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Research Article

Global and Regional Longitudinal Strains Predict Left Ventricular Dysfunction after Mitral Valve Repair: A Two Dimensional Speckle Tracking Study

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Abstract

Background: It has been well documented that reduced left ventricular ejection fraction (LVEF) has adverse effect on the outcome of patients with severe mitral regurgitation (MR) after mitral valve repair (MVr). However, the best method for early detection of LV dysfunction in asymptomatic or mildly symptomatic patients with MR still has not been established. Recently two dimensional speckle tracking echocardiography (2DSTE) has been used to identify subclinical alterations of myocardial deformation in many clinical settings.

Objectives: Our aim was to assess the value of regional and global LV two dimensional strains to predict postoperative LV dysfunction after MVr.

Methods: Twenty six patients with severe MR were evaluated. Patients were divided into two groups according to their post-operative LVEF difference, those with a post-op LVEF reduction of $< 10\%$ at 3 months (Group 1), and those with post-op LVEF reduction of $\geq 10\%$ at 3 months (Group 2). All data were measured after 3 months follow-up and compared with pre-operative measures.

Results: The occurrence of post-operative LV dysfunction was significantly related to left ventricular end-systolic dimension index (LVESDI), NYHA functional class and global longitudinal strain (GLS). A cut-off value of 19% for GLS could predict post-op LV dysfunction with a sensitivity of 89% and specificity of 77%. In addition a cut-off value of - 17.7% for long axis strain with a sensitivity of 78% and specificity of 77% and a cut off value of -20% for 2-chamber strain with a sensitivity of 77% and specificity 83% could predict LV dysfunction after MVr.

Conclusions: Among all measured data LV global longitudinal strain seems to be the most sensitive predictor of postoperative LV dysfunction in patients with severe MR and normal LVEF after surgical repair.

Keywords: Mitral Regurgitation, Mitral Valve Repair, Left Ventricular Function, Longitudinal Strain, Two Dimensional Speckle Tracking

1. Background

Left ventricular function is a well-known prognostic factor influencing outcome in valve diseases (1). It is clear that EF $\leq 60\%$ is associated with excess risk of events during follow-up and after surgery (2). Thus mitral valve surgery should be performed before LV dysfunction (LVEF $\leq 60\%$) occurs. However, left ventricular ejection fraction (LVEF) assessment by echocardiography has several limitations, including imaging quality for endocardial border detection and load dependency which is a major limiting factor in volume overloaded ventricle (2).

Therefore, this higher level of LVEF despite LV remodeling and impaired contractility in patients with severe MR does unmask after MV surgery. In severe MR, altered loading condition imposed by chronic MR may sustain normal stroke volume at rest; however, myocardial contractile reserve may already deteriorate even in asymptomatic patients. Therefore early surgical intervention should be considered even if LV systolic dysfunction is not detected by conventional echocardiography measurements of LVEF (3-5). But it is difficult to determine the time course of LV remodeling and LV dysfunction in chronic MR (3). There is a great controversy against watchful waiting strategy of referral to surgery after being symptomatic or development of LV enlargement, LV dysfunction, pulmonary hypertension or atrial fibrillation in asymptomatic patients with MR, because of different reported outcomes (6, 7). Thus in asymptomatic patients with severe MR and borderline LVEF or LVESD, other reliable methods are recommended.

In several studies it has been reported, that despite apparently preserved ‘normal’ LVEF, myocardial contractil-

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ity may be impaired, reflected by reduced longitudinal 2D strain (2, 8). Two-dimensional speckle tracking echocardiography (2DSTE) is a novel and promising technique with multiple clinical applications (2, 8). Its major advantage is angle-independency in comparison with tissue doppler (TDI) which enables us to evaluate regional and global myocardial deformation parameters using the grey scale pixels. Basically, strain measures the magnitude of myocardial fiber shortening, and therefore may detect early subtle subclinical LV dysfunction. 2DSTE provides complementary information to that obtained by clinical and conventional echocardiographic parameters such as LVEF and LVESD, and may help the clinician in the evaluation, risk stratification and optimization of the timing of surgery for asymptomatic patients with chronic severe MR (9).

2. Objectives

The aim of our study was to evaluate the predictive value of LV global and regional longitudinal strain for the occurrence of post-operative (post-op) LV dysfunction, compared with previously established predictive factors such as LVEF and LVESD.

3. Methods

The study population consisted of 26 consecutive patients scheduled for mitral valve repair (MVr) for chronic severe MR in Shaheed Rajaee Hospital since September 22, 2012 until May 22, 2013. In all patients a comprehensive 2D, M-mode and Doppler echocardiography was performed the day before surgery and after 3 months during follow up. Patients with history of ischemic heart disease or significant coronary artery stenosis on coronary angiography, cardiomyopathy, significant aortic valve disease, mitral stenosis more than mild, or congenital heart disease, poor image acquisition after MVr and unsuccessful MVr were excluded. Successful MVr defined as not more than mild residual mitral regurgitation, less than 5 mmHg mean transmitral pressure gradient, and no systolic anterior motion of the mitral valve causing left ventricular outflow obstruction. Since compared to patients with EF $>$ 60%, patients with EF $<$ 50% had more increase in the risk of all-cause and cardiac mortality (10) our patients were divided into 2 groups: those with a post-op LVEF reduction of $<$ 10% at 3 months (Group 1), and those with post-op LVEF reduction of $\geq$ 10% at 3 months (Group 2).

3.1. Echocardiography Evaluation

Transthoracic echocardiography was performed with available ultrasound equipment (GE, Vivid 7 dimension, Horten, Norway). The images were obtained with a 3.5 MHz transducer and digitally stored for off-line analysis. Mitral regurgitation was quantified by color doppler flow measuring the proximal isovelocity surface area (PISA), the effective regurgitant orifice (ERO) and regurgitant volume (RV). The left ventricle pressure/ time derivative (dp/dt) was measured using continuous wave doppler monitoring of MR jet in the apical 4-chamber view. LV dimensions were measured from the parasternal long-axis view and were indexed to body surface area. LV end-diastolic and end-systolic volumes were calculated from the apical two- and four-chamber views, by using Simpson's biplane method and were indexed to body surface area and then LVEF was calculated.

3.2. Speckle Tracking Echocardiography

Two-dimensional gray scale images were acquired in the apical four-chamber (4-ch), two-chamber (2-ch), and long axis (LAX) views with a frame rate of 45 - 60 frames per second. Data were averaged from three cardiac cycles in patients with sinus rhythm and in patients with atrial fibrillation cycles with the same heart rate was obtained. 2DSTE strain analysis was performed in each separate apical views to assess LV regional strains and then global longitudinal strain (GLS) was extracted by bulls eye display by averaging the peak strain values of 18 regional segments (Figure 1). All data were repeatedly measured at 3-months follow up.

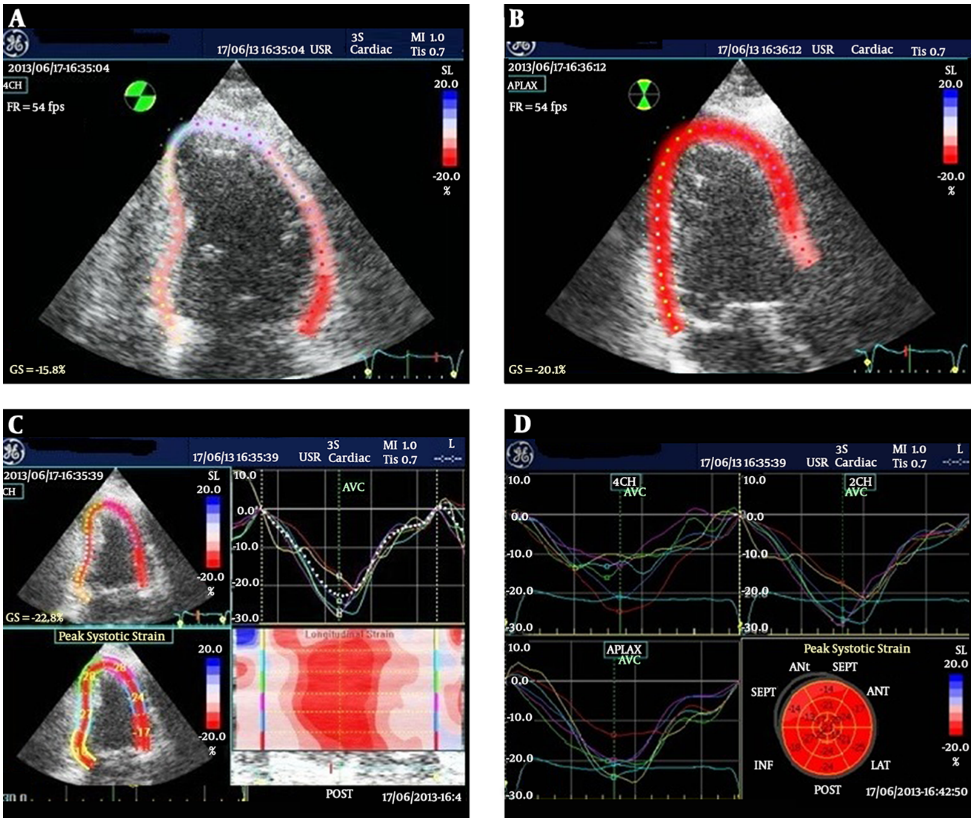
3.3. Statistical Analysis

Data are expressed as mean $\pm$ SD or as absolute number (percentage). Differences between groups were analyzed using student's t test for continuous variables and the chi-square test for categorical variables. The study population was divided according to reduced post-op LVEF at follow-up ($<$ 10% versus $\geq$ 10% reduction). Linear regression analysis was used to estimate correlations between continuous variables. Receiver operating characteristic (ROC) curves were plotted to determine the optimal cutoff values for individual parameters to predict post-op LVEF reduction and to establish the optimal cutoff values for clinical decision making. Univariate logistic regression analysis was used to analyze predictors of post-op LVEF impairment and for statistical adjustment. For all statistical tests, a P value of $<$ 0.05 was considered significant. All statistical analyses were performed with SPSS version 17.0 (SPSS, Inc., Chicago, IL, USA).

4. Results

Baseline clinical and echocardiographic characteristics of patients are shown in Table 1. The mean age of patients was 54 + 13 years; 69% male, 19% in atrial fibrillation.

Figure 1. LV regional and global strain assessment by 2D speckle-tracking analysis in a patient with severe MR



The myocardium is divided into six segments in the apical four-chamber view (a), apical long axis (b), and apical two-chamber view (c). Longitudinal shortening (negative strain) is calculated for each segment over the cardiac cycle and LV GLS is calculated as the average of peak longitudinal strain of all segments (d), which in this example was 20.17%.

In the majority of patients (88.5%) myxomatous or flail mitral valve was determined as the etiology of MR, however, rheumatic involvement in 2 patients and MR secondary to infective endocarditis in one patient were diagnosed. Most patients were asymptomatic or only mildly symptomatic (46.2% in NYHA class II).

4.1. Changes in Echocardiography Parameters After MVr

As shown in Table 2, LV EDV and LV dimensions revealed significant reduction after MVr after 3 months (LVEDV:120 ± 36 versus 91 ± 26 mL, P = 0.000, LVESD: 4.3 ± 0.67 versus 4 ± 0.65 cm, P = 0.034, LVEDD: 5.2 ± 0.61 versus 45.9 ± 0.67 cm, P = 0.00). The exception was LVESV (55.6 ± 19 versus 56.4 ± 20 mL, P = 0.940) which remained unchanged after surgery. This finding is partly supported by substantial effectiveness of valve surgery on LV volume overload leading to increased end diastolic volume.

A significant reduction in LVEF was noted after MVr during follow-up (53 ± 4 versus 42 ± 9%, P = 0.000). Additionally all regional and global LV strains showed significant reduction during follow up [GLS: -17.9 ± 3.5 versus -13.2 ± 2.4%, P = 0.00, LAX: -17.3 ± 5.3 versus 12.3 ± 4%, P = 0.02, 4-ch: -18.1 ± 3.5 versus -13.4 ± 3.4%, P = 0.00 and 2-ch: -18.3 ± 3.6 versus -13.3 ± 2.9, P = 0.01).

4.2. Predictors of LV Dysfunction After MVr

Significant LV dysfunction defined as ≥ 10% reduction in LVEF occurred in about 2/3 (65.4%) of patients and only 34.6% patients had < 10% reduction or no changes in LVEF after surgery. By univariate analysis, LV regional strains in LAX and 2-ch views, GLS, symptoms and LVESD index were associated with decreased LVEF ≥ 10% at follow-up. However, post-op LV function was not related to LV volumes, LVEDD, ERO, LVEF and LV strain in 4-ch view. Atrial fibrillation rhythm (P = 0.628), cross clamp time (P = 0.771), age (P = 0.637) and sex (P = 0.492) were not associated with more than 10% reduction in LVEF at follow-up (Tables 3-6).

Table 1. Baseline Clinical and Echocardiographic Characteristics of Patients (n = 26)[a]

Variable	Descriptive Index
Age(years)	54 ± 13
Male Gender, n (%)	18 (69)
NYHA class I/II/III/IV, n (%)	6/12/7/1
Atrial fibrillation, n (%)	5 (19)
LVEDD (mm/m^2)	59 ± 6 / 32 ± 3
LVESD (mm/m^2)	43 ± 6 / 23 ± 3
LVEDV(mL/m^2)	120 ± 36 / 61 ± 21
LVESV (mL/m^2)	55.6 ± 19 / 28 ± 11
LVEF (%)	53 ± 4
ERO (cm^2)	0.51 ± 0.11
LAX strain (%)	- 17.3 ± 5.3
2-ch strain (%)	- 18.3 ± 3.6
4-ch strain (%)	- 18.1 ± 3.5

Abbreviations: NYHA, New York Hear Association; LAX, long axis; LVEDD, left ventricular end-diastolic dimension; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension, LVESV, left ventricular end-systolic volume; 2-ch. 2 chamber; 4-ch, 4 chamber; ERO, effective regurgitant orifice area.

[a] Data are presented as mean ± SD or number.

To identify cut-off values for baseline LV GLS, LAX and 2-ch strains and ESDI to predict post-op LV dysfunction, ROC curve analysis was performed.

A cut-off value of - 19% for LV GLS (AUC = 0.807, 95% confidence interval [0.623 - 0.991] could predict post-op LV dysfunction with a sensitivity of 89% and specificity of 77%). A cut-off value of -17.7% for LV LAX strain (AUC = 0.824, 95% confidence interval [0.599 - 1] sensitivity of 78% and specificity of 77%) and a cut off value of -20% for LV 2C strain (AUC = 0.807, 95% confidence interval [0.629 - 0.985], sensitivity of 77% and specificity of 83%) could predict LV dysfunction after MVr. In addition a cut off value of 2.2 cm/m^2 for ESDI (AUC= 0.732, 95%) confidence interval [0.512 - 0.952] could predict LV dysfunction with a sensitivity of 70% and specificity of 67%.

4.3. Interobserver and Intraobserver Variability

Speckle tracking–derived strains and EF of the 10 enrolled patients were analyzed offline by two independent observers. The same images were also analyzed on a different day by one of these observers. Interobserver agreement, expressed as intraclass paired samples correlations, for global and regional strain and EF measurements was done with P value 0.678 for EF, P value 0.710 for global strain and P value 0.601 for LAX strain and P value 0.415 for 4 chamber strain and p value 0.456 for 2 chamber strain.

5. Discussion

Despite supporting current recommendations and successful surgical procedure, post-op LV dysfunction after MVr and even clinically overt heart failure may still occur. Hence identification of patients with subtle myocardial dysfunction is crucial to prevent significant post-op LV dysfunction. Although conventional echocardiographic parameters are still useful and applicable, these parameters fail to detect potential subclinical myocardial damage due to the volume-dependency and particularly to that low sensitivity (11). Therefore the attention has shifted towards deformation parameters which are able to identify subclinical changes in LV myocardial function. More recently, LV strain parameters assessed using different imaging techniques have been proposed to predict LV dysfunction after mitral valve surgery (12-14). New novel speckle-tracking analysis allows an angle-independent assessment of myocardial strain, with the advantages of a comprehensive evaluation of LV both regionally and globally.

In the present study the main findings were determination of LV GLS, and not LVEF, as an independent predictor of postoperative LV dysfunction in patients with severe chronic MR, together with LVESD index and NYHA functional class.

Our analysis showed that in severe chronic MR systolic myocardial deformations are impaired even early in the course of disease regardless of preserved LVEF. In severe MR, Left atrium makes an alternative low-impedance chamber for LV ejection, thus LVEF goes up. Therefore even in the early stage of disease, before the occurrence of overt LV dysfunction; recognized as reduced LVEF, any impairment in myocardial contractility may be masked by traditional methods for assessment of ventricular function (13). The reported incidence of long-term postoperative LV dysfunction (LVEF < 50%) including mitral valve replacement varies from 41% in early 1980s to 15% in patients operated with MVr in the late 1990s (15, 16).

However, in a recent study in a large series of patients undergoing MVr during last decade a long-term postoperative LV dysfunction was observed in only 12% of patients, confirming the benefits of improved surgical repair techniques (17).

We also found that LVEF is not a well-recognized predictor of post-op LV dysfunction particularly when preoperative LVEF is preserved (13).

In our series, about 2/3 of patients showed more than 10% decrease in LVEF post operatively. Based on the baseline LV GLS in our study compared to Tomasz G groups (-17.9 versus - 21.8%) the high incidence of LV dysfunction in our patients might be due to late consideration of surgical intervention which has been resulted to irreversible LV dys-

Table 2. Comparison of Changes in Echocardiographic Parameters Before and 3 Months After MVr[a]

	Paired Differences	95% CI		
	Mean Difference Between Groups	Lower	Upper	P Value
LVEDD	0.69 ± 0.5	0.46	0.92	0.000
LVESD	0.26 ± 0.5	0.02	0.49	0.034
LVEDV	30.95 ± 25.2	19.15	42.74	0.000
LVESV	0.35 ± 20.6	-9.32	10.02	0.940
GLS	4.27 ± 3.6	2.49	6.04	0.000
LAX	4.28 ± 5.1	1.78	6.79	0.002
4-ch	4.23 ± 4.1	2.18	6.29	0.000
2-ch	4.83 ± 2.3	2.35	7.30	0.001
LVEF	11.61 ± 9.7	7.69	15.53	0.000

Abbreviations: GLS, global longitudinal strain; LAX, long axis; LVEDD, left ventricular end-diastolic dimension; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension, LVESV, left ventricular end-systolic volume; 2-ch.2 chamber;4-ch,4 chamber

[a] Data are presented as mean ± SD.

Table 3. Relations Between Post-Op LV Dysfunction with Regional and Global LV Strains, Age and Cross Clamp Time[a]

	Group 1	Group 2	P Value
GLS	20.62 ± 3.18	16.57 ± 2.92	0.003
LAX strain	21.45 ± 5.44	15.21 ± 3.97	0.003
4-ch strain	19.43 ± 3.53	17.52 ± 3.40	0.192
2-ch strain	20.88 ± 2.42	17.01 ± 3.43	0.006
Age	52.67 ± 15.66	55.29 ± 11.99	0.637
Cross clamp time	77.11 ± 12.74	79.71 ± 24.59	0.771

Abbreviations: GLS, global longitudinal strain; LAX, long axis; 2-ch, 2 chamber; 4-ch, 4 chamber.

[a] Data are presented as mean ± SD.

function. This finding again confirms the benefits of lower threshold for surgical repair of patients with severe MR in which the feasibility of valve repair is high. The successfulness of mitral valve surgery on LV performance is mainly showed by a significant decrease in post-op LV size, mostly LV dimensions and more prominently LV end diastolic volume in comparison with LV systolic volume due to more effectiveness of reduced volume overload on LV end diastolic volume as seen in the study by Witkowski et al. (17). Some studies reported an LVESD $>$ 40 mm as a predictor of LV dysfunction after MVr (13, 17-19). However, we found an LVESD index ≤ 2.2 cm/m^2 as a predictor of LV dysfunction. Although the LVESD per se is important however, it seems that in volume overloaded LV the indexed systolic dimension is rather crucial for decision making.

Enriquez-Sarano et al. showed that patients with ERO $>$ 40 mm^2 had poor outcomes with medical management alone, despite the absence of symptoms (6). In de Isla LP et al. and our study ERO was greater in group 2 than group 1, but it was not a predictor of LV dysfunction after MVr (13). Our suggestion is most probably due to proximal isovelocity surface area method limitations, such as eccentric or multiple jets.

Functional capacity (NYHA functional class) has been reported previously as a predictor of LV dysfunction after surgery (17). Lee et al. showed LV contractile reserve, defined as a 4% increase in LVEF at peak of exercise; could be considered as a sensitive method of predicting LV dysfunction after mitral valve surgery (20, 21). In addition, Haluska et al. also reported correlation between contractile reserve on exercise echocardiography and LV function after MVr (22); however, this method was not practical and easy for routine follow up.

Even with concern of current guidelines to manage significant MR, many patients will be suffering from post-op LV dysfunction. Given excellent results for mitral valve repair, new imaging modalities will be needed for patients' selection for valve repair particularly during early stages

Table 4. Relation Between Post-Op LV Dysfunction and Sex

	Sex		Total	P Value
	Male	**Female**		
Group 1	7 (77.8%)	2 (22.2%)	9 (100.0%)	0.492
Group 2	11 (64.7%)	6 (35.3%)	17 (100.0%)	

Table 5. Relation Between Post-Op LV Dysfunction and NYHA Functional Class

	NYHA FC				P Value
	I	**II**	**III**	**IV**	
Group 1	5 (55.6%)	4 (44.4%)	0	0	0.008
Group 2	1 (5.9%)	8 (47.1%)	7 (41.2%)	1 (5.9%)	

Table 6. Relation Between Post-Op LV Dysfunction with LV Dimensions, Volumes and dp/dt[a]

	Group 1	Group 2	P Value
LVEDD	5.88 ± 0.55	6.04 ± 0.73	0.593
LVEDDI	3.07 ± 0.42	3.29 ± 0.28	0.142
LVESD	4.11 ± 0.52	4.47 ± 0.72	0.193
LVESDI	2.15 ± 0.38	2.43 ± 0.27	0.048
LVEDV	114 ± 0.31	122 ± 0.39	0.604
LVEDVI	60.28 ± 17.8	61.94 ± 23.3	0.861
LVESV	55.50 ± 14.2	55.75 ± 22.3	0.977
LVESVI	29.60 ± 9.7	28.08 ± 12.3	0.762
dp/dt	2489 ± 1348	2551 ± 1266	0.746

Abbreviations: dp/dt, pressure/ time derivative; LVEDD, left ventricular end-diastolic dimension; LVEDDI, left ventricular end-diastolic dimension index; LVEDV, left ventricular end-diastolic volume; LVEDVI, left ventricular end-diastolic volume index; LVESD, left ventricular end-systolic dimension; LVESDI, left ventricular end-systolic dimension index; LVESV, left ventricular end-systolic volume; LVESVI, left ventricular end-systolic volume index.

[a] Data are presented as mean ± SD.

of disease before the development of obvious contractility impairment shown by traditional imaging techniques.

Our findings are in agreement with those of recent studies (12, 13, 17, 23). The benefits of speckle-tracking echocardiography for detecting of early contractile dysfunction has been demonstrated (13, 17). In addition de Isla et al. (13) also demonstrated superiority of speckle-tracking technology over TDI measurements due to angel independency of this method and also lower interobserver and intraobserver variability with speckle-tracking measurements compared with DTI (24, 25). Witkowski et al. reported a cut-off value of 19.9% for GLS (AUC = 0.88, 95% CI [0.83 - 0.93], sensitivity of 90% and specificity of 79%) for prediction of post-op LV dysfunction after MVr (17).We found a cut-off value of -19% for GLS (AUC = 0.807, 95% CI [0.623 - 0.991] with the same sensitivity (89%) and specificity (77%)). Additional finding in our study was the predictive value of regional LV strain in LAX view (sensitivity of 78% and specificity of 77%) and 2-ch view (sensitivity of 77% and specificity of 83%) to predict LV dysfunction.

However, GLS seems to be much better as a predictor of LV dysfunction in comparison with LAX and 2-ch strains, associated with higher sensitivity and specificity.

5.1. Study Limitations

Tracking quality is better in regions close to the transducer than in the far field of the image and could be suboptimal if the regions of the myocardium are poorly visualized or spatial, temporal resolution of the image acquisition is insufficient (26). In our study five patients were excluded because of poor image acquisition after MVr.

3D echocardiography has the same limitations that affect 2D speckle tracking and has lower temporal and spatial resolution than 2D imaging (26).

Achievement of strain values by 3D-STE is significantly higher than those by 2D-STE and the differences are more affected with the magnitude of longitudinal displacement especially in nor-mal subjects rather than patients with LV dysfunction (27).

The limitation of this study was short follow up of our patients to determine the role of 2D speckle tracking study in the prediction of midterm and long term left ventricular dysfunction after mitral valve repair.

In our study we had hardness in achievement of strain values, if patient's rhythm was AF (with considering of five cardiac cycles in comparison with tree cardiac cycles in patients with normal sinusal rhythm) but nobody was excluded due to these reason.

5.2. Conclusions

Mitral valve repair should be considered as a treatment of choice in patients with severe MR early in the course of disease to prevent postoperative LV dysfunction. LV GLS seems to be sensitive enough to predict subtle abnormalities of LV contractility and supposed to be the best predictor of postoperative LV dysfunction.

Footnote

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