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ORIGINAL PAPER

Determinants of post-operative left ventricular dysfunction in degenerative mitral regurgitation

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Aims

Chronic degenerative mitral regurgitation leads to volume overload causing left ventricular (LV) enlargement and eventually LV impairment. Current guidelines determining thresholds for intervention are based on LV diameters and ejection fraction (LVEF). There are sparse data examining the value of LV volumes and newer markers of LV performance on outcomes of surgery in mitral valve prolapse. The aim of this study is to identify the best marker of LV impairment after mitral valve surgery.

Methods and results

Prospective, observational study of patients with mitral valve prolapse undergoing mitral valve surgery. Pre-operative LV diameters, volumes, LVEF, global longitudinal strain (GLS), and myocardial work measured. Post-operative LV impairment defined as LVEF < 50% at 1 year post-surgery. Eighty-seven patients included. Thirteen percent developed post-operative LV impairment. Patients with post-operative LV dysfunction showed significantly larger indexed LV end-systolic diameters, indexed LV end-systolic volumes (LVESVi), lower LVEF, and more abnormal GLS than patients without post-operative LV dysfunction. In multivariate analysis, LVESVi [odds ratio 1.11 (95% CI 1.01–1.23), $P = 0.039$] and GLS [odds ratio 1.46 (95% CI 1.00–2.14), $P = 0.054$] were the only independent predictors of post-operative LV dysfunction. The optimal cut-off of 36.3 mL/m^2 for LVESVi had a sensitivity of 82% and specificity of 78% for detection of post-operative LV impairment.

Conclusion

Post-operative LV impairment is common. Indexed LV volumes (36.3 mL/m^2) provided the best marker of post-operative LV impairment.

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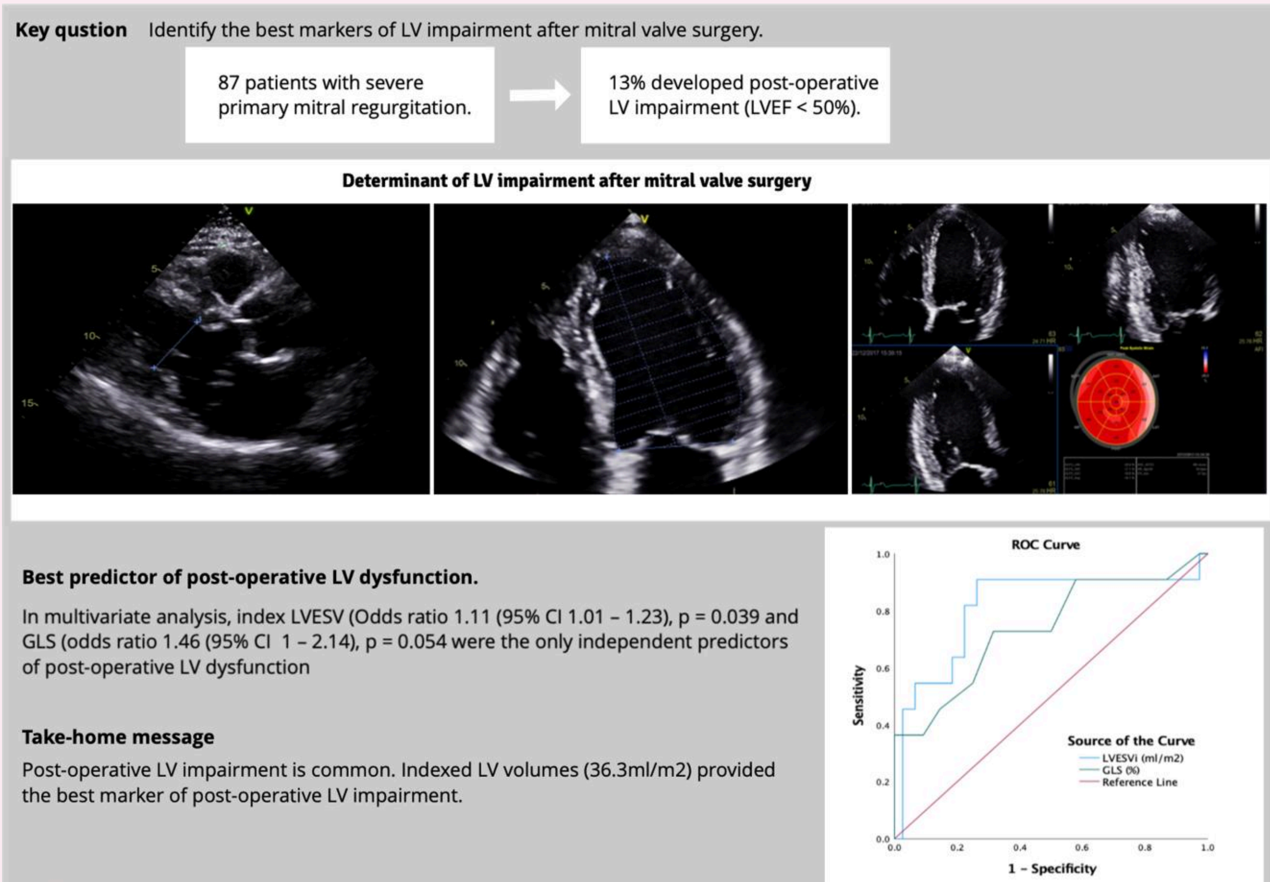
Graphical Abstract



Keywords mitral valve prolapse • surgery • mitral regurgitation • global longitudinal strain • LV volumes

Introduction

Degenerative mitral regurgitation is the most common form of primary mitral regurgitation.[1] Guidelines recommend surgery in symptomatic patients. In asymptomatic patients, intervention is recommended in patients with left ventricular (LV) dilatation or dysfunction.[2]

Chronic mitral regurgitation leads to volume overload and increases in LV preload. Adaption to the volume overload causes LV enlargement.[3] Although initially normal in compensated states, systolic wall stress and afterload increase during the transition from a compensated to decompensated state.[4] Despite a normal LV ejection fraction (LVEF), LV contractile function can be impaired.[5] In addition, LV end-systolic diameter (LVESD) does not reflect the extent of LV remodelling in response to mitral regurgitation as it does not account for mid to apical LV remodelling.[6] There are sparse data examining the impact of LV volumes on outcomes in chronic mitral regurgitation. It is not uncommon for patients to have persistent LV dysfunction (LVEF <50%) post-mitral repair despite preserved LVEF (>60%) prior to surgery.[7] A post-operative LVEF < 50% predicts poor long-term outcome.[8]

Global longitudinal strain (GLS) has been shown to be a more sensitive marker of LV dysfunction than LVEF and a better predictor of post-operative LV function and outcome.[9,10] However, GLS is load dependent. Myocardial work is a non-invasive method of measuring myocardial demand and performance accounting for changes in afterload.[11] Myocardial work components including work index, constructive, and wasted work have been assessed in a range of myocardial and valve disease.[12,13]

We sought to examine the newer markers of LV remodelling and cardiac performance to predict post-operative outcome in chronic primary mitral regurgitation.

Methods

Patients with severe, primary degenerative mitral valve regurgitation scheduled to undergo mitral valve surgery were recruited from valve clinics at St Bartholomew's hospital between 2017 and 2021. The study was approved by the Health Research Authority (REF 17/SW/0237). All participants provided written, informed consent. Patients with known coronary artery disease, previous myocardial infarction, heart failure, or more than mild other concomitant valve disease were excluded.

A baseline comprehensive echocardiogram was performed using commercially available ultrasound machines (General Electric E95, General Electric Norway). Image analysis was performed using EchoPac (version 204, General Electric, Norway). LVEF and LV volumes were calculated using Simpson's Biplane method. Mitral regurgitation was quantified using effective regurgitant orifice area and regurgitant volume (RVol), calculated using the proximal isovelocity surface area (PISA) method.[11] The radius of the PISA was measured in zoom mode. Continuous wave Doppler was used to measure the peak mitral regurgitant jet velocity and velocity time integral.

In patients with atrial fibrillation, the average of three different cardiac cycles was used. Tricuspid regurgitant velocity was measured using continuous-wave Doppler velocity.

GLS was measured offline using automated function imaging (GE Medical Systems, Waukesha, WI). The frame rate was between 40 and 80 frames per second. The blood pressure of the patient was measured using a simple brachial cuff. Readings of the systolic blood pressure and diastolic blood pressure were added to the application (peak systolic arterial pressure was assumed to be equal to peak systolic LV pressure in the absence of aortic valve gradient or LV outflow tract gradient). The following components of myocardial work were measured: global constructive work (GCW), global wasted work (GWW), global work index (GWI), global work efficiency (GWE) (GCW/(GCW + GWW). The units of GCW, GWW, and GWI are (mmHg%), and GWE is expressed as a percentage (%).

Follow-up and end-points

A follow-up echocardiogram was performed 1 year after surgery. Post-operative LV dysfunction was defined as an LVEF < 50%. All-cause mortality was identified by medical chart review and the National Health Service spine.

Statistical analysis

Data were tested for normality distribution with the Kolmogorov–Smirnov test. Continuous variables are presented as mean ± standard deviation or as median and interquartile range (IQR), as appropriate. Categorical variables are presented as absolute values and percentages. Student's *t*-tests were used for parametric data; the Mann–Whitney *U* test was used for non-parametric data to analyse the differences in parameters between patients with and without impaired post-operative LVEF. Univariate and multivariate logistic regression analyses were used to identify predictors of post-operative LVEF dysfunction. Receiver operator curves were analysed to identify the optimal cut-off value for identifying impaired post-operative LVEF. Statistical analyses were performed using the SPSS version 28.0 (SPSS Inc., Chicago, USA). A *P*-value of <0.05 was considered significant.

Results

One hundred and fourteen participants were recruited. Twenty-seven participants were excluded (11 due to the insufficient image quality and 16 due to loss of follow-up). A total of 87 patients who fulfilled the study criteria were successfully included. All patients had severe primary mitral regurgitation due to mitral valve prolapse or flail leaflet and underwent mitral valve surgery. Baseline demographics are shown in *Table 1*. This shows most patients were male (60%) with a median age of 64 years. Baseline echocardiographic characteristics are shown in *Table 2*. Quantification of mitral regurgitation showed severe MR with a median effective regurgitant orifice of 0.60 (IQR 0.40–0.90) cm^2 and a RVol of 80 (IQR 55–129) ml. Of the 87 patients, 67 (77%) underwent mitral valve repair. Eleven (13%) patients had post-operative LV dysfunction (post-operative LVEF < 50%), and 76 (87%) patients had normal post-operative LV function (LVEFLVEF < 50%). Flail leaflet was found in 17 (20%) patients. The proportion of patients with flail mitral valve leaflets was comparable in patients who developed post-operative LV impairment (18%) and those who did not (20%) (*P*-value = 0.903). Twenty-three percent of patients had mitral valve replacement. The proportion of patients with mitral valve replacement was comparable in patients who developed post-operative LV impairment and those who did not (*P*-value = 0.259).

LV, GLS, and myocardial work parameters in the patients with and without post-operative LV dysfunction group are shown in *Table 3*. Patients with post-operative LV dysfunction showed significantly larger indexed LVESDs (LVESDi), indexed LV end-systolic volumes (LVESVi), lower LVEF, and more abnormal GLS than patients without post-

Table 1 Baseline clinical characteristics

Variables	All patients (*n* = 87)
Age, years	64 (54–72)
Male, *n* (%)	52 (60)
Risk factors, *n* (%)	
Atrial fibrillation	12 (14)
Hypertension	27 (31)
Hypercholesterolaemia	24 (28)
Diabetes	1 (1)
Smoking	23 (26)
Mitral valve prolapse, *n* (%)	
Flail	17 (20)
Posterior	45 (52)
Anterior	3 (3)
Bi leaflets	22 (25)
Mitral valve surgery, *n* (%)	
MV repair	67 (77)
MVR (mechanical)	9 (10)
MVR (bioprosthetic)	11 (13)

Values are mean ± standard deviation, *n* (%), or median (interquartile range).
MV; mitral valve, MVR; mitral valve replacement.

Table 2 Baseline echocardiography characteristics

Variables	All patients (*n* = 87)
LAVi, mL/cm^2	48 (50–86)
LVEDDi, cm/m^2	3.0 ± 0.5
LVESDi, cm/m^2	1.9 ± 0.3
LVEDVi, mL/cm^2	86 (69–97)
LVESVi, mL/cm^2	30 (26–39)
LVEF, %	62 (58–66)
PASP, mmHg	25 (19–39)
ERO, cm^2	0.60 (0.40–0.90)
Rvol, ml	80 (55–129)
TAPSE, mm	24 ± 6
E/A ratio	1.6 (1.3–2.1)
E/E' ratio	11.1 ± 3.5
GLS, %	−20 ± 3
GWI, mmHg %	1995 ± 435
GCW, mmHg %	2592 ± 474
GWW, mmHg %	127 (90–178)
GWE, %	94 (92–96)

Values are mean ± standard deviation, median (interquartile range).
E/A; ratio of the early to late ventricular filling velocities, E/E; ratio between early mitral inflow velocity and mitral annular early diastolic velocity, ERO; effective regurgitant orifice, GWE; global work efficiency, LAVi; indexed left atrial volume, LVEDDi; indexed left ventricular end-diastolic diameter, LVEDVi; indexed left ventricular end-diastolic volume, PASP; pulmonary artery systolic pressure, TAPSE; tricuspid annular plane systolic excursion.

Table 3 Comparison of echocardiographic parameters according to the occurrence of post-operative left ventricle dysfunction

Variables	Post-operative LVEF ≥ 50% (n = 76, 87%)	Post-operative LVEF < 50% (n = 11, 13%)	P-value
LVESDi, cm/m^2	1.9 ± 0.3	2.1 ± 0.4	0.030
LVESVi, mL/m^2	31 ± 9	42 ± 11	<0.001
LVEF, %	63 ± 5	56 ± 8	<0.001
GLS, %	−21 ± 3	−17 ± 5	<0.001
GWI, mmHg %	2058 ± 389	1559 ± 500	<0.001
GCW, mmHg %	2632 ± 431	2317 ± 666	0.039
GWW, mmHg %	141 ± 64	144 ± 78	0.889
GWE, %	94 ± 3	92 ± 6	0.245

Values are mean ± standard deviation.
GWE; global work efficiency.

Table 4 Logistic regression analysis for variables associated with post-operative LVEF < 50%

Variable	Univariable	
	Odds ratio (95% CI)	P value
Age, years	1.07 (1.01–1.15)	0.031
LVESDi, cm/m^2	10.16 (1.16–89.05)	0.036
LVESVi, mL/m^2	1.12 (1.03–1.20)	0.002
LVEF, %	0.83 (0.73 to.94)	0.004
GLS, %	1.39 (1.12–1.72)	0.003
GWI, mmHg %	0.99 (0.99–1.00)	0.001
GCW, mmHg %	1.00 (0.99–1.00)	0.004

CI; confidence interval.

operative LV dysfunction. Patients with post-operative LV dysfunction showed lower values of GWI (1559 ± 500 mmHg % vs. 2058 ± 389 mmHg, P-value < 0.001) and lower value of GCW (2317 ± 666 mmHg % vs. 2632 ± 431mmHg %, P-value = 0.039) than patients with normal post-operative LV function. GWW and GWE mean values were similar in the two groups (P-value = 0.889 and 0.245), respectively.

Univariable logistic regression analyses were performed to identify predictors of post-operative LVEF dysfunction (*Table 4*). On univariable logistic regression analysis, age, LVESDi, LVESVi, LVEF, and GLS were associated with post-operative LVEF dysfunction. In multivariate analysis, LVESVi [odds ratio 1.11 (95% CI 1.01–1.23), P = 0.039] and GLS [odds ratio 1.46 (95% CI 1.00–2.14), P = 0.054] were the only independent predictors of post-operative LV dysfunction (*Table 5*).

Receiver operator curve analysis for predicting post-operative LV dysfunction showed LVESVi had the greatest area under the curve

Table 5 Logistic multivariate regression analysis for variables associated with post-operative LVEF < 50%

Variables	Multivariable	
	Odds ratio (95% CI)	P value
Age, years	1.06 (0.98–1.14)	0.133
LVESDi, cm/m^2	2.32 (0.13–41.18)	0.563
LVESVi, mL/m^2	1.11 (1.01–1.23)	0.039
LVEF, %	1.05 (0.84–1.30)	0.679
GLS, %	1.46 (1.00–2.14)	0.054

CI, confidence interval.

compared to GLS (*Table 6*) (*Figure 1*). The optimal cut-off for GLS of 19.5% had a sensitivity of 73% and specificity of 68% with an area under the curve of 0.738 and Youden index of 41%. The optimal cut-off of 36.3 mL/m^2 for LVESVi had a sensitivity of 82% and specificity of 78% with an area under the curve of.812 (95% CI: 0.65–0.98) and Youden index of 60%.

Discussion

This study shows in patients undergoing mitral valve repair, LV dysfunction is not uncommon. Although baseline LVEF, LVESDi, and GLS were predictive of post-operative LV dysfunction, only LVESVi and GLS were independent predictor of post-operative LV dysfunction.

Enriquez-Sarano *et al.* showed LV diameters, and LVEF predict post-operative LV impairment.[8] However, despite guidelines incorporating these parameters and threshold for intervention in primary organic MR lowering, LV dysfunction remains common and is associated with long-term mortality and morbidity.[7] There is a curvilinear relationship between LV diameters and volumes. Small increases in LV diameter may represent a larger increase in LV volume. In addition, diameters do not always account for mid to apical LV remodelling.[6] Our study shows baseline pre-operative LVESVi is a better marker of post-operative LV dysfunction than LVESDi, GLS, or LVEF. The optimal cut-off for optimal sensitivity and specificity was 36.3 mL/m^2.

GLS has emerged as a powerful marker of myocardial dysfunction. It has been shown to offer incremental prognostic value after cardiovascular surgery for organic mitral regurgitation.[9,10] However, it remains load dependent. Although, compensated MR is associated with normal afterload, as MR progresses afterload increases.[4] Myocardial work offers an attractive method to assess LV performance as it accounts for afterload.[11,12,13] An earlier study examined the prognostic value of GWI in functional MR and found that GWI was independently related to cardiovascular mortality or heart failure hospitalization.[14] In the present study, we included patients with primary mitral regurgitation and found that GLS was more abnormal, and pre-operative myocardial work index was lower in patients who developed post-operative LV dysfunction than those who did not. However, only GLS predicted post-operative LV impairment. This may be due to intervention being performed in a compensated state prior to changes in afterload which impact myocardial work. GLS had a low Youden index; at a cut-off of −19.5% GLS had a sensitivity of 73% and a specificity of 68% for identification of post-operative LV impairment. Therefore, it is difficult to integrate GLS into clinical decision-making due to the modest diagnostic value.

Timing of valve intervention in degenerative MR is based on symptoms or identification of high risk features which identify the deleterious effects of MR on the ventricle. Chronic MR leads to LV

Table 6 Receiver operating curve for post-operative LV impairment for indexed left ventricular end-systolic volume and global longitudinal strain

	AUC (95% CI)	*P*-value	Cut-off pg/mL	Sensitivity, %	Specificity, %
LVESVi, mL/m^2	0.812 (0.65–0.98)	0.001	34.0	91	74
			36.3	82	78
			36.6	73	78
GLS, %	0.738 (0.56–0.91)	0.011	−17.5	46	86
			−18.5	55	75
			−19.5	73	68

AUC; area under curve, LVESVi; indexed left ventricular end-systolic volume.

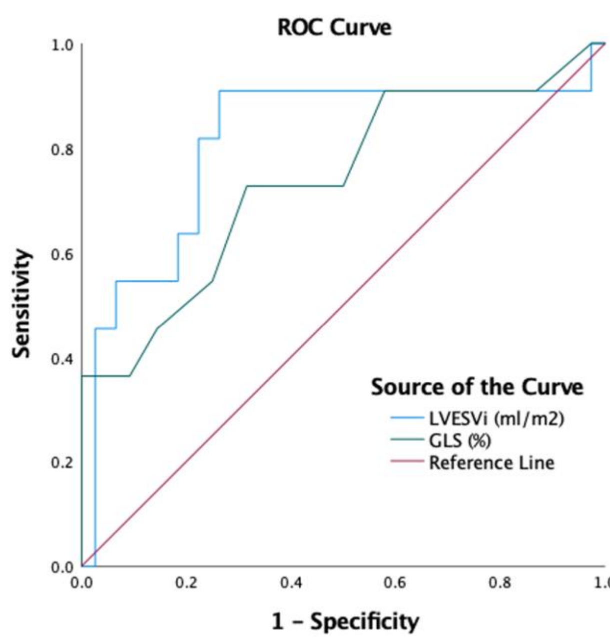


Figure 1 Receiver operating characteristic curves of indexed left ventricle end-systolic volume and global longitudinal strain for detecting post-operative left ventricle dysfunction.

remodelling and compensatory ventricular dilatation with normal contractility and LVEF.[4] Further remodelling leads to reduction in contractile function. We hypothesized that using LV volumes allows better assessment of the LV remodelling than diameters prior to changes in contractile function. Dujardin *et al.* previously showed LV diameters correlate with volumes; however, there is a potential for substantial error particularly in enlarged ventricles.[15]

It has been shown that in comparison with valve replacement, mitral valve repair results in lower operative mortality, higher postoperative LVEF, and a better long-term survival rate.[16] However, in our study, there was no difference in the proportion of patients with mitral repair/replacement between those patients who developed LV impairment and those who did not develop LV impairment.

There are several limitations to this study. This was a single, tertiary centre study. However, referrals to the centre originate from several district general hospitals as well as from further afield. The software analysis for myocardial work is currently available on one vendor. GLS does have inter-vender variability, and therefore cut-offs may not be the same using different vendors. Another limitation of our study is the lack of cardiac MRI and 3D echocardiography measurements for LVEF. The study was underpowered to assess the prognostic value of LV volumes and myocardial parameters on mortality as the number of patients with post-operative events was small. Further, larger, multi-centre studies are required to determine the impact of LV volumes on long-term outcomes including mortality.

In conclusion, in patients with degenerative mitral valve disease, post-operative LV impairment is common. Indexed LV volumes (36.3 mL/m^2) provided the best marker of post-operative LV impairment.

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Conflicts of interest: Consultancy, Circle Cardiovascular Imaging Inc., Calgary, Alberta, Canada (S.E.P.).

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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