the peak of the R wave on an average of four cycles.

Left ventricular end-diastolic and end-systolic volumes for determination of ejection fraction (EF) were calculated from the apical four-chamber view, using the ellipsoid single-plane algorithm[14]. End-diastolic and end-systolic frames from five consecutive beats were selected and the endocardial outlines traced. Mean EF was automatically calculated by the echocardiograph processing system. In our laboratory the EF calculated on five consecutive beats permitted optimal reproducibility and accuracy.

We also carried out a standard pulsed and continuous Doppler echocardiographic examination[15] to exclude pathological spectral flow patterns (valve regurgitation and/or stenosis).

LEFT VENTRICULAR INFLOW TRACT STUDY

Pulsed Doppler examination of transmitral blood flow was performed, as previously described[16], from the apical chamber view on subjects while they were in a partial left lateral recumbent position. The sample volume was positioned at the level of the mitral anulus and the cursor oriented parallel to an imaginary line bisecting the left ventricle from apex to mitral valve (Fig. 1).

We measured the following variables: the RR' interval, peak E (PE) and A (PA) velocities, area under the E (E area) and A (A area) portions of the diastolic flow velocity–time integral (the components of the total flow velocity–time integral in the early passive period of ventricular filling and the late active period of atrial emptying, respectively), acceleration (AHT) and deceleration (DHT) half-times of early diastolic rapid inflow[17], the time from the onset of diastolic flow to the peak E velocity

Table 2   Structural and functional data derived from M-mode and two-dimensional echocardiography. Values are mean ± standard deviation

	MVP group	Control group	P <
LVM (g)	138 ± 14	133 ± 20	ns
EDV (ml)	112 ± 30	109 ± 32	ns
ESV (ml)	42 ± 18	40 ± 19	ns
EF (%)	63 ± 7	64 ± 9	ns

LVM = left ventricular mass; EDV = left ventricle end diastolic volume; EDS = left ventricle end systolic volume; EF = left ventricle ejection fraction.

(acceleration time), total diastolic filling time (DFT), the deceleration of early diastolic flow (Dec E), measured as the slope of a straight line drawn between the peak E velocity and the point where peak E decreases to peak E/2 on the descending limb of the early diastolic inflow. From these measurements, the following were calculated: heart rate (HR), peak A/E ratio (A/E), E area/A area, the early filling fraction (early FF) as E area/total area, the atrial filling fraction (atrial FF) as A area/total area, AT/DFT ratio.

All Doppler measurements reported are the average of three cardiac cycles detected at end expiration.

DATA ANALYSIS

Measurements were made on digitized images by measuring functions of the echocardiograph processing unit; the ellipsoid single-plane algorithm was also taken into consideration. Averages were automatically calculated.

Values are reported as mean ± standard deviation. A 2-tailed unpaired t-test was used for statistical analysis and $P < 0.05$ indicated a significant difference between groups.

Results

The results are shown in Tables 1 and 2. There were no significant differences between the two groups in terms of left ventricular mass, volumes and ejection fraction. As regards Doppler measurements, mean peak A velocity, E/A velocity ratio, deceleration half-time and atrial filling fraction were each significantly higher in subjects affected by MVP (60 ± 12 cm . s^{-1} vs 49 ± 14, $P < 0.008$; 98 ± 13% vs 64 ± 12%, $P < 0.0001$; 120 ± 36 ms vs 92 ± 11, $P < 0.002$; 0·45 ± 0·14 vs 0·36 ± 0·08, $P < 0.02$). On the other hand, the mean deceleration of early diastolic flow was significantly lower (290 ± 150 cm . s^{-2} vs 410 ± 122, $P < 0.007$). None of the remaining parameters showed a significant difference between the two groups.

Discussion

Abnormalities of diastolic filling have been described in various pathological conditions[18]. Nevertheless, despite computerized literature searches of Medline and *Index*

Table 3   Doppler transmitral flow parameters: comparison of MVP patients (MVP group) with healthy subjects (control group). Values are mean ± standard deviation

	MVP group	Control group	P <
PE (cm . s^{-1})	68 ± 13	77 ± 17	ns
PA (cm s^{-1})	60 ± 12	49 ± 14	0·008
A/E ratio (%)	98 ± 13	64 ± 12	0·0001
AT (ms)	67 ± 18	72 ± 24	ns
DFT (ms)	382 ± 57	410 ± 60	ns
AT/DFT ratio	0·17 ± 0·06	0·17 ± 0·03	ns
AHT (ms)	51 ± 16	53 ± 10	ns
DHT (ms)	120 ± 36	92 ± 11	0·002
Dec E (cm . s^{-2})	290 ± 150	410 ± 122	0·007
FVI (cm)	0·16 ± 0·03	0·16 ± 0·03	ns
E area (cm)	0·09 ± 0·03	0·10 ± 0·03	ns
A area (cm)	0·06 ± 0·03	0·06 ± 0·01	ns
E/A areas	1·63 ± 1·01	1·77 ± 0·35	ns
Early FF	0·58 ± 0·09	0·62 ± 0·06	ns
Atrial FF	0·45 ± 0·14	0·36 ± 0·08	0·02

ns = not significant; PHT = pressure half time; PE = peak E velocity; PA = peak A velocity; AT = acceleration time; DFT = total diastolic filling time; AHT = acceleration half time; DHT = deceleration half time; Dec E = deceleration of early diastolic flow; FVI = total flow velocity-time integral; E area = area under E portion of the diastolic flow velocity-time integral; A area = area under A portion of the diastolic flow velocity-time integral; Early FF = early filling fraction as E area/total area; Atrial FF = atrial filling fraction as A area/total area.

Medicus for echo-Doppler evaluation of diastolic function in MVP, we identified no previous relevant study. We thought it would be interesting to assess left ventricular filling in patients with MVP to clarify the pathophysiology of this disorder. In our study, we considered several types of indices of left ventricular diastolic filling, with particular emphasis on the factors affecting mitral flow velocity measurements. The Doppler time intervals and peak velocities vary with cardiac cycle lengths. The position of the sample volume can also alter the mitral valve Doppler tracing[19]. In addition, the mitral valve Doppler indices vary with the phases of respiration[20]. During tachycardia, the early and late diastolic portions of the mitral flow curve progressively fuse and may become indistinguishable. When this occurs, it is very difficult, if not impossible, to use the Doppler flow curve to evaluate left ventricular diastolic function. Finally, early diastolic left ventricular filling is affected not only by the left ventricular relaxation properties but also by the left atrial pressure at the onset of left ventricular filling[21]. Factors that increase left atrial pressure will alter left ventricular diastolic filling patterns. For example, mitral regurgitation increases left atrial pressure and causes an increase in mitral valve flow velocity, left ventricular filling rate and mitral volumetric flow.

For these reasons we applied a strict selection process for both patients and matched controls. The main difficulties were encountered in selecting subjects with MVP according to current rigid echocardiographic diagnostic criteria plus mid-systolic click, but without mitral regurgitation, other pathological flow patterns or changes in the

loading conditions that can affect mitral flow measurements. Moreover, it was difficult to find a satisfactory matched volunteer control for each investigated patient. Our results indicate, therefore, that patients with MVP have a different mitral flow velocity pattern as compared to controls. In the patients we found a decreased peak early mitral flow velocity (not significant), an increased mitral flow velocity at atrial contraction, an increased A/E ratio, a prolonged mitral deceleration time and a slow deceleration of early diastolic flow. Moreover the atrial filling fraction of the MVP group was higher than in the control group. This was in agreement with the higher A/E ratio seen in the MVP group even though the E/A area flow-velocity integrals showed no difference between groups. The flow velocity integral represents a very exacting measurement and slight modifications beyond the possibility of instrument precision may not be detected. Thus, there was no statistically significant difference between the two groups as regards the A area and the E area/A area of the diastolic flow velocity-time integral. The difference was significant only when the A area was normalized for the total diastolic flow velocity integral.

Since subjects were selected so as to clinically exclude loading alterations and other factors that can affect diastolic filling, there is no reason to think that the two groups were not homogeneous and comparable. Therefore, our echo-Doppler findings may be due to impaired left ventricular diastolic function. In fact this pattern appears to occur when there is impaired left ventricular relaxation[22]. Assuming that left atrial pressure at the time of mitral valve opening remains constant, a slower rate (reduced slope) of fall in left ventricular isovolumetric pressure would result in a decrease in peak early flow velocity. With less filling in early diastole, the percentage of left ventricular filling due to atrial contraction is probably increased by a compensatory mechanism. The long mitral deceleration time (DHT) may reflect a prolonged fall of left ventricular pressure associated with the impaired relaxation and the low early diastolic filling rates. In conclusion, the pattern of ventricular filling that we have documented in patients affected by idiopathic MVP may be the result of an abnormal ventricular relaxation.

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