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Echocardiographic estimates of left ventricle remodeling in mitral regurgitation according to the type of surgical correction: mitral valve repair or replacement

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Ehokardiografska procena remodelovanja leve komore kod mitralne regurgitacije u odnosu na tip hirurške korekcije: reparacije ili zamene mitralne valvule

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Echocardiographic estimates of left ventricle remodeling in mitral regurgitation according to the type of surgical correction: mitral valve repair or replacement

Pathophysiology of chronic primary mitral regurgitation (MR) is mostly based on a degenerative process. Inadequate adaptation of the left ventricle (LV) due to volume loading leads to gradual dilatation and weakness. The only complete therapeutic option in this case is surgical intervention. This study was aimed at evaluating early echocardiographic parameters of LV remodeling in chronic primary MR between two types of operative correction, a mechanical mitral valve replacement (MVR) and mitral valve prosthetic ring annuloplasty (MVA). Using 2D and M mode echocardiography a number of variables were measured or calculated. In addition, the variables are assessed according to early postoperative LV dysfunction (LVD) (ejection fraction (EF) < 50%). Thirty-six asymptomatic patients with primary severe MR (grade 3-4) undergoing surgical correction were included. The LV end-diastolic diameter improved significantly (6.11 ± 0.9 vs. 5.50 ± 0.7 cm) in both groups ($p < 0.006$) after interventions, while there were no significant differences in LV volumes between the groups. Immediate postoperative LV systolic dysfunction showed similar incidence in the groups (43%). A significant distinction between the groups was revealed in patients without LVD, that is a higher preoperative forward LVEF in MVA compared to MVR patients. Interestingly, an opposite direction of forward LVEF change was seen in LVD between the groups. We can conclude that there are subtle differences in early postoperative echocardiographic parameters between the MVA and MVR procedures reflecting subtle specificities of early LV remodeling in patients with chronic primary MR.

Key words: annuloplasty, end-diastolic diameter, ejection fraction, left ventricular dysfunction, end-systolic volume

Ehokardiografska procena remodelovanja leve komore kod mitralne regurgitacije u odnosu na tip hirurške korekcije: reparacije ili zamene mitralne valvule

Patofiziologija hronične primarne mitralne regurgitacije (MR) uglavnom se zasniva na degenerativnom procesu. Neadekvatna adaptacija leve komore (LV) usled zapreminskog opterećenja dovodi do postepene dilatacije i slabosti. Jedina potpuna terapijska opcija u ovom slučaju je hirurška intervencija. Ovo istraživanje je imalo za cilj procenu ranih ehokardiografskih parametara remodeliranja LV u hroničnoj primarnoj MR između dve vrste operativne korekcije, mehaničke zamene mitralne valvule (MVR) i anuloplastike mitralnog zalistka protetskim prstenom (MVA). Ehokardiografske varijable su izmerene ili izračunate korišćenjem 2D i M tehnike. Pored toga, varijable su procenjene u odnosu na ranu postoperativnu disfunkciju LV (LVD) (ejekciona frakcija (EF) < 50%). Uključeno je 36 asimptomatskih pacijenata sa primarnim teškim MR (stepen 3-4) koji su podvrgnuti hirurškoj korekciji zalistaka. Krajnji dijastolni prečnik LV se značajno poboljšao ($6,11 \pm 0,9$ vs. $5,50 \pm 0,7$ cm) u obe grupe ($p < 0,006$) nakon intervencija, dok nije bilo značajnih razlika u zapreminama LV između grupa. Neposredna postoperativna sistolna disfunkcija LV pokazala je sličnu incidenciju u grupama (43%). Značajna razlika između grupa je utvrđena kod pacijenata bez LVD, odnosno veća preoperativna prednja LVEF u MVA u odnosu na pacijente sa MVR. Nasuprot tome, kod pacijenata sa LVD postojao je suprotan smer promene prednje LVEF-a. Možemo zaključiti da postoje suptilne razlike u ranim postoperativnim ehokardiografskim parametrima između MVA i MVR procedura koje odražavaju suptilne specifičnosti ranog remodelovanja LV kod pacijenata sa hroničnom primarnom MR.

Ključne reči: anuloplastika, end-dijastolni dijametar, ejakciona frakcija, disfunkcija leve komore, end-sistolni volumen

Introduction

Mitral regurgitation (MR) is the second most common valvular lesion, with its prevalence rising with age. Considering an increase of population aging, MR prevalence is likely to increase further (1-4). Mitral regurgitation develops due to a failure of mitral leaflets during left ventricular (LV) contraction. It can be classified as primary, related to valve abnormalities, or secondary, due to distortion of LV shape. According to the disease course MR can present as an acute or chronic disorder. The etiology of chronic secondary MR is either ischemic or non-ischaemic, resulting in annular dilatation and the papillary muscles displacement causing mitral valve failure (3-5).

Primary MR is considered a degenerative disease in about two-thirds of all cases, without defined causative factors. Nevertheless, long-term exposure to elevated blood pressure is observed to predispose to a substantial share in these patients. Specifically, each 20 mmHg increment in systolic blood pressure was associated with a 26% higher risk of MR. Similar associations are reported for each 10 mmHg increase in diastolic blood pressure. The effects were mediated directly and secondary to high BP complications (4).

During insidious development of chronic primary MR, there is progressive LV dysfunction and a reactive remodelling in an attempt to provide an adequate forward stroke volume (SV). Initial hemodynamic changes, such as increase in left atrial (LA) volume, reduction in forward SV, and rise in LV preload, further respond by eccentric hypertrophy. The compensation attempt implies the increase in wall thickness and increased LV filling, that normalizes forward SV. However, this is found insufficient to fully compensate for the wall stress (3).

The inadequate hypertrophy is supposed to occur partly because volume overload in MR does not trigger substantial increases in the rate of protein synthesis. Instead, the early wall thickening is due to a decrease in the rate of protein degradation (6). Other mechanisms include altered cytoskeletal changes, increase in reactive oxygen species, change in matrix metalloproteinase expression and activation, initiation of inflammatory and apoptotic pathways, and other. Ensuing disruption of the myocardial extracellular matrix architecture results in sliding displacement of cardiomyocytes and cell death. Adversely remodelled and dilated LV progresses to the decompensated MR with a thin myocardial wall and increase in wall stress (3, 7, 8).

Therefore, surgical repair or mitral valve replacement (MVR) is currently the recommended therapy for severe primary MR, in patients who are surgical candidates. Without proper treatment, severe mitral valve regurgitation can cause abnormal cardiac rhythm and inevitably leads to heart failure (3, 4).

This study was aimed at evaluating the first week's echocardiographic parameters of LV remodeling between two types of operative correction in patients with chronic primary MR: a mechanical mitral valve replacement (MVR) and mitral valve prosthetic ring annuloplasty (MVA).

Methods

We conducted a prospective study that included 36 consecutive patients diagnosed as having grade 3-4 MR according to the 2020 the American College of Cardiology/American Heart Association (ACC/AHA) guideline for the management of patients with valvular heart disease and using appropriate validated techniques (1, 9, 10). The patients were recruited at the Clinic for Cardiac Surgery, University Clinical Center of Serbia, (University of Belgrade, Serbia), between years 2019-2021.

Inclusion criteria comprised: asymptomatic patients with primary severe MR, of non ischemic and non rheumatic causes, with a routine transthoracic echocardiography performed with quantification of MR. Excluded patients were those with ischemic cardiomyopathy, acute cardiac events, those who underwent bypass surgery, a percutaneous angioplasty, or had an aortic valve disease, mitral stenosis or other heart diseases.

Criteria for quantitative gradation of severe primary MR (grade 4), based on 2D echocardiography, included: effective regurgitant orifice area (EROA) (2D proximal isovelocity surface area (PISA), mm²) of ≥ 40 mm², regurgitant volume (mL/beat) of ≥ 60 mL, and regurgitant fraction (%) $\geq 50\%$ (1, 9).

Patient-centred and integrative approach to evaluation of a specific lesion causative of MR was applied in accordance to current guidelines. The approach provides prognostic implications and is of vital importance for assessing possibilities of surgical or transcatheter valve repair (1, 10).

Patients were divided in two age-matched groups of those who underwent a MVR with a mechanical prosthesis and those with restrictive prosthetic ring annuloplasty (downsizing of 2.7 +/- 0.8 ring sizes). As per guidelines, MVR is commonly performed in patients with severe MV disease unsuitable for surgical repair (11).

All patients were routinely assessed by transthoracic echocardiography before and three to four days after the surgical procedure (early follow-up). The obtained echocardiographic parameters were compared between these two periods and between the groups (MVA vs. MVR).

Using 2D and M mode echocardiography a number of variables were measured or calculated (through the Teicholz method), including: dimensions (end-diastolic (EDD), end-systolic (ESD)) and volumes of the LV (EDV, ESV, SV), thickness of myocardial wall and septum in diastole. Ejection fraction (EF%) and shortening fraction (FS%) were also evaluated, as well as derived measures of forward LVEF ($100 \times \text{forward stroke volume} / \text{LV EDV}$), right ventricle systolic pressure (RVSP) and left ventricle wall stress (WS).

We further assessed differences in echocardiographic parameters in relation to an early postoperative LV dysfunction, which is defined as LV EF < 50% after mitral valve surgery.

Statistical analysis

Results are expressed as mean \pm standard deviation (SD) or median \pm interquartile range (IQR), or percentages, as required. The Wilcoxon signed-rank test, Mann-Whitney U test or independent / paired t-tests were used, based on the normality distribution of data (assessed by Shapiro-Wilk test). Pearson correlation coefficient test was also used. A significance threshold was set at $p < 0.05$. Statistical analysis was carried out using SPSS 25.0 software (SPSS Inc, Chicago, IL, USA).

Results

Out of 36 patients included in the study, 21 (58.3%) underwent MVA, while 15 (41.7%) had MVR intervention. There was 28 (77.8%) males and 8 (22.2%) females, median years of age 66.5 ± 12 . Demographic data and risk factors were comparable between the groups. Baseline characteristics of the patients are shown in table 1. There was no significant difference in the type of procedure according to gender or body mass index (BMI). All patients recovered in the postoperative period. Mitral regurgitation grades at discharge were 1.18 ± 0.34 (mean \pm SD).

Table 1. Baseline characteristics of the patients (total)	
Gender (male), n (%)	28 (77.8%)
BMI (kg/m ²)	26.72 ± 3.18
MR duration (months)	12 ± 11
TA systolic (mmHg)	131.28 ± 15.895
TA diastolic (mmHg)	80.0 ± 18.0
Hypertension arterial, n	26 (72.2%)
Atrial fibrillation, n	21 (58.3%)
Type 2 diabetes mellitus, n	7 (19.4%)
Cigarette smoking, n	11 (30.6%)
BMI – body mass index, MR – mitral regurgitation, TA – tension arterialis.	

Early echocardiographic parameters of LV remodeling

There was a significant difference in EF% before and after the MR surgery (57.53±12.32 vs. 49.78±10.46, p=0.000; r=0.537), as well as in FS% (36.27±7.23 vs. 30.73±4.71, p=0.045; r=0.668), but without significant difference between the type of surgical correction.

Forward LVEF values were significantly higher after the procedure (32.67±10.97 vs. 43.49±16.77, p=0.005), but again, similar according to the type of procedure. The postoperative forward LVEF positively correlated with RVSP (r=0.541, p=0.025).

End-diastolic diameter of the LV improved significantly (6.11±0.9 vs. 5.50±0.7) in both groups (MVA p=0.000, MVR p=0.006) (r=0.654, p=0.000) after interventions, while ESD measurements remained mostly unaffected (3.85±1.0 vs. 3.95±0.9; p>0.05) (r=0.754, p=0.000). There were no differences in the LV dimensions between the groups in this early period. Similarly, left atrial (LA) diameters decreased postoperatively in both groups (5.30±1.33 vs. 4.60±0.88, p=0.02).

We determined a significant difference in the median between EDV, before and after the MR correction (190.46±59.12 vs. 147.4±40.14 ml, p=0.000) (r=0.701 p=0.000), but not for end-systolic volumes (67.96±45.58 vs. 67.95±34.21 ml, p>0.05) (r=0.805, p=0.000).

Similar findings were obtained for mean level of SV before and after the surgery (115.95 ± 34.92 vs. 77.62 ± 24.53 ml, $p=0.000$) in both groups ($p < 0.003$), but without correlation. There were no distinct differences in EDV, ESV nor SV according to the type of MR surgery.

Right ventricular systolic pressure was elevated (≥ 30 mmHg) before (48.9 ± 15.0 vs. 49.6 ± 13.5 mmHg) and after (37.7 ± 8.8 vs. 42.3 ± 9.6 mmHg) the interventions in MVA and MVR group respectively, but without significant difference between the two periods nor between the groups. Also, the LV WS remained almost the same in the two periods (116.54 ± 0.65 vs. 116.16 ± 14.92 kdynes/cm², $p > 0.05$).

After the treatment, the mitral velocity propagation (V_p) recordings were different between the groups, with higher velocity in MVR (1.400 ± 0.345 vs. 1.681 ± 0.259 m/s, $p=0.015$), which was related to characteristics of mechanic valves.

Comparison according to postoperative LV systolic dysfunction (LVD)

Out of 36 patients, 8 (22.2%) had EF% lower than 50% prior to the mitral correction and therefore were excluded from analysis of postoperative LVD. Twelve out of 28 patients (42.9%) with adequate preoperative EF developed early LVD, half of them had underwent MVA (6/15) and another half had MVR procedure (6/7) ($p > 0.05$). There was no significant difference in the number of subjects that developed LVD depending on the type of MR correction.

In total, patients with higher preoperative EDD showed a tendency to develop LVD (6.39 ± 0.77 vs. 5.95 ± 0.40 , $p=0.06$), but without group difference. Postoperative EDD was also higher in those with LDV (5.45 ± 0.56 vs. 5.38 ± 0.39 , $p > 0.05$).

A significantly higher preoperative EDD was determined in MVA patients who progressed to LVD (6.50 ± 0.27 vs. 6.01 ± 0.46 , $p=0.038$), as well as in the measurements of postoperative ESD (4.26 ± 0.43 vs. 3.73 ± 0.38 , $p=0.035$). In MVR group, there was a tendency of higher preoperative ESD values and higher postoperative EDV in those who developed LVD (Table 2).

Table 2. Echocardiographic parameters according to the early postoperative left ventricular

dysfunction (LVD) and the type of operative procedure				
		LVD	Non-LVD	P value
EDD preop. (cm)	1	6.50±0.27	6.01±0.46	p=0.038
	2	6.28±1.10	5.87±0.32	ns
EDD post. (cm)	1	5.63±0.26	5.47±0.35	ns
	2	5.22±0.78	5.27±0.44	ns
ESD preop. (cm)	1	4.23±0.39	3.87±0.47	ns
	2	4.13±0.68	3.51±0.48	p=0.080
ESD post. (cm)	1	4.26±0.43	3.73±0.38	p=0.035
	2	3.90±0.62	3.53±0.37	ns
EDV preop. (ml)	1	216.28±77.85	185.11±31.40	ns
	2	207.40±34.59	176.36±31.39	ns
EDV post. (ml)	1	174.11±90.12	148.74±20.62	ns
	2	164.03±23.59	134.72±24.9	p=0.053
ESV preop. (ml)	1	100.54±78.28	64.72±21.84	ns
	2	87.15±31.61	66.38±31.61	ns
ESV post. (ml)	1	79.29±59.56	72.84±37.15	ns
	2	84.66±29.13	61.68±18.72	ns
FLVEF preop. (ml)	1	28.50±16.01	38.63±8.73	ns
	2	35.00±8.80	29.50±4.14 *	ns
FLVEF post. (ml)	1	39.95±20.61	41.94±17.63	ns
	2	43.17±15.47	48.04±15.57	ns
FS% preop. (%)	1	34.86±5.51	35.49±7.62	ns
	2	33.65±7.72	40.25±6.30	ns
FS% post. (%)	1	23.69±6.76	31.79±4.13	ns
	2	25.22±6.23	33.11±6.23	ns
RVSP preop. (mmHg)	1	56.00±12.99	44.67±16.01	ns
	2	55.17±12.92	50.00±11.73	ns

RVSP post. (mmHg)	1	36.80±9.45	34.44±8.92	ns
	2	45.50±10.89	40.64±9.73	ns
1 - mitral valve annuloplasty, 2 - mechanical mitral valve, EDD – end-diastolic dimension, ESD – end-systolic dimension, EDV – end-diastolic volume, ESV – end-systolic volume, FLVEF – forward LV ejection fraction, FS – fractional shortening, RVSP – right ventricular systolic pressure. bold * p=0.045 compared to MVA				

In both groups, a significantly lower postoperative FS% were determined in patients with LVD compared to those with stable LV function, that is: in MVA 23.69±6.76 vs. 31.79±4.13%, p=0.016, and in MVR 25.22±6.23 vs. 33.11±3.24%, p=0.044, respectively.

In total, preoperative forward LVEF was lower in LVD patients (31.45±13.06 vs. 37.41±8.34, p>0.05). There was a significant difference in preoperative forward LVEF measures according to the group in those who did not develop LVD. Specifically, MVA patients with normal postoperative LV function had higher preoperative forward LVEF compared to MVR patients (38.63±8.73 vs. 29.50±4.14, p=0.045). Interestingly, we documented opposite direction of forward LVEF change related to LVD between the groups. Mean values of forward LVEF were lower in MVA patients who developed LVD compared to those who did not (28.5% vs. 38.63%), while the values were higher in MVR patients with LVD versus those with stable function (35.00% vs. 29.5%).

Discussion

Severe MR (4+) is associated with progressive ventricular remodeling that results from chronic volume overload. Several studies demonstrated better survival of these patients when mitral valve operative intervention was performed before the onset of symptoms. However, due to established risks of surgery, only patients with a severe degree of MR are selected for the intervention (12-14). Estimation approach using M-mode-derived dimensions is simple, noninvasive, and successful which allow it become recommended as a criterion for intervention in mitral valvulopathy. Moreover, LV diameters, volumes, EF% and wall stress are commonly used to assess LV remodeling process (9).

An individualized consideration needs to be performed when deciding on the type of surgical correction for MR, including both patient-related status and specificities of procedure with its

potential adverse effects. Studies report that mitral valve replacement is associated with lower occurrence of valve-related complications but greater rates of thromboembolic events and structural impairment of the valve that reflects on ventricular tethered loop and LV contraction (8, 15, 16).

Despite no significant difference in mortality between MVA and MVR for ischemic mitral valve incompetence by the end of 7 years follow-up in the study of Micovic et al. (17), the 30-day mortality rates were significantly higher in MVR group (9.6% vs. 5.8%). Similarly, in a meta-analysis, clinical outcomes of repair and replacement for severe ischemic MR showed lower perioperative mortality in MVA patients and no differences in long-term survival. However, MVA was associated with higher recurrence of MR compared to MVR procedure (15).

We detected subtle changes in the early postoperative period between the two types of procedures for degenerative severe MR, specifically when comparing mitral valve correction with implantation of annuloplastic ring with MVR using mechanical valve. Following both types of intervention, EDD and EDV decreased significantly compared to initial values, as well as LA diameter, but these were not distinctly different between the groups. Patients with MVA who progressed to LVD (defined as EF < 50%) had significantly higher preoperative EDD ($p=0.038$), while other patients showed the same tendency. Postoperative LVD was associated with higher postoperative ESD in MVA patients, while there was a tendency of higher preoperative ESD in the mechanical valve replacement group. Left ventricular contractile dysfunction is an early and frequent complication of MR surgery. It interferes and prolongs LV recovery and influences patients survival. Nevertheless, the issue of early LVD following mitral valve surgery is still poorly evaluated (14, 18, 19). Despite preoperative EF $\geq 60\%$, it is suggested that there is an ongoing myofibrillar degeneration and diffuse interstitial fibrosis in myocardium with MR leading to contractile dysfunction that remains asymptomatic and unrecognised until surgical correction. The mitral valve surgery removes the confounding effects of regurgitant volume, reduces preload but increases afterload pressures, thereby it unmasks the actual state of LV function (12, 14, 20).

In a study that evaluated short- and long-term changes in postoperative LVEF after mitral valve repair, preoperative LVEF and ESD were found important in defining these changes. There was a greater decrease in LVEF after repair the higher preoperative LVEF was, along with preoperative ESD greater than 40 mm compared to < 40 mm (21).

Forward LVEF was shown to be superior to the total EF in predicting outcomes in MR, with higher risk for adverse events in those patients having forward LVEF less than 50%. A preoperative forward EF less than 40% was found associated with risk of developing LV systolic dysfunction after MR corrective procedure (12). Nevertheless, LVD occurs in patients with previously normal LV function as well (14, 18). This parameter could predict early LVD, 3-4 days after a MR repair, with an optimal cut-off of 31.8% reported in patients with preoperative LVEF \geq 60%. It also correlated with mitral regurgitant volume and fraction (14).

We determined a significant difference in preoperative forward LVEF values according to the type of intervention in patients with preserved postoperative LV function. Those who undergone annuloplasty presented with higher preoperative forward LVEF than others (valve replacement). Although we did not find statistical significance, our MVA patients with postoperative LVD had lower forward LVEF compared to non-LVD. This change had opposite direction in MVR patients.

Preoperative forward LVEF of less than 40% accurately predicts postoperative LV dysfunction three months after surgery for chronic organic MR (22). Both our groups with LVD had forward LVEF below this limit. Additionally, the results of MVA patients are comparable to the study of Kim et al. who determined even lower cut-off of 31% for forward LVEF in those progressing to LVD (14).

Other factors reported to be associated with LVD after MR surgery include enlargement in systolic dimension, midwall and stress-corrected midwall FS%, decrease in RVSP after a repair, preoperative RVSP, LA diameters, global longitudinal strain and global circumferential strain (14, 18, 19, 23).

Similarly to others (14, 21), we detected a significantly reduced postoperative FS% compared to the preoperative in our patients (36.3 vs. 30.7%). A fall in FS% is indicating LV systolic dysfunction. Also, LVD was associated with significantly lower postoperative FS% in both our groups (23.7% in MVA and 25.2% in MVR). It is suggested that midwall FS may represent preoperative intrinsic LV contractility that is not obvious before surgical MR correction due to a compensation mechanism for LV volume overload (14, 21).

Left atrial dimensions decreased after MR correction in both our groups. There were slightly lower dimensions of LA in LDV patients in both groups, but still being higher than normal ($>$ 4 cm). Left atrial size is a simple parameter affected by MR severity and thus may identify patients who are

suitable for early elective valve surgery. Moreover, it is found the strongest independent echocardiographic predictor of outcome in severe but asymptomatic MR (23).

The information presented here provides valuable insight into the subtle specificities of early LV remodeling according to the type of operative MR correction. Beside MR correction and prevention of recurrence, types of operative intervention represent a new basis that later on defines long-term outcomes.

Conclusion

We can conclude that there are subtle differences in preoperative and early postoperative echocardiographic parameters between the MVA and MVR procedures of surgical MR correction in patients with chronic primary MR. Forward LVEF values were significantly higher after the procedure in general. Left ventricle EDD improved significantly after the interventions, while no significant differences in LV volumes was determined between the groups.

There was a similar incidence of immediate postoperative LV systolic dysfunction in the groups. Each group had distinct alterations in relation to LVD: a significantly higher preoperative EDD and postoperative ESD were present in MVA patients, while MVR group showed only a tendency of higher preoperative ESD and postoperative EDV.

A significant distinction between the groups was revealed in patients without LVD, that is a higher preoperative forward LVEF in MVA compared to MVR patients. Interestingly, an opposite direction of forward LVEF change was seen in LVD between the groups.

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