Preoperative left ventricular function in degenerative mitral valve disease

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Aim The aim of the study is to determine the impact of the underlying etiology (Barlow's disease or fibroelastic deficiency) on left ventricular function in patients with degenerative mitral valve disease and severe mitral regurgitation.

Methods We studied 233 patients (mean age: 53.8 ± 12.9) undergoing surgery for severe mitral regurgitation due to degenerative mitral valve disease at Almazov Federal Heart Centre between 2009 and 2011. Pathologic diagnoses for valvular tissue specimens were provided by an experienced pathologist. Preoperative strain and strain rate were determined using speckle tracking (Vivid 7 Dimension, EchoPAC'08).

Results Barlow's disease was identified by the pathologist in 60 patients (25.8%), and fibroelastic deficiency in 173 patients (74.2%). There were no significant differences between groups in preoperative mitral regurgitation volume (70.5 ± 9.6 vs. 71.6 ± 8.5 ml, $P = 0.40$), and in global systolic (ejection fraction: 52.7 ± 6.6 vs. $52.0 \pm 7.4\%$, $P = 0.53$) and diastolic (E/e': 12.2 ± 3.9 vs. 12.8 ± 4.2 , $P = 0.35$) left ventricular function. Despite the lack of difference in ejection fraction and diastolic tissue Doppler parameters, in

patients with Barlow's disease in comparison with fibroelastic deficiency a significant decrease of the left ventricular longitudinal systolic strain (-13.5 ± 2.2 vs. $-15.6 \pm 2.3\%$, $P = 0.00001$) and early diastolic strain rate (1.04 ± 0.20 vs. 1.14 ± 0.18 s⁻¹, $P = 0.0004$) were detected.

Conclusion Patients with severe mitral regurgitation due to Barlow's disease have a lower preoperative left ventricular systolic function than those with fibroelastic deficiency, which may affect their postoperative prognosis.

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Keywords: Barlow's disease, fibroelastic deficiency, preoperative left ventricular function, severe mitral regurgitation, speckle-tracking echocardiography

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Introduction

Degenerative mitral valve disease (DMVD) is a common disorder affecting around 2% of the population.^{1,2} Barlow's disease and fibroelastic deficiency (FED) are the two dominant forms of DMVD in which morphologic changes in the connective tissue of the mitral valve cause structural lesions that are responsible for the syndromes of billowing mitral leaflet, mitral valve prolapse (MVP), floppy mitral valve and flail leaflet.³

Barlow's disease is characterized by diffuse excess tissue. Valve size is large, and multiple segments are affected with myxomatous pathological changes, resulting in thickened and distended 'floppy' leaflets. Diffuse chordal thickening, elongation and varying degrees of annular calcification may be observed.² The pathological hallmarks are myxoid infiltration and collagen alteration, which destroys the normal three-layer leaflet architecture. Severe mitral regurgitation in Barlow's disease results from the marginal prolapse due to chordal elongation and typically occurs in the mid-to-late phase of systole.³

In FED, the main pathological mechanism is connective tissue deficiency.⁴ Impaired production of connective tissue, with deficiency of collagen, elastins and

proteoglycans results in thinning of leaflet tissue. The three-layer architecture of the leaflet tissue is preserved.³ Alterations in FED are characterized by disrupted, fragmented and granular elastic fibers that form an amorphous clump.⁴ Myxoid degeneration of single prolapsing segment may occur. Rupture of thin, connective tissue-deficient chords is the mechanism of severe holosystolic mitral regurgitation in FED.³

DMVD is the most common cause of mitral regurgitation in developed countries and one of the most frequent cardiovascular disorders requiring surgery.⁵ Surgery is warranted in symptomatic patients with severe mitral regurgitation and has been recommended in asymptomatic patients who develop signs of left ventricular dysfunction.⁶ For detecting left ventricular myocardial dysfunction, parameters such as left ventricular cavity dimensions and ejection fraction have been widely used, but these standard parameters are often overestimated in the presence of severe mitral regurgitation.⁷ Preoperative left ventricular systolic function is also an important prognostic factor of early postoperative left ventricular decompensation and poor prognosis in patients undergoing mitral valve repair or replacement.^{8,9}

Two-dimensional speckle-tracking echocardiography (STE) is a widely available technique used for the evaluation of myocardial function. Strain and strain rate analysis increase sensitivity in detecting subclinical cardiac involvement in some conditions including severe mitral regurgitation.¹⁰

The purpose of this study was to determine the impact of the underlying etiology (Barlow's disease or FED) on left ventricular function in patients with DMVD undergoing surgery for severe mitral regurgitation.

Methods

Study population

A total of 233 patients undergoing surgery for severe mitral regurgitation due to DMVD at Almazov Heart Centre between 2009 and 2011 were enrolled in our retrospective, single-center study. Only patients with surgically excised mitral valves (segment of the posterior leaflet or the entire valve) suitable for pathomorphological examination were included in this study. Mean age of the patients was 53.8 ± 12.9 years. Patients with severe mitral regurgitation due to ischemic heart disease or cardiomyopathy (based on the preoperative coronary angiogram), with Marfan syndrome, with associated mitral stenosis, or any other form of valve disease were excluded. All patients gave informed consent and the protocol was approved by the local ethics committee.

Patients were qualified for surgery according to the American Heart Association/American College of Cardiology (AHA/ACC) guideline.⁶ Seventy-three patients (31%) were symptomatic (I class of indication), 132 patients (57%) were asymptomatic with ejection fraction less than 60% and/or end systolic diameter more than 40 mm (I class), and 28 (12%) asymptomatic patients had pulmonary hypertension more than 50 mmHg (IIa class of indication). Repair was feasible in 196 (84%) patients. Quadrangular or triangular resection of prolapsed scallop, ring annuloplasty, and additionally, when required, artificial cords were used. In 37 patients (16%), including five patients (2%) with unsuccessful primary repair, mitral valve replacement with chordal sparing procedure was performed.

Echocardiography

Standard echocardiography extended with STE (strain rate and strain imaging) was performed in all patients before surgery. All echocardiographic measurements were performed by an experienced, certified echocardiographer using a Vivid 7 ultrasound system (GE Healthcare, Milwaukee, Wisconsin, USA), equipped with a harmonic 3.5 MHz phased-array transducer.

The presence of prolapsed or flail segments was reported. MVP was diagnosed by billowing of one or both mitral leaflets more than 2 mm above the mitral annulus in the long-axis parasternal view, whereas a flail segment was

noted as a protruding, highly mobile segment with torn chordae. The localization of the pathology was performed according to the Carpentier nomenclature.

Mitral regurgitation was assessed according to the European Association of Echocardiography (EAE) recommendations,¹¹ vena contracta imaging of the mitral regurgitation jet was obtained, and proximal isovelocity surface area (PISA) imaging was performed (Fig. 1). An effective regurgitant orifice area (EROA) at least 0.3 cm^2 or a regurgitant volume at least 60 ml indicated severe mitral regurgitation.

The end-diastolic and end-systolic left ventricular diameters were measured using B-mode echocardiography. The left ventricular end-diastolic and end-systolic volumes, and left ventricular ejection fraction were calculated using a modified Simpson's rule. The transmitral flow velocity was recorded from the apical four-chamber view. The mitral annular motion velocity was recorded at the septum and lateral wall using pulsed tissue Doppler imaging.

Two-dimensional speckle-tracking echocardiography

Longitudinal strain and strain rate were determined from three standard apical views, as well as radial and circumferential strain rate from three parasternal short-axis views at basal, mid-papillar and apical levels, using two-dimensional STE with a gray-scale frame rate of 50–85 fps by two experienced physician echocardiographers, blinded to each other's recordings.

At each plane, one cardiac cycle was acquired (while the participant held his or her breath) and stored. Image analysis was performed offline on an EchoPAC'08 workstation (GE Healthcare) with automatically tracked speckles frame by frame throughout the cardiac cycle. The left ventricle was divided into 16 segments, with

Fig. 1

Measure of the proximal isovelocity surface area radius for quantitative assessment of mitral regurgitation severity (apical four-chamber view, color-flow display).

only four segments at the apical level. Segments with tracking difficulties, reverberations or poor image quality were excluded manually [from 7456 recorded left ventricular segments, only 5854 (78.5%) were accepted for deformation analysis].

Systolic strain rate was determined as the maximal negative (for longitudinal and circumferential) or positive (for radial) value during the ejection phase, and peak systolic strain as the magnitude of strain at the aortic valve closure. Peak longitudinal early diastolic filling strain rate was also measured.

Pathology

Surgically excised valve tissue, consisting of the resected abnormal segment of the leaflet with chordae tendineae, was examined by an experienced pathologist, blinded to echocardiographic findings.

Gross examination of excised mitral valve segment from patients with Barlow's disease revealed the thickened leaflet. The chordae tendineae were irregularly thickened. In patients with FED, prolapsed segments were irregularly thickened with areas appearing more transparent than the remaining leaflet. The chordae tendineae showed irregular thinning or thickening. Almost one-quarter of patients with fibroelastic deficiency (39 patients, 22.5%) showed thickened prolapsed segment by gross examination. In these cases, the distinction was based on the condition of adjacent leaflet segments (thinned) according to direct visual assessment by the surgeon.

For histologic examination, 5- μ m thick sections were cut and stained with hematoxylin-eosin and with orcein, with a Van Gieson counterstain. The slides were examined under light microscopy. Myxomatous infiltration was characterized by significant thickening of the spongiosa with pooling of glycosaminoglycans. The spongiosa proliferates (Fig. 2) and invades the fibrosa. FED was characterized by fragmentation of the collagenous bundles within fibrosa (Fig. 3) and fragmentation, splitting and coiling of elastic fibers.

Statistical analysis

The variables are presented as mean $\pm$ SD. The categorical variables are presented as percentages. Differences between groups were analyzed using the two-sided Student's *t*-test for continuous variables and the χ^2 test for categorical variables. Effect sizes for deformation indices were measured by Cohen's *d* using means and standard deviations. Accuracy and predictive value of echocardiography for the detection of Barlow's disease and FED were calculated according to standard formulae. The relationship between pairs of continuous variables was expressed by the Pearson correlation. Myocardial deformation indices were tested as dependent variables using univariate linear regression analyses to explore the significance of possible influencing factors. The

Fig. 2

Histologic section of mitral valve showing extensive myxomatous changes in the leaflet in Barlow's disease. Hematoxylin-eosin, $\times 400$.

reproducibility was expressed by the coefficient of repeatability (COR), interclass correlation coefficient (ICC), and the mean error (%). Statistical significance was set at $P < 0.05$. All statistical analyses were performed using Statistica 8 software (StatSoft Inc., Tulsa, Oklahoma, USA).

Results

According to results of gross and histologic examination of the resected abnormal mitral valve segments, patients were divided into two groups. Barlow's disease was identified by pathologist in 60 patients (25.8%), and FED in 173 patients (74.2%). The main pathologic findings by microscopy of valvular tissue specimens in

Fig. 3

Alterations of collagenous bundles in mitral valve leaflet. Collagenous bundles are fragmented and coiled. Hematoxylin-eosin, $\times 200$.

Table 1 Clinical characteristics of groups of patients with Barlow's disease or fibroelastic deficiency before surgery

	Barlow's disease (n = 60)	FED (n = 173)	P
Age (years)	48.2 ± 12.7	55.8 ± 13.3	0.0002
Sex (men, %)	66%	65%	0.89
NYHA class			
I	11 (18%)	36 (21%)	0.68
II	25 (42%)	88 (51%)	0.22
III	20 (33%)	40 (23%)	0.12
IV	4 (7%)	9 (5%)	0.67
Preoperative duration of the symptoms (mo.)	7.9 ± 2.7	8.2 ± 2.9	0.48
Mitral regurgitation recognition to operation time (mo.)	6.5 ± 2.1	6.8 ± 2.4	0.39
Atrial fibrillation (%)	7 (12%)	26 (15%)	0.57
Heart rate (b.p.m.)	73.9 ± 15.2	75.4 ± 16.8	0.54
SBP (mmHg)	135.2 ± 14.3	137.9 ± 16.2	0.25
DBP (mmHg)	79.8 ± 8.7	77.4 ± 9.4	0.08
Arterial hypertension, %	24 (40%)	82 (47%)	0.35
Diabetes (%)	3 (5%)	10 (6%)	0.82
Medical therapy			
β-Blockers (%)	25 (42%)	83 (48%)	0.42
ACEI/ARB (%)	37 (62%)	102 (59%)	0.68
Diuretics (%)	16 (27%)	58 (34%)	0.32
BSA (m ²)	1.98 ± 0.18	1.97 ± 0.16	0.69

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BSA, body surface area; FED, fibroelastic deficiency; NYHA, New York Heart Association.

Barlow's disease patients were myxomatous degeneration in 100% and fibrosis in 33.2% of cases.

Patients with Barlow's disease, not surprisingly,³ were significantly younger than those with FED (Table 1). Both groups contained more men than women. Preoperatively, most patients in each group had mild symptoms (New York Heart Association, NYHA class I or II) and reported the same duration of symptoms (shortness of breath or fatigue). Also, according to the case reports, patients in both groups had a similar period between the first recognition of severe mitral regurgitation and surgery (Table 1). Atrial fibrillation was present only in 12% patients of Barlow's disease group and 15% of FED group. There were no significant differences between groups in medical treatment, heart rate and blood pressure.

Standard echocardiographic parameters of the studied patients before surgery are presented in Table 2. There were no significant differences in left ventricular dimensions and volumes nor in global systolic function between the groups (preoperative left ventricular end diastolic volume was increased and ejection fraction slightly decreased in both). Also there were no significant differences between the groups in number of patients with left ventricular enlargement and systolic dysfunction. Other chamber dimensions and volumes did not vary significantly from group to group. Preoperative global diastolic left ventricular function, evaluated by transmitral and tissue Doppler, was depressed equally in FED and Barlow's disease groups. There was no difference between groups in systolic pulmonary pressure.

Table 2 Preoperative echocardiographic parameters of the two groups of patients

	Barlow's disease (n = 60)	FED (n = 173)	P
EDD (mm)	55.5 ± 5.3	56.8 ± 5.2	0.10
ESD (mm)	39.1 ± 7.2	38.1 ± 7.0	0.34
ESD >40 mm (n/%)	19 (32%)	64 (37%)	0.49
EDV (ml)	157.5 ± 23.4	155.6 ± 21.7	0.57
ESV (ml)	76.4 ± 18.1	73.2 ± 17.6	0.23
SV (ml)	83.0 ± 16.6	80.4 ± 15.2	0.27
LVEF (%)	52.7 ± 6.6	52.0 ± 7.4	0.53
LVEF <60% (n/%)	25 (42%)	82 (47%)	0.50
E, m/s	1.38 ± 0.30	1.36 ± 0.27	0.63
E/e'	12.2 ± 3.9	12.8 ± 4.2	0.35
Ar-A (ms)	36.6 ± 7.9	38.7 ± 8.8	0.10
IVRT (ms)	52.5 ± 12.7	49.6 ± 10.7	0.09
IVRT/T _{E-e'}	2.8 ± 0.9	2.6 ± 1.1	0.20
Left ventricular mass index (g/m ²)	161.8 ± 34.7	159.4 ± 43.9	0.70
LAVI (ml/m ²)	69.6 ± 33.4	72.4 ± 38.3	0.61
RVEDD (mm)	23.5 ± 3.7	24.3 ± 3.4	0.16
Systolic pulmonary pressure (mmHg)	43.9 ± 7.2	45.4 ± 9.3	0.26

Ar-A, the time difference between atrial reversal and mitral A-wave duration; E, peak early diastolic velocity; E/e', ratio of transmitral and annular early diastolic velocities; EDD, end-diastolic diameter; EDV, end-diastolic volume; ESD, end-systolic diameter; ESV, end-systolic volume; FED, fibroelastic deficiency; IVRT, isovolumetric relaxation time; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; RVEDD, right ventricular end-diastolic diameter; T_{E-e'}, time interval between the onset of E and e'.

Table 3 Mitral valve and aortic root features of both groups of patients before surgery

	Barlow's disease (n = 60)	FED (n = 173)	P
Anterior leaflet prolapse	5 (8%)	2 (1%)	0.005
Posterior leaflet prolapse	36 (60%)	24 (14%)	<0.0001
Bileaflet prolapse	7 (12%)	4 (2%)	0.003
Anterior flail leaflet	2 (3%)	21 (12%)	0.05
Posterior flail leaflet	10 (17%)	122 (71%)	<0.0001
Anterior leaflet length (mm)	29.4 ± 2.9	25.6 ± 3.3	<0.0001
Anterior leaflet thickness (mm)	4.2 ± 0.9	3.4 ± 1.1	<0.0001
Posterior leaflet length (mm)	16.1 ± 2.3	14.2 ± 2.8	<0.0001
Posterior leaflet thickness (mm)	5.1 ± 0.8	3.5 ± 1.2	<0.0001
Mitral annular diameter (mm)	37.1 ± 3.5	31.3 ± 3.7	<0.0001
VC width (mm)	7.5 ± 2.5	7.9 ± 2.8	0.33
PISA radius (mm)	11.5 ± 1.8	11.8 ± 2.1	0.32
R Vol (ml)	70.5 ± 9.6	71.6 ± 8.5	0.40
EROA (cm ²)	0.39 ± 0.05	0.41 ± 0.09	0.10
Aortic root (mm)	35.6 ± 2.7	34.7 ± 2.4	0.016
Z-score (cm/m ²)	1.88 ± 0.21	1.79 ± 0.18	0.002
Ascending aorta (mm)	33.7 ± 3.8	33.4 ± 3.5	0.58
Aortic valve prolapse	5 (8%)	—	0.0002
Aortic regurgitation, mild or moderate	8 (13%)	28 (16%)	0.58

EROA, effective regurgitant orifice area; FED, fibroelastic deficiency; PISA, proximal isovelocity surface area; R Vol, regurgitant volume; VC, vena contracta; Z-score, aortic root diameter corrected for age and body size.

As shown in Table 3, the most common echocardiographic finding in patients with Barlow's disease was isolated posterior leaflet prolapse (typically of the middle scallop). Flail posterior leaflet with ruptured chordae was found in majority of the FED patients. Anterior or both leaflets were involved in Barlow's disease significantly more often than in FED group. Patients with Barlow's disease, as expected, also had significantly longer and thicker mitral valve leaflets (echocardiographic signs of myxomatous degeneration) and a larger mitral annulus diameter than the FED patients. Echocardiography had a very high diagnostic accuracy to identify the affected leaflet and scallop [0.91, confidence interval (CI) 0.74–0.98] and to determine valvular thickening (0.87, CI 0.70–0.95) compared with morphologic description. In contrast, trans-thoracic echocardiography was able to correctly identify ruptured chordae tendinae in only 76% of cases.

The presence of valvular thickening, prolapse of both mitral valve leaflets, and annular enlargement had a high positive predictive value (0.92, CI 0.83–0.99) in identification of Barlow's disease. In contrast, the typical echocardiographic features of FED were thin leaflets and chordal rupture (positive predictive value = 0.88, CI 0.70–0.95).

Mitral regurgitation had the similar EROA and R Vol by PISA in both groups, mostly late-systolic in the Barlow's disease patients ($P = 0.004$).

Barlow's disease patients, when compared with the FED group, had also larger aortic root dimensions at the level of the Valsalva sinus and higher Z-score, but the ascending aorta was the same in both groups. Despite the larger aortic root diameter and higher prevalence of aortic valve prolapse in Barlow patients, the mild/moderate aortic regurgitation rate was the same in both groups (Table 1).

Two-dimensional speckle-tracking echocardiography

In both groups, global longitudinal deformation indices were reduced (Table 4) compared to reference values from population HUNT (the Nord-Trøndelag Health Study) study.¹² Although there are no population reference values on the radial and circumferential strain and strain rate, in our study, these were decreased in both groups in comparison with the data from Oxborough *et al.*¹³

Despite the lack of difference in ejection fraction, systolic longitudinal, radial and circumferential strain and strain rate values were significantly lower in the Barlow's

Table 4 Preoperative global myocardial deformation indices of both groups of patients in comparison to reference values

	Barlow's disease (n = 60)	FED (n = 173)	P*	d**	Reference values
Longitudinal strain (%)	-13.5 ± 2.2 [‡]	-15.6 ± 2.3 [‡]	0.00001	0.93	-16.7 ± 4.1 ^a
Longitudinal systolic strain rate (s ⁻¹)	-0.89 ± 0.15 [‡]	-0.94 ± 0.15 [‡]	0.03	0.33	-1.03 ± 0.27 ^a
Longitudinal early diastolic strain rate (s ⁻¹)	1.04 ± 0.2 [‡]	1.14 ± 0.18 [‡]	0.0004	0.53	1.24 ± 0.35 ^b
Circumferential strain (%)	-14.6 ± 3.0 [‡]	-15.9 ± 2.8 [‡]	0.003	0.44	-19.4 ± 3.6 ^b
Circumferential systolic strain rate (s ⁻¹)	-1.02 ± 0.25 [‡]	-1.11 ± 0.26 [‡]	0.02	0.35	-1.30 ± 0.27 ^b
Radial strain (%)	29.7 ± 9.3 [‡]	33.6 ± 10.2 [‡]	0.01	0.40	49 ± 15 ^b
Radial systolic strain rate (s ⁻¹)	1.08 ± 0.3 [‡]	1.2 ± 0.36 [‡]	0.02	0.36	1.68 ± 0.50 ^b

FED, fibroelastic deficiency. ^a Data from Dalen *et al.*¹² ^b Data from Oxborough *et al.*¹³ * Student's *t*-test significance when compared Barlow's disease and FED groups. [‡] Student's *t*-test significance when compared with reference value ($P < 0.00001$ for all). ** Cohen's *d* for effect sizes when compared Barlow's disease and FED groups.

Fig. 4

The examples of low longitudinal (a), radial (b), and circumferential (c) strain in a patient with fibroelastic deficiency (FED) and severe mitral regurgitation (two-dimensional speckle-tracking echocardiography).

disease group compared to the FED group (Fig. 4). Similarly, longitudinal early diastolic strain rates were lower in the Barlow's disease group (Table 4), although we found no differences between the groups in tissue Doppler parameters able to predict left ventricular filling, such as isovolumetric relaxation time (IVRT) and the ratio of IVRT to T_{E-c} (Table 2).¹⁴ But effect sizes, when Barlow's disease and FED groups were compared, were large (≥ 0.8) only for longitudinal strain and medium (≥ 0.5) for longitudinal early diastolic strain rate. All other deformation indices had low values of effect sizes (Table 4).

There was a significant correlation of preoperative longitudinal strain and strain rate with ejection fraction (strain: $r = -0.67$, $P < 0.001$; strain rate: $r = -0.65$, $P < 0.001$). A correlation was also found between radial deformation and ejection fraction (strain: $r = 0.48$, $P < 0.001$; strain rate: $r = 0.51$, $P < 0.001$). Strain and strain rate indices in the Barlow's disease group correlated with the aortic root diameter (longitudinal strain: $r = -0.56$, $P < 0.001$; circumferential strain rate: $r = 0.42$, $P < 0.001$).

In the univariate linear regression analyses, longitudinal strain was affected by Barlow's disease diagnosis ($P < 0.001$), sex ($P = 0.006$), maximal depth of mitral leaflet prolapse ($P = 0.01$), but not duration of the mitral regurgitation ($P = 0.48$) or symptoms ($P = 0.64$), diuretic ($P = 0.57$) or β -blocker ($P = 0.69$) therapy.

Reproducibility

The interobserver mean error, COR and ICC for calculated global myocardial deformation indices are shown in

Table 5. Mean error and COR for radial and circumferential deformation were higher than for longitudinal deformation. Likewise, ICC was lower for radial and circumferential strain and strain rate.

Discussion

Preoperative left ventricular systolic function is an important prognostic factor in patients with severe mitral regurgitation undergoing mitral valve repair/replacement.⁹ The purpose of this study was to assess the alteration of left ventricular preoperative function in patients with severe mitral regurgitation due to different forms of the DMVD.

In both groups of patients (Barlow's disease and FED), we revealed a similar decrease in preoperative left ventricular systolic and diastolic function assessed by conventional methods. In chronic severe mitral regurgitation, progressive left ventricular remodeling, with increasing wall stresses, ultimately leads to irreversible changes in the myocardium, resulting in the development of left ventricular contractile dysfunction.⁹ However, load dependence of ejection fraction constitutes considerable limitations in the accurate assessment of left ventricular systolic function.¹⁵ In contrast, strain and strain rate analysis is less load-dependent, increases sensitivity in detecting cardiac involvement in severe mitral regurgitation, and is currently used as a diagnostic tool that facilitates the identification of myocardial dysfunction in such patients.^{8–10}

The main finding of the current study was the significant decrease of the longitudinal systolic strain and early

Table 5 Interobserver reproducibility in speckle-tracking echocardiography assessment of the left ventricular global myocardial deformation indices

	Mean error (%)	Coefficient of repeatability	Interclass correlation coefficient
Longitudinal systolic strain	6	1.4%	0.86
Longitudinal systolic strain rate	8	0.15 c^{-1}	0.82
Longitudinal early diastolic strain rate	8	0.19 c^{-1}	0.75
Circumferential systolic strain	14	2.1%	0.65
Circumferential systolic strain rate	11	0.24 c^{-1}	0.76
Radial systolic strain	11	1.7%	0.74
Radial systolic strain rate	9	0.19 c^{-1}	0.79

diastolic strain rate in patients with Barlow's disease compared with FED, despite the lack of difference in ejection fraction and diastolic tissue Doppler parameters between groups. Circumferential and radial strain and strain rate also were statistically significantly different, but had low values of effect sizes. Longitudinal strain is thought to be one of the earliest to be altered in the case of systolic dysfunction.¹⁶ Measurement of longitudinal strain is simple and reproducible; circumferential and radial strain/strain rate, in contrast, are not yet validated and accepted for use in a wide clinical setting.¹⁰ In our study, longitudinal strain likewise showed a good inter-observer reproducibility, and large effect size when Barlow's disease and FED groups were compared.

Reduction of longitudinal systolic strain and early diastolic strain rate in patients with Barlow's disease was observed in our study in the absence of differences between Barlow's disease and FED patients in medical treatment. As previously reported, angiotensin II receptor blockers modulate extracellular matrix production in myxomatous sporadic MVP,¹⁷ and β_1 -adrenergic receptor blockade improves left ventricular function in chronic, isolated, degenerative mitral regurgitation.¹⁸ Also, according to the case reports, patients in both groups had a similar period between the recognition of severe mitral regurgitation and surgery, and reported the same duration of the symptoms, although patients with Barlow's disease commonly have a long history of cardiac murmur.³ Regression analysis, likewise, has not revealed an influence of duration of the mitral regurgitation or symptoms on longitudinal systolic strain. To eliminate the influence of comorbidities on left ventricular function impairment, we excluded patients with coronary artery disease according to results of the preoperative coronary angiogram. Accompanying disorders such as hypertension and diabetes mellitus were equally prevalent in both groups. Patients with Barlow's disease were significantly younger, but this, actually, results in the increase of the longitudinal strain.¹²

We have suggested that the greater reduction of left ventricular function detected by STE in patients with myxomatous Barlow's disease may be explained by damage of the intramyocardial extracellular matrix. In our study, myxomatous degeneration in the patients of the Barlow's disease group was proved with gross and histologic examination of the surgically excised valve tissue. Some previous pathology studies provided evidence for intramyocardial extracellular matrix changes in patients with MVP and concluded that derangement of valvular tissue in MVP is but one specific reflection of a more general myxomatous alteration in cardiac connective tissue.^{19,20} Function of the myocardium, herewith, is highly dependent on the cardiac extracellular matrix.²¹ In some inherited connective tissue disorders with extracellular matrix damage and involvement of the cardiovascular system (Marfan, Loeys–Dietz syndromes), the

primary impairment of the left ventricular systolic function, which does not depend on aortic or mitral regurgitation, has also been reported.^{15,22}

We revealed in the Barlow's disease group larger aortic diameter and higher prevalence of aortic valve prolapse, which have been described in previous studies for patients with MVP^{23,24} and also associated with damage of the extracellular matrix.^{25,26} Of interest was our observation that the longitudinal systolic strain correlates with aortic root size in Barlow's disease group, which may result from the same defect in structure of the extracellular matrix. Alpéndurada *et al.*²⁷ have shown that Marfan syndrome patients with reduced left ventricular ejection fraction (LVEF) had a significantly larger aortic annulus and ascending aorta, and a trend for a larger aortic sinus in the absence of significant valvular regurgitation.

Lower preoperative left ventricular systolic function in patients with Barlow's disease may affect their postoperative medium and long-term survival, because recently it has been shown that the low longitudinal myocardial deformation is useful for predicting the deterioration of the LVEF following surgery in patients with chronic severe mitral regurgitation.^{9,28}

Study limitations

It should be noted that in our study, only the resected valvular segment was examined. The lesions in the prolapsed resected area may be similar in Barlow's disease and FED. There were a greater proportion of men than women in both groups, and this difference could affect the magnitude of myocardial deformation indexes, which are normally higher in women. Also we did not follow up after correction of mitral regurgitation, which would confirm the impact of low preoperative longitudinal myocardial deformation on postoperative medium and long-term prognosis.

In conclusion, patients with Barlow's disease have a lower preoperative left ventricular systolic and diastolic function than those with FED. Although our results indicate a link between Barlow's disease and myocardial dysfunction, histological evidence supporting the underlying pathogenetic pathways of myocardial dysfunction in Barlow's disease needs to be investigated in depth.

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