Research Article

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Use of Left Ventricular Global Longitudinal Strain to predict Reverse Left Ventricular Remodeling after MitraClip Repair

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ABSTRACT

Purpose: *Mitral Regurgitation (MR) can cause left ventricular dilation (remodeling). Reverse remodeling describes improved volumes after intervention. Reverse remodeling carries favorable prognosis, but not all MitraClip patients undergo reverse remodeling. We hypothesized pre-procedural global longitudinal strain (pre-GLS) will predict reverse remodeling one-year post MitraClip in all-cause MR patients.*

Methods: *Of the 189 MitraClips performed at our institution between 2007-2019, 57 patients had complete echocardiographic data,. Echocardiograms 0-120 days prior to and 6-24 months after procedure were retrospectively reviewed. Reverse remodeling was defined as reduction in end diastolic volume (EDV).*

Results: *In 20 sample echocardiograms, intra and inter-reader GLS variability was r=0.95 and r=0.90, respectively. Our population consisted of 55.2% female, 12.3% functional , 61.4% degenerative and 26.3% mixed mitral regurgitation. A reduction in EDV was demonstrated in 38 patients (67%). EDV, ESV, LAVi, and RVSP significantly decreased post-clip (all p<0.01) but not LVEF. Regression models showed pre-EDV (p<0.01) and pre-ESV (p<0.01) had significant crude and adjusted linear associations and │pre-GLS│ had a significant crude curvilinear association (linear p=0.04, quadratic p =0.04) with EDV reductions post clip. The curvilinear association showed among lower, more abnormal │pre-GLS│ values, higher │pre-GLS│ was associated with greater reductions in EDV. When adjusted for pre-EDV and pre-ESV, GLS lost significance(linear p=0.29, quadratic p=0.29).*

Conclusion: *Our study shows a majority of MitraClip patients demonstrate reverse remodeling and pre-GLS to be associated with reverse remodeling, though not robustly. A study with larger sample sizes is needed to better define the association.*

Keywords

Echocardiography, Global longitudinal strain, MitraClip, Mitral regurgitation.

Abbreviations

TTE: Transthoracic echocardiography; echo: Echocardiogram; GLS: Global Longitudinal Strain; pre-GLS: Preprocedural GLS; LV: Left Ventricular; EDV: End Diastolic Volume; ESV: End Systolic Volume; EF: Ejection Fraction; LAVi: Left Atrial Volume index; RVSP: Right Ventricular Systolic Pressure; MR: Mitral Regurgitation, FMR: Functional Mitral Regurgitation; DMR: Degenerative Mitral Regurgitiation; MMR: Mixed Mitral Regurgitation.

Background and Purpose

Mitral Regurgitation (MR), which is found in 9.3% of people over age 75 years [1], independently worsens prognosis [2]. MR can be clasified as primary or degenerative (DMR), when there is a structural abnormality of the mitral valve (MV); as secondary or functional (FMR), when the MR is due to left atrial or left ventricular (LV) dysfunction; or as mixed (MMR),when there is a combination of both [1,3]. LV dysfunction and remodeling leads to papillary muscle displacement, leaflet tethering and dilation of the mitral anulus, all impairing valve closure [1,3]. MR creates a volume overload state, promoting LV dilation. A detrimental remodeling cycle develops in which further LV dilation worsens MR, which worsens LV dilation and onward [4]. Therapeutic interventions reducing MR can lessen LV volume overload, breaking the remodeling cycle. This allows for reverse remodeling, with normalization or improvement of the dilated volume dimensions [5]. Post-surgical MR patients demonstrate more favorable prognoses when improvements in LV size and function are detected [4]. The absence of reverse remodeling post MitraClip has been shown to correlate with recurrence of MR and symptom progression [6].

Through a percutaneous femoral venous trans-septal approach, the MitraClip (Abbott Vascular) reduces MR by coapting the mitral leaflets [7], and narrowing the MV annulus [8]. In the EVEREST trials, the Mitraclip reduced the severity and mortality in MR patients [7,9]. More recently, the COAPT trial in 2018 showed in moderate-severe MR patients with HFref a 32.1 % absolute reduction in heart failure hospitalizations at 2 years and 16% absolute reduction in all cause death with a number needed to treat of six [10]. In other studies, the Mitraclip has shown to induce long term reverse remodeling, as evident by reduced end diastolic diameter (EDD) and index (EDI), reduced end systolic diameter (ESD) and index (ESI), and improved LV ejection fraction (EF) [4,11-13].

Not all MitraClip patients experience reverse remodeling and the associated improved outcomes. In one study, only 77.3% demonstrated reverse remodeling, defined as at least 10% reduction in end diastolic volume (EDV) [4]. Predicting patients likely to experience reverse remodeling from MitraClips can aid clinical decision making regarding intervention candidacy [14].

Known predictors of reverse remodeling include: ischemic etiology, shorter pre-procedure duration of congestive heart failure [6], pre-operative LV EDD and ESD [5], and longitudinal strain [15]. Recently, global longitudinal strain (GLS) in a small sample of FMR patients demonstrated predictability for reductions in ESV [16]. However, no study yet has evaluated reverse remodeling, in terms of EDV change, after MitraClip procedure in all types of MR patients predicted by global longitudinal strain (GLS).

GLS is a speckle echocardiographic parameter describing the change in length (deformation) of the entire myocardial LV wall [17]. GLS is more reproducible than EF, is unaffected by tethering effects and is not reliant on geometric assumptions like EF [18,19]. Clinically, GLS has been shown to accurately identify early heart failure and subclinical LV dysfunction [14,18-23]. Also, it has been recognized as the best echocardiographic predictor of mortality [24]. Impaired preoperative GLS has demonstrated the ability to predict post-operative LV dysfunction among MR patients [14,21,25,26], and has the strongest correlation when compared to other known prognostic markers such as LVEF, atrial fibrillation, and LVESD [25].

Our primary objective was to evaluate if preprocedural GLS (Pre-GLS) predicts LV reverse remodeling at one year, defined by 10% reduction in EDV, in moderate-severe and severe MR patients undergoing MitraClip procedure for all types of MR. As secondary objectives, we compared pre and post clip echocardiographic parameters and evaluated for GLS predictability differences between DMR and FMR subgroups.

Methods

Study Population

All 189 patients who underwent MitraClip procedures between 2007-2019 at our institution were reviewed retrospectively. Patients were included if they were nonpregnant, greater than 18 years old, and had severe (4+) or moderate/severe (3+) mitral regurgitation. Patients were excluded if their pre- and post-procedural echocardiograms were outside the pre-specified time window or if the images were inadequate. Pre-procedural echocardiograms were identified as within 0-120 days prior to the procedure and post-procedure echocardiographs as within 6-24months post procedure. Echocardiograms were considered inadequate if the image quality was of poor quality to apply GLS or to acquire accurate 2D measurements, or if one of the three views necessary for GLS measurements (apical 4-Chamber, 3-Chamber, and 2-Chamber) was missing. Any patient chart or echocardiogram with conflicting or uninterpretable data was excluded. Complete echocardiographic data was available on 57 patients. See Figure 1 describing patient record selection.

Outcome measures

Demographics: The names, medical record numbers, gender, date of procedure, dates of echocardiograms, and age were collected through searching the electronic medical record.

2D echocardiographic data: The echocardiograms (echo) were performed with Philips iE33 or Epic systems. The data was collected from the accompanying reports, including chamber volumes, function, and valvular descriptions.

MR type was determined from the medical record and echo report. When echo or chart evidence demonstrated both functional MR and degenerative (such as calcified mitral valve) the patient was categorized as mixed.

MR severity, based on qualitative assessment, graded as 0 (none/trace) to +4 (Severe) and chamber parameters, included left ventricular end diastolic volume (EDV), end systolic volume (ESV), ejection fraction (EF), left atrial volume index (LAVi), and right ventricular systolic pressure (RVSP) were abstracted from the reports.

If any of these parameters were not available on the reports, they were obtained by direct review of the echos by an echocardiography-certified cardiologist using the American

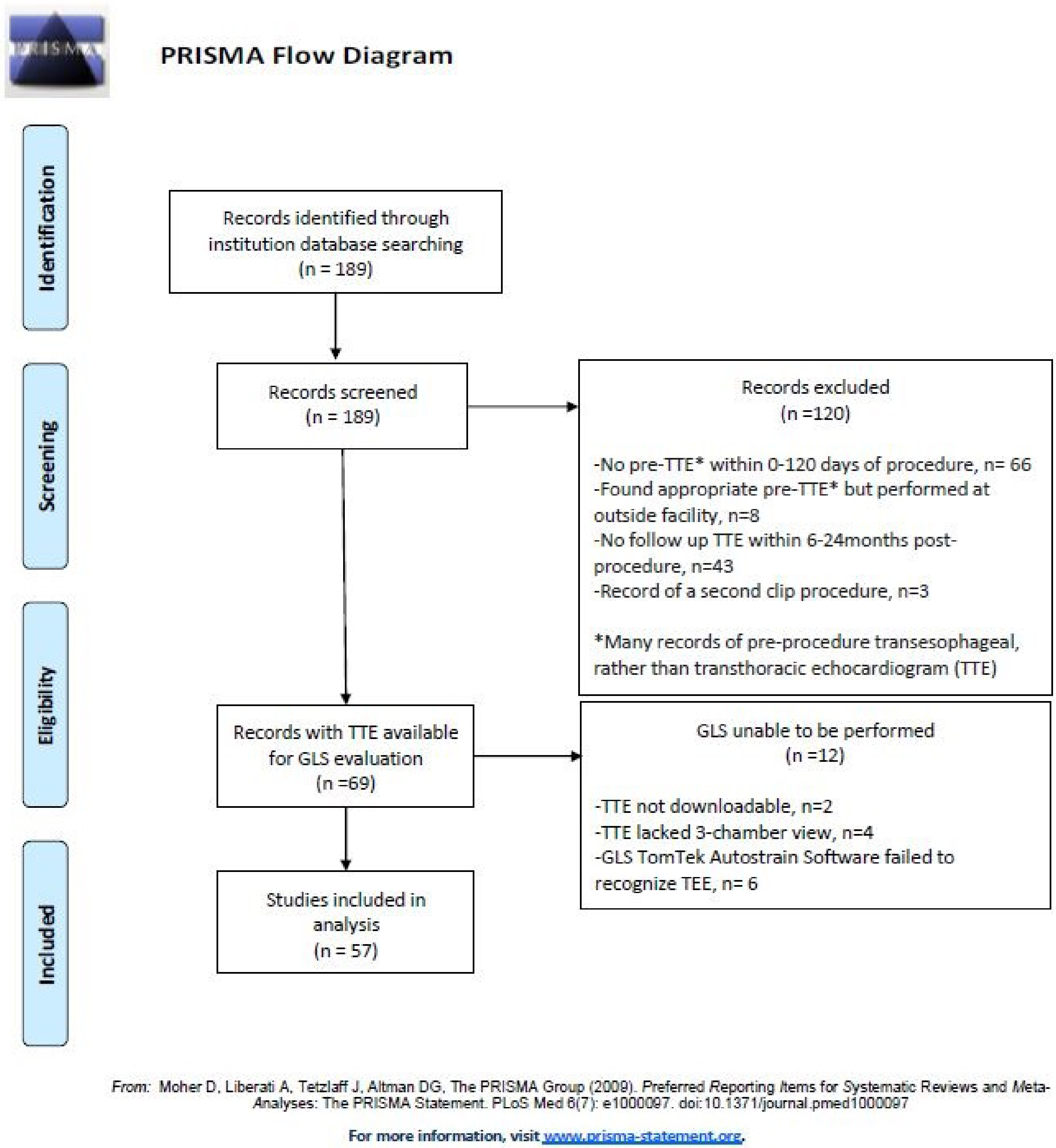

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement, Global longitudinal Strain (GLS), Transthoracic echocardiogram (TTE).

Society of Echocardiography (ASE) Guidelines for Chamber and MR Quantification.

Speckle Imaging Global Longitudinal Strain Data

Global longitudinal strain (GLS) was obtained with the Philips QLab TomTec AutoSTRAIN© software. We measured endocardial GLS from the apical 2-chamber, apical 3-chamber and apical 4-chamber views, to generate the global value. GLS, typically a negative percentage value as the deformation is a shortening dimension, was reported in absolute value throughout this manuscript. The autostrain measurement was first obtained, and then minor edits performed by the clinician were applied to better approximate the endocardial boarder and more accurately identify the mitral anulus. Two independent clinicians performed edited autostrain GLS measurements on 20 echocardiograms on two separate occasions to determine inter- and intra-reader reliability. See Figure 2 for a sample GLS Autostrain report.

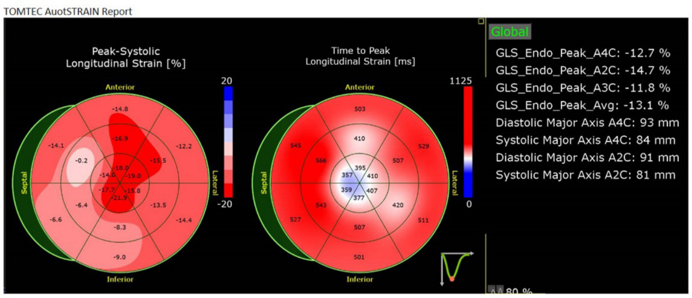

Figure 2: TOMTEC Autostrain Report for a representative patient. Note the Global Longitudinal Strain (GLS) is measured along the endocardial border in three standard echocardiographic views: apical 4 chamber, apical 2 chamber, and apical 3 chamber. Then the composite average is reported, and in this study, recorded as an absolute value term for each patient.

Statistical Analysis

All statistical analyses except inter- and intra-reader reliability analyses were carried out in SAS 9.4 (SAS Institute, Cary, N.C.). To assess inter- and intra-reader reliability, Pearson correlation coefficients were calculated for edited autostrain GLS measurements within and between readers. Demographics were summarized by pre/post group using means and standard deviations for numeric variables and frequencies and percentages for categorical variables. Mean pre-post changes in LVEDV, LVESV, LVEF, LAVI, and RVSP were calculated and were tested for significance using paired t-tests. The effect of pre-procedural GLS (Pre-GLS) on the odds of a 10% change in EDV was modeled using logistic regression. This was done for the entire sample and for several sub-groups.

Finally, the effect of GLS on the numeric change in EDV was modeled using linear regression, as were the effects of LVEDV, LVESV, LVEF, LAVI, and RVSP on numeric change in EDV. For this final set of linear regression models, crude (single-predictor) models were fit for each predictor first. Linear and quadratic models were fit to assess the best functional form. GLS and any other predictors that were significant in their respective crude models were included as predictors in a final multivariable model.

Results

In 20 sample echocardiograms, the edited autostrain GLS measurements determined by two different clinicians demonstrated minimal inter- and intra-reader GLS variability, r=0.90 and r=0.95, respectively.

Our population of 57 patients was composed of 55% female, 12.3% functional mitral regurgitation (FMR), 61.4% degenerative mitral regurgitation (DMR) and 26.3% mixed mitral regurgitation (MMR). A reduction in EDV was demonstrated in 38 patients (67%); the pre- GLS averaged 12.5% (SD 4.2) mean, 12.4% median (Table 1).

Table 1: Demographics and Pre/Post Echocardiogram Characteristics.

Variable	Category	Pre	Post	Combined Cohort
Age (years)[1]		82 ± 15	82 ± 15	82 ± 15
Body Surface Area (m^2) [1]		1.8 ± 0.2	1.8 ± 0.3	1.8 ± 0.2
Heart rate (bpm)[1]		77 ± 17	69 ± 14	73 ± 16
Blood pressure Systolic (mmHg)[1]		121 ± 19	125 ± 22	123 ± 21
Blood Pressure Diastolic (mmHg)[1]		68 ± 10	69 ± 11	68 ± 11
Gender[2]				
	Female			32, 55%
	Male			26, 45%
GLS mean (absolute value, %)[2]		12.5 ± 4.1		12.5 ± 4.1
MR Type[2]				
	Degenerative			35, 61.4%
	Functional			7, 12.3%
	Mixed			15, 26.3%

[1]Estimates are mean ± standard deviation; [2]Estimates are count, %

There were significant drops in EDV, ESV, LAVi, and RVSP (all p<0.01). EDV dropped by 17ml (95% CI: 7 to 28; p<0.01). ESV decreased by 9ml (95% CI: 3 to 16; p<0.01). LAVi dropped by 6ml/m2 (95% CI: 1 to 11; p=0.01). RVSP dropped by 9mmHg (95% CI: 4 to 14; p<0.01). There was no significant change in LV EF (p=0.42) (Table 2).

Table 2: Pre-Post Changes.

Variabl*e*	Mean Change (95% CI)	p-Value
LVEDV	-17 (-28, -7)	<0.01
LVESV	-9 (-16, -3)	<0.01
LVEF	1 (-2, 4)	0.42
LAVI	-6 (-11, -1)	0.01
RVSP	-9 (-14, -4)	<0.01

GLS was not a significant predictor of 10% change in EDV in the overall population (p=0.51) nor in the following sub-populations: top 50% EDV (p=0.42), degenerative MR (p=0.84), mixed MR (p=0.29), mixed and functional MR (p=0.41). See Table 3 for odds ratio estimates and 95% confidence intervals. However, higher │pre-GLS│ sample averages were noted in patients with at least 10% reduction in EDV compared to those without, as shown in Table 4.

Table 3: GLS as a predictor of 10% change in EDV in various populations.

Predictor	Population	Odds Ratio (95% CI)	p-Value
GLS	All	1.04 (0.92, 1.19)	0.51
GLS	Top 50% EDV	1.09 (0.87, 1.37)	0.42
GLS	Degenerative MR	1.02 (0.86, 1.21)	0.85
GLS	Mixed MR	1.16 (0.86, 1.57)	0.29
GLS	Mixed and Functional MR	1.10 (0.87, 1.40)	0.41

Pre-LAVi (p=0.38), pre-EF (p=0.66) and pre-RVSP (p=0.32) did not have significant crude (univariable) associations with EDV change. Pre-EDV (p<0.01) and pre-ESV (p<0.01) had significant crude associations with change in EDV and were therefore included in the adjusted model. Both were also significant predictors in the adjusted model (pre-EDV p<0.01; pre-ESV p<0.01). │Pre-GLS│

had a significant crude association with EDV change when linear (p=0.04) and quadratic (p=0.04) GLS terms were included in the model, as depicted in Figure 3. However, when adjusted for pre-EDV and pre-ESV, │Pre-GLS│ was no longer a significant predictor of EDV change (linear p=0.29, quadratic p=0.29) (Table 5).

Table 4: Comparison of with (w) 10% reduction in Post-procedural EDV to without (w/o) in sub-groups.

Sub Group	GLS (absolute value %)	
	w	w/o
All patients (n=57)	12.9% (n=28)	12.2% (n=29)
DMR (n=35)	13.5% (n=18)	13.4% (n=17)
MMR (n=15)	12.8% (n=7)	10.3% (n=8)
MMR+FMR (n=22)	11.9% (n=10)	10.4% (n=12)
Top 50th percentile of pre-procedural EDV (all>110ml) (n=28)	12.2% (n=18)	11.0% (n=10)
ASE defined Abnormal EDV, mild: M>150ml and F>106ml (n=22)	11.9% (n=14)	9.9% (n=8)
ASE defined Abnormal EDV, moderate: M>174ml and F>120ml (n=17)	11.7% (n=11)	9.8% (n=6)

Table 5: Predictors of EDV change in crude and adjusted models.

Predictor		Crude		Adjusted	
		Regression Coefficient Estimate (95% CI)	p-Value	Regression Coefficient Estimate (95% CI)	p-Value
Pre GLS	Linear	-15.9 (-30.9, -0.8)	0.04	-6.2 (-17.7, 5.3)	0.29
	Quadratic	0.6 (0.03, 1.2)	0.04	0.2 (-0.21, 0.7)	0.29
LAVI (pre)		-0.14 (-0.45, 0.17)	0.38		
LVEDV (pre)		-0.39 (-0.52, -0.27)	<0.01	-0.83 (-1.14, -0.53)	<0.001
LVEF (pre)		0.16 (-0.57, 0.89)	0.66		
LVESV (pre)		-0.34 (-0.54, -0.14)	<0.01	0.64 (0.22, 1.07)	0.004
RVSP (pre)		0.24 (-0.25, 0.73)	0.32		

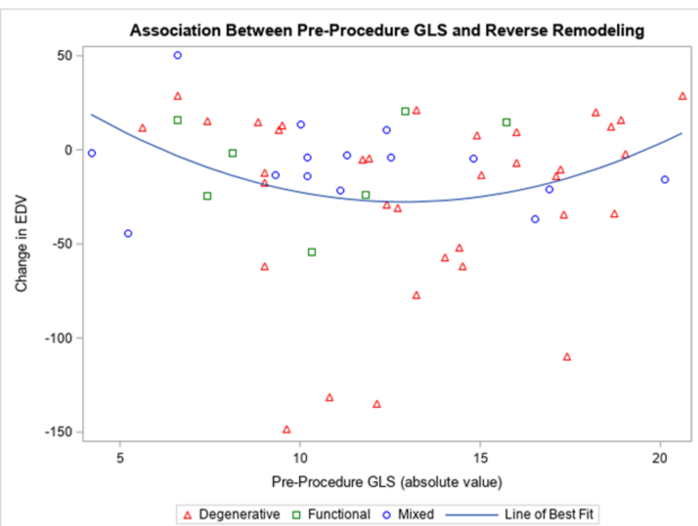

Figure 3: Association Between Pre-Procedural Global Longitudinal Strain (GLS) and Reverse Remodleing (depicted as change in End Diastolic Volume, EDV).

When the linear functional form for GLS is used as a predictor of change in EDV, the result is not significant (p=0.8196). The regression coefficient for linear │pre-GLS│ is -0.3008 (-2.9301, 2.3285; p=0.8196). Assuming the same regression coefficient and the same variability in the data, a sample size of 641 observations would be smallest sample size that would result in a significant p-value, as it reduces the standard error just enough to obtain a Wald confidence interval with zero as an upper bound. In that case, the result would be -0.3008 (-0.6016, 0.0000; p=0.05).

All but two patients demonstrated a change of at least -1 in severity post-clip with improvement to moderate (+2) MR or better post-clip. The two patients that failed to improve were mixed etiology. Mean pre-clip MR severity rating of 3.6 improved to post-clip mean rating of 1.2. Of those with mean gradients reported, 9 patients had mean gradients >7mmHg post clip and the post-clip average mean gradient was 4.55mm Hg. Also, while most patients underwent elective procedures, five were urgent and one was emergent.

Discussion

The average 2D echocardiographic volume and pressure dimensions, including EDV, ESV, LAVi, and RVSP, all significantly decreased after Mitraclip placement, consistent with other studies. However, the LVEF and GLS, as more discrete markers of LV function, demonstrate more complex findings. Given that mean LVEF was 52% and only 25% of patients had LVEF<40%, many of our patients did not have signifanct LV dysfunction detectable by LVEF. LVEF showed less change post clip than standard 2D estimating variation (about +/- 8% [27]). GLS, which detects earlier dysfunction and is less load dependent [28], likely offers amore sensitive assessment of LV dysfunction in our patients, and our data suggests more pronounced GLS associations at more extreme GLS values, particularly severely impaired GLS.

Our population consisted largely of patients with abnormal pre-GLS, 51/57 (89%), abnormal as defined by ASE as GLS <|18%| [29]. Notably, GLS <│7%│ was recently showed to demonstrated worse all-cause mortality outcomes than GLS>│7%│ among functional MR patients [28], and only six of our study patients were below │7%│. In our study, the curvi-linear graph (Figure 3) shows that among the lower, more abnormal │pre-GLS│ values on the left-side of the graph, a higher │pre-GLS│ is associated with greater reductions in EDV as depicted by the greater curvature. That pattern changes at higher, more normal │pre-GLS│ values. If studied in a more abnormal GLS population of <│7%│, the trend seen in the more left-sided part of our curve may be more apparent. The left-sided curvilinear trend is supported by findings in subgroups, where higher │pre-GLS│ sample averages were noted in patients with at least 10% reduction in EDV compared to those without, as seen in Table 4, though not statistically significant odd ratios as seen in Table 3. In such, our data's association among more severely abnormal GLS values, although not robust, may be more clinically useful.

In a study of 41 FMR patients in Italy, worse GLS was shown to predict lack of reverse remodeling, as defined by 10% reduction in ESV at 6 months. GLS was the only independent correlate of reverse remodeling (<p=0.01), and a GLS cut off of -9.25% (<0.01) was associated with reverse remodeling on a ROC curve, 81% sensitivity and 74% specificity [16]. Our results likely differ because our population was more heterogenous including FMR, DMR and mixed. This seemingly prominent impact of etiology on GLS predictive ability may reflect the inherent pathophysiologic relationship of functional MR with LV dysfunction. Combining MR types may therefore be clinically impractical. Also, our study allowed for a longer follow up, which may have underestimated our observed effect as over time other cardiac impairments could develop. Furthermore, we used EDV, where this study used ESV. Our average LVEF and │pre-GLS│ values were higher at 52% vs 34.4% (SD5.4) LVEF and 12.5% (SD 4.2) vs 11.3% (SD 3.9) │pre-GLS│ [16]. The early, left-sided portion of our curvilinear graph shows similar findings seen in this Italian study which addressed patients with more severe LV dysfunction. Our finding that EDV was stronger than ESV in the multivariable analysis supports our use of EDV change as the volume dimension for evaluating reverse remodeling in our population. To minimize type I error, we only looked at reverse remodeling in terms of change of EDV but perhaps evaluating other markers of reverse remodeling for correlation to GLS such as ESV, LAVi, RVSP, or EF could have detected significant predictability.

Our study supports other studies in finding automated GLS highly reproducible, despite needing practitioner edits. Inter and intra reliability in our study, r=0.90 and r=0.95, respectively was similar other mainstream studies (0.89 inter, 0.93 intra observer reproducibility) [28].

Limitations and Hypothesis-generating Considerations

A sample size of 641 patients would have been required to confidently state GLS fails to predict reverse remodeling (avoiding type II error), rendering our study significantly underpowered. Many of our limitations stem from small sample size and our efforts to reduce type I error risk. Our sample only had 7 FMR patients, and we therefore chose to combine the clinically similar FMR and mixed MR subgroups. The combined group better matches our larger proportion of DMR when performing statistical comparisons.

With only 57 patients, the adjusted model significantly reduces the power allotted to any regression co-efficient, and may explain the loss of significance in GLS. Since ESV and EDV correlate clinically as heart size changes and the crude regression values are very similar, and multicollinearity likely explains the ESV change from negative to positive regression coefficients seen in Table 5.

To be most generalizable, we looked at all MitraClip patients, rather than selecting just those that demonstrated evidence of pre-clip remodeling. Perhaps we would have seen more reverse remodeling if we targeted just those with pre-clip remodeling. This is difficult to identify clinically without a clear gold standard, particularly in FMR patients where LV dilation may be due to reasons other than MR.

Our graph depicts four patients with particularly large EDV changes, and while these patients are all DMR with at least moderately enlarged pre-EDV (all >200ml) and │pre-GLS│ greater than │9.25│, discrete factors affording specifically them major improvements are unknown and warrant further study. Additional sources of bias with unknown significance include the primarily elderly population, average age of 82 years, and the small group of patients (30%, 57 of 189 total MitraClip procedures) with complete echo data, most attributable to pre-procedural transesophageal echocardiogram rather than transthoracic or lack of follow up.

Tomtech software is unable to accurately calculate strain with heart rate variability >10%, such as in atrial fibrillation or arrythmia. We did not exclude patients based on heart rate or arrythmia as we felt the GLS autostrain values were not grossly unexpected compared to clinician visual estimates, and we favored including all patients to increase sample size and generalizability. We avoided additional adjusting as that further reduces power. However, the precision in GLS measurement may have been compromised slightly.

Conclusion

Our study shows that most patients that undergo the MitraClip procedure demonstrate reverse left ventricular remodeling and that there is a soft association between pre-GLS and reverse remodeling. Our findings encourage further prospective studies with larger sample sizes, diverse MR etiologies and various LV dysfunctional states to better characterize the association between GLS and reverse remodeling. A validated predictive association will then help guide clinical decision making regarding MitraClip candidacy.

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