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Effects of Mitral Valve Surgery on Ventricular Arrhythmia in Mitral Valve Prolapse Patients: Five-Year Eollow-up

Aim	To evaluate the effect of mitral valve (MV) repair and replacement on the incidence of ventricular arrhythmias (VA) and to identify risk factors for the persistence of VA in patients with MV prolapse and severe mitral regurgitation (MR) during a mid-term follow-up.
Material and methods	A single-site observational, prospective study successively enrolled 30 patients (mean age, 55.2±9.9 years, 60% men) who underwent MV repair or replacement for severe MR due to MV prolapse or chordal avulsion. Transthoracic echocardiography and Holter monitoring were performed in all patients before and annually after surgery. A pathomorphological study of MV fragments excised during surgery was performed.
Results	During the five-year follow-up period (144 person-years), one case of sudden cardiac death outside a health care facility was recorded. MR severity progressed in three patients after MV repair. The total number of all VAs decreased during the follow-up period, with a significant decrease in the number of paroxysms of unstable ventricular tachycardia during the first two years after surgery. The presence of VA in the postoperative period was correlated with the severity of postoperative left ventricular (LV) remodeling: end-diastolic volume (EDV) (rs=0.69; p=0.005), LV ejection fraction (EF) (rs = –0.55; p=0.004) and severity of MV myxomatous alterations according to histological study data (rτ=0.58; p=0.045). The beta-blocker treatment did not influence the VA frequency and severity (rs= –0.18; p=0.69). According to a univariate regression analysis only EDV (p = 0.001), LVEF <50% (p = 0.003), and myxomatous MV degeneration (p = 0.02) were risk factors for persistent ventricular tachycardia in the postoperative period.
Conclusion	Surgical intervention on MV in patients with MV prolapse and severe MR decreased the number of cases of malignant VAs and was correlated with the postoperative changes in LV volume and function, as well as the severity of MV myxomatous alterations.

Keywords	Ventricular arrhythmias; mitral valve prolapse; mitral regurgitation; mitral valve repair; mitral valve replacement; myxomatous changes in the mitral valve
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Introduction

Mitral valve prolapse (MVP) is one of the most prevalent types of heart valve disease [1]. Two pathomorphological forms of MVP are distinguished: myxomatous MVP (Barlow's disease) with pronounced abnormalities in the mitral valve (MV) leaflets and annulus and non-mixomatous MVP without thickening of the MV leaflets and dilatation of the mitral annulus (fibroelastin deficiency) [2]. Most patients with MVP without thickening of the MV leaflets can be considered to be at low risk and have a favorable prognosis, their annual mortality is not higher than 0.1% [3]. However, patients with myxomatous MVP are significantly more likely to have ventricular arrhythmia and sudden cardiac death (SCD) [4, 5]. The prevalence of myxomatous MVP in young people with SCD, according to the literature, ranges from 4% to 7% and reaches 13% in the female subgroup [6]. The ten-year probability of SCD reaches 20% in patients with MVP complicated by severe mitral valve insufficiency (MVI) who did not have surgery [7].

Areas of myocardial fibrosis in the heads of papillary muscles and the basal segment of the left ventricular (LV) posterior wall, and the mitral annular disjunction are described as arrhythmogenic substrates (Figure 1) [8, 9]. Fibrosis develops in the heads of the papillary muscles due to chord overstretching when the leaflets prolapse, and the posterior annular disjunction and LV basal posterior wall fibrosis is due to the pathological mobility of the mitral annulus associated with the myxomatous changes [10, 11].

Isolated observations reported in recent years the positive effect of MV repair on the incidence of malignant

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ventricular arrhythmias (VAs) due to the elimination of the described pathological mechanisms [12–14]. However, not enough data is available in the literature on long-term follow-up of operated patients with MVP and VAs with the estimation of primary endpoints (cardiovascular morbidity and mortality, all-cause hospitalizations) and secondary endpoints (changes in the dimensions and volumes of the heart chambers, progression of recurrent MVI and VAs).

Objective

Evaluate the effect of MV repair and replacement on the prevalence of VAs and identify risk factors (RFs) of their persistence in patients with MVP and severe mitral regurgitation (MR) during middle-term follow-up.

Material and Methods

A single-center observational longitudinal cohort study consecutively included 30 patients (mean age 55.2 ± 9.9 years, 60% of males) who underwent MV repair or replacement for severe MR due to myxomatous prolapse or MV chordal rupture. Patients with rheumatic MV disease (by pathomorphological study), coronary artery stenosis (by preoperative coronary angiography) were excluded from the study. Patient characteristics, preoperative drug therapy, and MV morphology, and the types of surgical intervention are provided in Table 1.

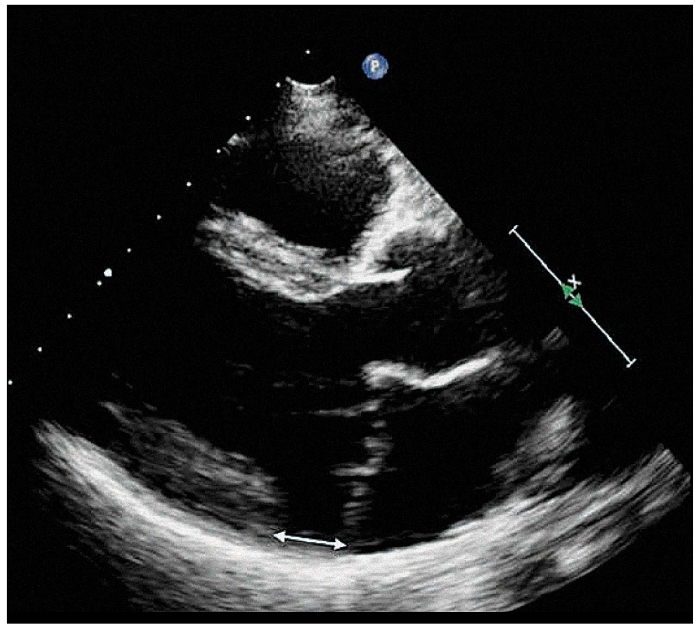
The majority of patients were middle-aged (which is typical for myxomatous MVP); coronary artery disease (which could affect the frequency of SCD and LV contractility) was excluded by coronary angiography; the prevalence of comorbidities (chronic obstructive pulmonary disease, diabetes mellitus) was low with the exception of arterial hypertension (AH).

Indications for surgical treatment were determined according to the AHA/ACC guidelines; 73% of patients had chronic heart failure (HF) of NYHA class III–IV, a smaller part (27%) had signs of LV dysfunction (left ventricular ejection fraction (LVEF) less than 60% or LV end-systolic dimension more than 40 mm) [15]. MV repair (quadri- or triangular resection of the prolapsing segment, Carpentier repair or suture annuloplasty) was performed in 20 (67%) patients, and 10 (33%) patients underwent MV replacement with preservation of the chordal apparatus.

Hard endpoints were assessed during the five-year prospective follow-up: cardiovascular mortality and morbidity (hospitalizations), repeated surgical interventions on MV. The prevalence of arrhythmias, echocardiographic changes of MR, morphology of mitral leaflets, LV remodeling were also examined.

Pathomorphological examination of the MV leaflets partially or completely resected during the surgery was performed, as well as histological examination of 2 μm thick sections stained with hematoxylin-eosin and resorcinol-fuxin according to the Weigert van Gieson method. The distribution of myxomatosis in all leaflet layers, fragmentation and lysis of collagen and elastic fibers, lysis of the subendothelial elastic membrane were evaluated. Macroscopic signs of Barlow's disease were diffuse or uneven thickening of the leaflets of more than 3 mm, jelly-like consistency, the presence of interchordal hoods, focal or diffuse thickening and gelatinous appearance of chords [16].

Figure 1. Mitral annular disjunction in a patient with myxomatous MVP



The white arrow shows the distance between the mitral annulus and the basal posterior LV wall.
MVP, mitral valve prolapse; LV, left ventricle.

Preoperative and postoperative drug therapy of HF and AH included mainly beta-blockers and angiotensin-converting enzyme inhibitors. Antiarrhythmic therapy (amiodarone) was prescribed to two patients with identified runs of unstable ventricular tachycardia (VT) in the postoperative period.

Transthoracic echocardiography was performed for all patients before and annually after surgery using Vivid 7 with 3.5 MHz matrix phased array transducers. The degree of MR was assessed by the volume of regurgitation and the regurgitation orifice area by proximal isovelocity surface area (PISA). The dimensions and volumes of the heart chambers and LVEF were measured according to the ASE guideline [17]. Longitudinal strain was assessed in three apical sections using speckle tracking following the ASE and EACVI guidelines [18].

24-hour electrocardiogram (ECG) and blood pressure monitoring was carried out using the Cardiotechnica-04 AD complex. 12 ECG leads were monitored for a total of 22–25 hours.

The study was conducted following the Declaration of Helsinki. The study protocol was approved by the ethics committee of the Almazov National Medical Research Centre. All patients signed the informed consent.

The data obtained were analyzed in Statistica 12.0. Quantitative variables were expressed as the means and standard deviations (M ± SD), qualitative variables were presented in the absolute numbers and percentages. The statistical significance of the differences of the quantitative variables was determined using the Student's t-test. The differences in two categorical variables were determined using the chi-squared test. The significance of differences in repeated measurements of quantitative and qualitative variables was assessed using analysis of variance (ANOVA) and Cochran's Q-test, respectively. The linear relationship of the two quantitative variables was estimated using the Pearson correlation coefficient. The Spearman (rs) or Kendall (rτ) rank correlation coefficient was used for the qualitative variables. A univariate linear regression analysis was performed to identify risk factors for VT persistence in the postoperative period as a dependent variable. The differences were statistically significant at $p < 0.05$. Survival analysis was performed, and Kaplan-Meier survival curves were constructed in MedCalc.

Results

One case of out-of-hospital SCD was reported but there was a high rate of all-cause hospitalizations during a five-year follow-up of 144 person-years (Figure 2), although most patients were middle-age, coronary angiography was conducted to exclude coronary artery disease, the prevalence of comorbidities and RFs, except for AH, was low (Table 1).

The changes of VAs detected during the 24-hour ECG monitoring conducted in the preoperative and postoperative periods and annually during the five-year follow-up is presented in Table 2.

The total number of all VAs decreased during the follow-up period without statistically significant differences in isolated and couplet ventricular extrasystoles (VEs), but with a significant decrease in the number of paroxysmal nonsustained VT in the first 2 years after surgery (Figure 3).

Beta-blockers did not affect the prevalence and severity of VAs (rs = –0.18; p = 0.69), amiodarone was prescribed in the postoperative period to patients with unstable VT, which is why this association was not analyzed. Table 3 compares the results of transthoracic echocardiography performed in the preoperative and postoperative period and annually during the five-year follow-up.

Severe MR was corrected during surgery in the majority of patients, only one patient who underwent MV

Figure 2. Cardiovascular mortality and all-cause hospitalization rates within the five-year follow-up presented as Kaplan-Meier curves

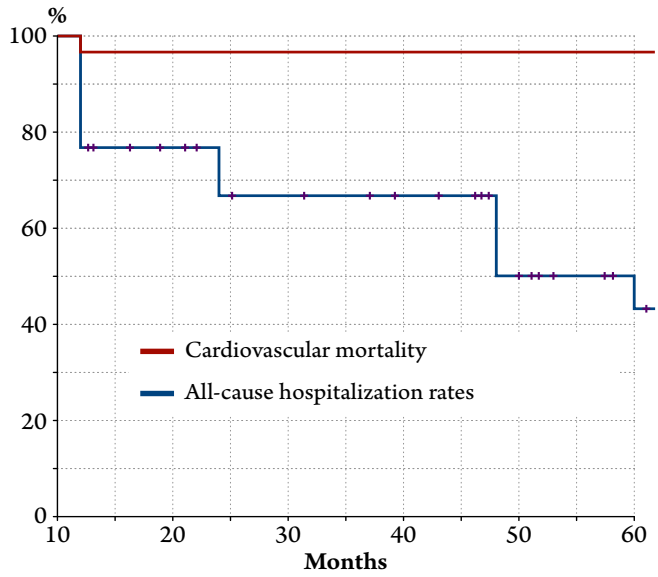


Table 1. Characteristics of the examined patients (n = 30)

Parameter	Value
Age, years	55.2 ± 9.9
Sex, male/female, n	18 / 12
Body mass index, kg/m²	25.8 ± 6.1
Arterial hypertension, n (%)	16 (55)
Chronic obstructive pulmonary disease, n (%)	2 (7)
Diabetes mellitus, n (%)	2 (7)
Smoking, n (%)	5 (17)
Chronic heart failure (before surgery):	
• NYHA class I-II, n (%)	8 (27)
• NYHA class III, n (%)	22 (73)
Mitral annular diameter, cm	37.9 ± 3.2
Mitral annular disjunction, mm	19 (63)
MV pathomorphology:	
• Myxomatous degeneration, n (%)	21 (70)
• Leaflet thinning, n (%)	9 (30)
MV replacement, n (%)	10 (33)
MV repair:	
• by Carpentier, n (%)	12 (40)
• Suture annuloplasty, n (%)	8 (27)
Preoperative therapy:	
• Beta blockers, n (%)	16 (55)
• ACE inhibitors, n (%)	26 (87)
Postoperative therapy:	
• Amiodarone, n (%)	2 (7)
• Beta blockers, n (%)	23 (77)
• ACE inhibitors, n (%)	19 (63)

The data are expressed as the means and standard deviations (M ± SD), if not otherwise specified. NYHA, New York Heart Association; MV, mitral valve; ACE, angiotensin-converting enzyme.

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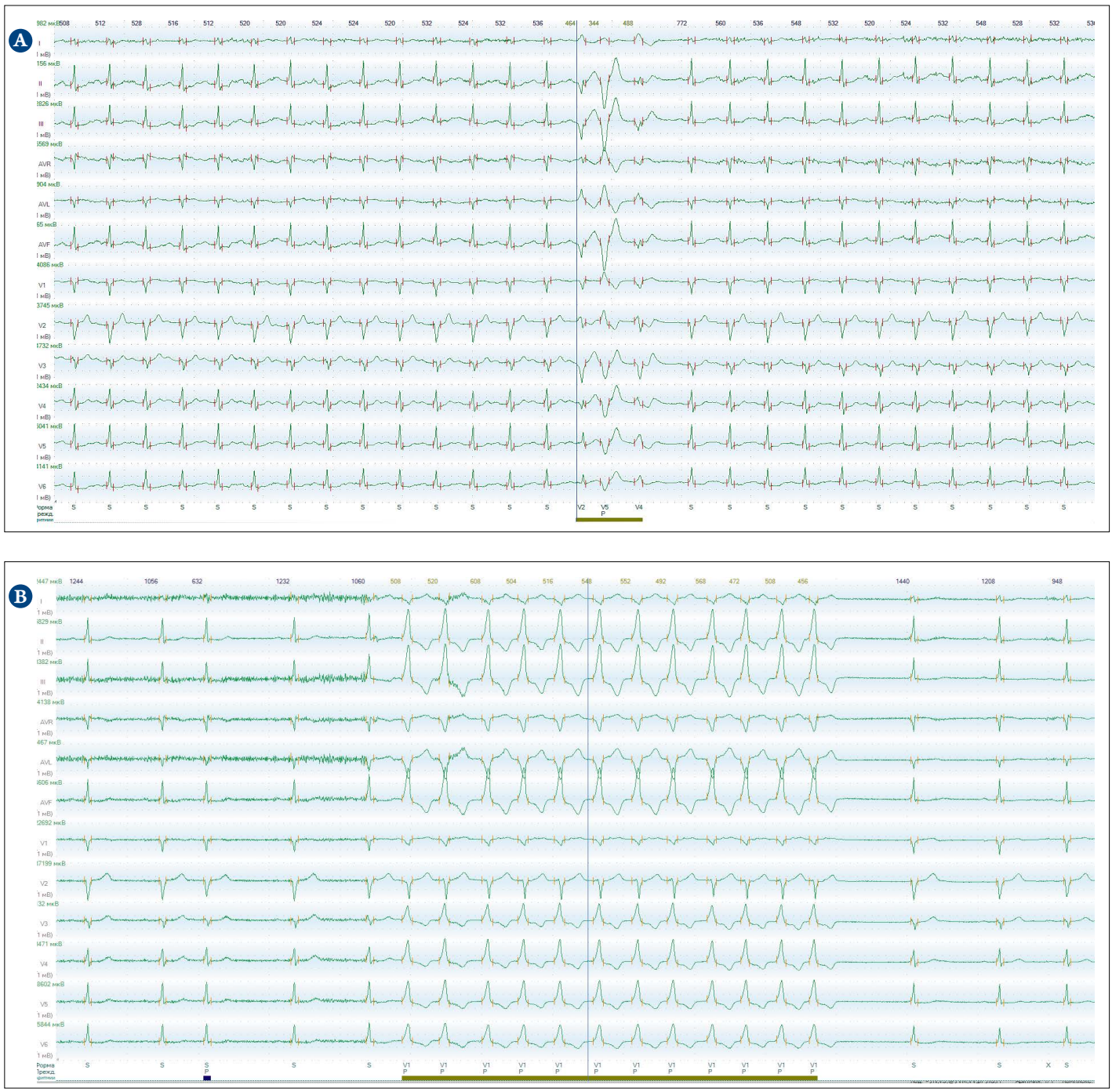
Table 2. Changes in ventricular arrhythmias in the examined patients in the follow-up period (24-hour ECG monitoring)

Parameter	Before surgery	After surgery	Follow-up year 1	Follow-up year 2	Follow-up year 3	Follow-up year 4	Follow-up year 5	p*
Isolated ventricular extrasystoles, n (%)	25 (83)	24 (80)	21 (70)	23 (77)	24 (80)	24 (80)	25 (83)	Q = 1.25 p = 0.97
Couplet ventricular extrasystoles, n (%)	12 (40)	11 (37)	8 (27)	11 (37)	9 (30)	8 (27)	7 (23)	Q = 4.5 p = 0.61
Nonsustained paroxysmal ventricular tachycardia, n (%)	4 (13)	2 (7)	0	0	2 (7)	0	1 (3)	Q = 20.3 p = 0.002

ECG, electrocardiogram. * Cochrane Q-test.

Figure 3. Examples of VAs shown by Holter monitoring in the postoperative period (follow-up year 3)



A – paroxysmal event of unstable polymorphic ventricular tachycardia;
B – paroxysm event of unstable monomorphic ventricular tachycardia. VAs, ventricular arrhythmias.

Table 3. Changes in the main echocardiographic parameters during the follow-up period

Parameter	Before surgery	After surgery	Follow-up year 1	Follow-up year 2	Follow-up year 3	Follow-up year 4	Follow-up year 5	p*
LV end-diastolic dimension, mm	66.3 ± 7.9	59.4 ± 7.3	54.8 ± 7.6	55.6 ± 5.9	54.7 ± 6.3	54.5 ± 6.6	57.3 ± 8.1	F = 11.3 p < 0.00001
LV end-diastolic volume, ml	156.6 ± 32.1	104.1 ± 22.8	109.7 ± 26.9	103.5 ± 28.3	108.3 ± 29.5	107.1 ± 22.0	106.1 ± 27.3	F = 13.5 p < 0.00001
LVEF, %	65.3 ± 9.7	55.8 ± 10.8	60.6 ± 8	63.3 ± 8.1	62.4 ± 7.8	61.3 ± 10.3	58.7 ± 10.5	F = 4.85 p = 0.00016
LV global longitudinal strain, %	-13.8 ± 2.5	-14.0 ± 3.1	-14.6 ± 2.7	-15.5 ± 4.9	-14.3 ± 3.5	-15.0 ± 4.7	-14.6 ± 3.9	F = 3.52 p = 0.0009
LV mass, g	351.9 ± 131	294.1 ± 66.1	263.2 ± 88.7	278.8 ± 78.4	272.4 ± 63.3	271.5 ± 64.6	271.3 ± 112	F = 14.1 p < 0.00001
Mitral regurgitation, moderate-to-severe, n (%)	30 (100)	1 (3)	1 (3)	1 (3)	1 (3)	3 (10)	3 (10)	Q** = 10.0 p < 0.00001

* ANOVA of repeated measurements; ** Cochrane Q-test.

repair had moderate MR immediately after surgery. The severity of MR progressed during the five-year follow-up after MV repair: moderate MR was detected in 3 patients by the fourth year, and by the fifth year, one patient had severe MR, which required repeated surgery-MV replacement. A positive association of postoperative VAs was observed with the degree of recurrent MR (rs = 0.76; p = 0.0018).

After the MV intervention, a significant decrease in the LV diastolic size and volume was observed. The presence of VAs in the postoperative period was positively associated with the severity of postoperative LV remodeling-left ventricular end-diastolic dimension (LVEDD; rs = 0.69; p = 0.005) and LV posterior wall thickness (rs = 0.62; p = 0.019).

LVEF decreased after surgery (from 65.3 ± 9.7% to 55.8 ± 10.8%; p = 0.002) and increased during the five-year follow-up period. The global longitudinal strain was –13.8 ± 2.5% before surgery and –14.6 ± 2.7% after surgery. The LV contractile function was correlated in the postoperative period with the persistence of VAs, greater severity of which was associated with worse LV contractility (rs = –0.55; p = 0.004).

Morphological examination of the MV leaflets, partially or completely resected during the surgery, was performed for the differential diagnosis of Barlow's disease

Central illustration. Effects of Mitral Valve Surgery on Ventricular Arrhythmia in Mitral Valve Prolapse Patients: Five-Year Eollow-up

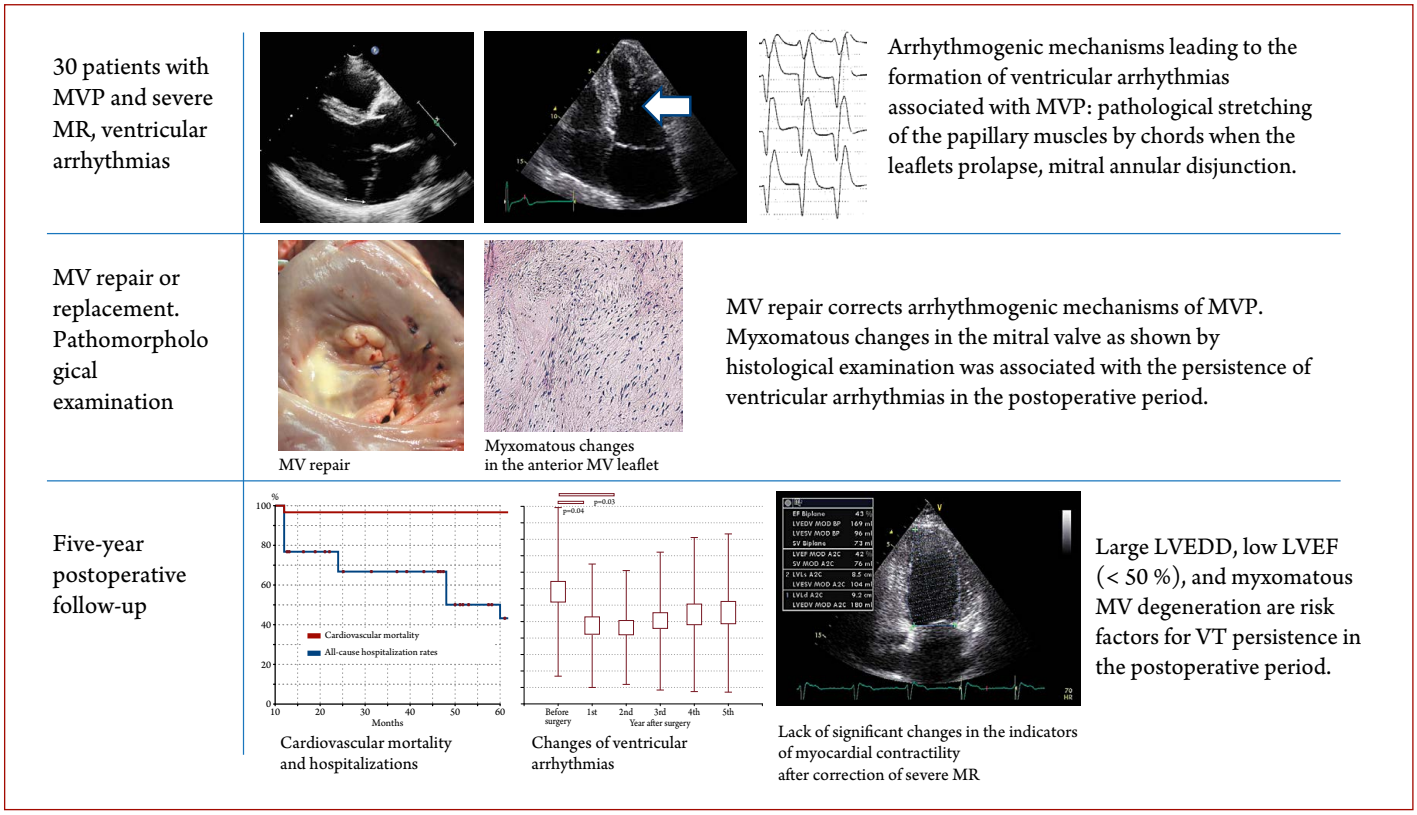


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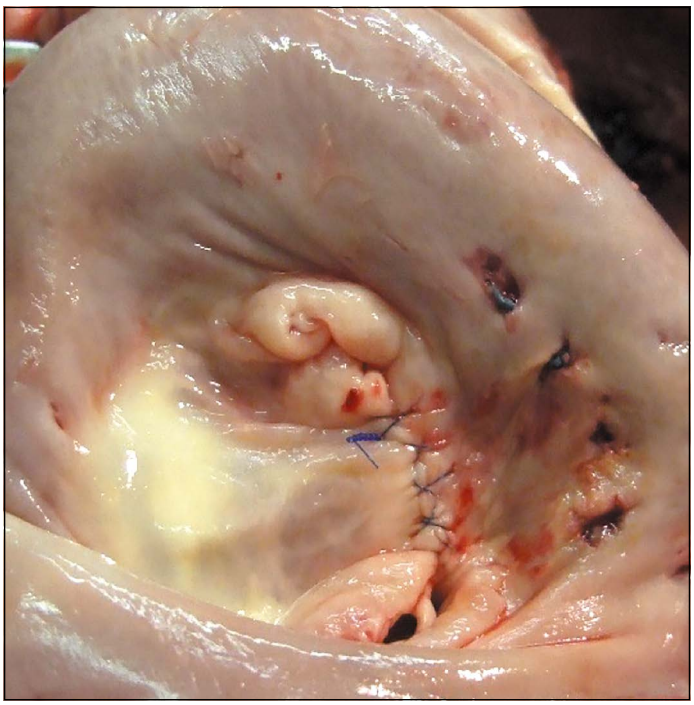
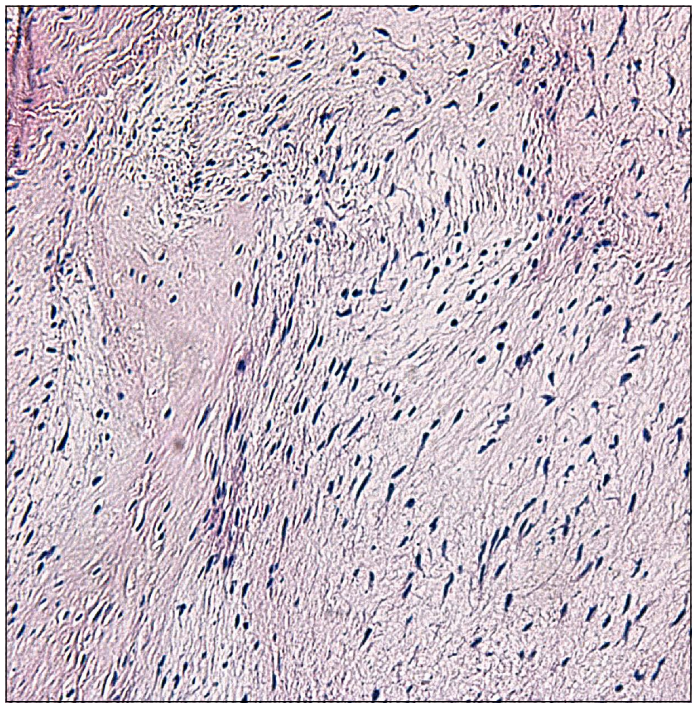
Figure 4. MV repair in fibroelastic deficiency



Enlarged and thinned MV leaflet. MV, mitral valve.

Figure 5. Anterior MV leaflet with myxomatous changes spread to all layers and lysis of the subendothelial elastic membrane



Hematoxylin-eosin staining, x 200. MV, mitral valve.

(myxomatous degeneration-diffuse or uneven thickening of the leaflets, jelly-like consistency) and fibroelastic deficiency (without signs of myxomatous degeneration-the leaflets are thinned; Figure 4).

21 (70%) of the patients had signs of myxomatous degeneration of the MV leaflets typical for Barlow's disease (Figure 5), the rest of the patients had signs of fibroelastic deficiency.

Myxomatous changes by histological examination was associated with the persistence of VAs in the postoperative period ($r\tau = 0.58$; $p = 0.045$).

According to the univariate linear regression analysis, only LVEDD, LVEF < 50%, and myxomatous degeneration of the MV leaflets are RFs for VT persistence in the postoperative period (Table 4).

Discussion

Our study included patients with MVP complicated by severe MR, who are at greatest risk of SCD associated with VAs. The high incidence of cardiovascular complications detected in our study is common for such patients both before and after surgical intervention [7]. VAs make a significant contribution to this high frequency of complications [19]. Surgical treatment is the only method of resolving severe MR associated with MVP. The MV repair and replacement technique also corrects many arrhythmogenic mechanisms leading to the development of ventricular arrhythmias in patients with mitral valve prolapse, such as pathological tension of the papillary muscles by chordae during leaflet prolapse and mitral annulus disjunction [12, 20].

Our study showed a significant decrease in the number of VT after MR correction. This is the first prospective study to demonstrate the effect of MV repair/replacement on the incidence of malignant VAs. Similar results have been previously described only in isolated clinical cases [12–14].

We analyzed the impact of left ventricular volume overload elimination on systolic function and reverse left ventricular remodeling, and their influence on the persistence of ventricular arrhythmias after mitral valve prolapse correction. A decrease in the LV diastolic dimension and volume is expected when the LV volume overload is resolved. LVEF decreased after surgery due to a reduced regurgitation component in the LV ejection (from 65.3 ± 9.7% to 55.8 ± 10.8%; $p = 0.002$), which is consistent with the literature data [21]. The absence of an increase in LV myocardial strain after the correction of severe MR, which was shown in our study, does not contradict the results of previous studies, which demonstrated a worsening of LV myocardial strain during long-term follow-up [22] due to LV myocardial fibrosis [23], which is a strong predictor of all-cause mortality and cardiovascular complications [24]. The relationship of malignant VAs with the severity of postoperative LV remodeling and worse LV contractility may indicate that

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Table 4. Results of the univariate linear regression analysis

Parameter	Coefficient β	95 % CI	p
LV end-diastolic dimension	0.31	1.37 (0.66–2.04)	0.001
LVEF< 50 %	-0.20	1.76 (0.46–2.34)	0.003
Myxomatous degeneration of the mitral valve leaflets	0.17	1.28 (0.23–2.61)	0.008

CI, confidence interval.

fibrotic changes in the myocardium are an independent proarrhythmogenic factor that does not depend on the correction of arrhythmogenic mechanisms associated with impaired MV structure and function.

The relationship of myxomatous changes in MV by the histological examination with the presence of VAs established in our study has been detected earlier. In the review by Han et al. [25] MV leaflet redundancy was the only predictor of SCD in patients with MVP. At the same time, in a retrospective study by Sriram et al. [26], a triad of SCD associated with MVP was identified, which included myxomatous prolapse of both MV leaflets, VAs, and repolarization abnormalities.

Drug therapy is insufficiently effective to prevent SCD in patients with MVP. According to Hong-TaoYuan et al. [27], antiarrhythmic drugs cause a borderline decrease in the number of VEs, however, amiodarone did not prevent SCD of one of two patients with nonsustained VT in our study.

Beta-blockers are often used in patients with MVP and ventricular arrhythmias. In the study by Basso et al. [28], 21% of young patients with MVP received beta-blockers when SCD occurred, which questions their efficacy. The absence of a clinically significant effect of beta-blocker therapy on VA correction in patients with MVP was also demonstrated by Hong-TaoYuan et al. [27], which was probably due to organic changes in the LV myocardium without a significant contribution from sympathetic tone. Similarly, we did not reveal the effect of beta-blockers on the incidence and severity of VAs, but worse LV contractility was associated with the persistence of VAs in the postoperative period. The correction of severe MR before the onset of LV dysfunction is likely to contribute to a lesser severity of ventricular arrhythmias after surgery-Enriquez-Sarano et al. [29] demonstrated a better long-term prognosis for patients with early correction of severe MR.

Conclusion

This study revealed a decrease in the number of malignant ventricular arrhythmias after surgical correction of some arrhythmogenic mechanisms associated with altered morphology and mechanics of the MVP. However, during mid-term follow-up, a high frequency of cardiovascular complications was observed. The risk factors for the persistence of ventricular arrhythmias were determined, including worse left ventricular contractility, greater severity of postoperative left ventricular remodeling, baseline myxomatous changes in the mitral valve.

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No conflict of interest is reported.

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