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Mechanisms of Functional Mitral Regurgitation in Ischemic Cardiomyopathy Determined by Transesophageal Echocardiography (From the Surgical Treatment for Ischemic Heart Failure [STICH] Trial)

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Abstract

The mechanisms underlying functional mitral regurgitation (MR), and the relation between mechanism and severity of MR have not been evaluated in a large multicenter randomized controlled trial. Transesophageal echocardiography (TEE) was performed in 215 patients at 17 centers in the Surgical Treatment of Ischemic Heart Failure (STICH) trial. Both two-dimensional (2D, n=215) and three-dimensional (3D, n=81) TEE were used to assess multiple quantitative measures of the mechanism and severity of MR. By 2D TEE, leaflet tenting area, anterior and posterior leaflet angles, mitral annulus diameter, left ventricular (LV) end-systolic volume index, LV ejection fraction (LVEF), and sphericity index ($p < 0.05$ for all) were significantly different across MR grades. By 3D TEE, mitral annulus area, leaflet tenting area, LV end-systolic volume index, LVEF, and sphericity index ($p < 0.05$ for all) were significantly different across MR grades.

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A multivariable analysis showed a trend for annulus area ($p=0.069$) and LV end-systolic volume index ($p=0.071$) to predict effective regurgitant orifice area (EROA) and for annulus area ($p=0.018$) and LV end-systolic volume index ($p=0.073$) to predict vena contracta area. In the STICH trial, multiple quantitative parameters of the mechanism of functional MR are related to MR severity. The mechanism of functional MR in ischemic cardiomyopathy is heterogeneous but no single variable stands out as a strong predictor of quantitative severity of MR.

Keywords

mitral regurgitation; ischemic cardiomyopathy; heart failure

Functional mitral regurgitation (MR) is a common complication of ischemic heart disease that is associated with increased mortality.^{1–5} Early studies of the mechanism of functional MR focused on mitral annular dilation and loss of systolic annular contraction due to left ventricular (LV) dilation,⁶ diminished mitral leaflet closing force,⁷ and abnormal LV shape.⁸ More recently, it has been shown that functional MR is caused by leaflet tethering as the papillary muscles are displaced apically and laterally by LV dilation.^{9–13} Papillary muscle displacement may be due to global or regional wall motion abnormalities and may be symmetric or asymmetric.¹⁴ Understanding the mechanisms of functional MR in any given patient has important implications regarding the correct approach to repairing it. To date, no large prospective studies have examined the mechanism(s) underlying functional MR in ischemic cardiomyopathy, nor has the relation between mechanism and severity of functional MR been determined. This is a report of a prospectively defined ancillary study to the Surgical Treatment of Ischemic Heart Failure (STICH) trial, in which 2-dimensional (D) and 3D transesophageal echocardiography (TEE) were used to define the mechanism(s) of functional MR in a large clinical trial of patients with ischemic cardiomyopathy randomized to medical therapy, coronary bypass grafting, or coronary bypass grafting plus surgical ventricular restoration.^{15,16}

Methods

All participating STICH study sites were invited to participate in the STICH MR TEE Substudy; 17 accepted. All 17 sites were provided with a detailed study protocol for obtaining TEE images to define the mechanism and severity of functional MR.^{17–19} IRB approval was obtained from each site and written, informed consent was obtained from all patients. At the time the STICH trial was initiated, real-time 3D imaging was not available. Sites equipped with a Philips ultrasound machine (Philips Ultrasound, Andover, MA) were capable of 3D TEE acquisitions using a rotational reconstruction algorithm.²⁰ Philips graciously provided the 3D software to those sites. For STICH patients randomized to medical therapy, TEE was done within one week of randomization. For patients randomized to surgery, a baseline, preoperative TEE was done within one week prior to surgery. Intraoperative TEE was excluded by the study protocol because general anesthesia dramatically reduces the severity of MR by TEE.²¹

TEE was performed during intravenous conscious sedation and local oropharyngeal anesthesia. Heart rate, blood pressure, oxygen saturation, and ECG were monitored throughout the procedure. Transgastric short-axis views of the LV were obtained at the mid-papillary muscle level and mitral leaflet levels. A transgastric long-axis view was also oriented to show both papillary muscles with their chordal attachments to the mitral leaflets. From the mid-esophagus, the probe was retroflexed to obtain a 4-chamber view with care to maximize LV cavity length and width while keeping the LV long-axis in the center of the imaging sector. From this position, the imaging plane was manually rotated to obtain a

commissural view, a two-chamber view, and a long-axis view. For sites with 3D capability, a least two 3D rotational scan was obtained in each patient. Translational artifacts secondary to patient respiration were minimized using proprietary software to automatically capture images within a defined respiratory threshold. After obtaining a well-aligned 4-chamber view, the probe was rotated automatically in 6° increments by the 3D TEE software across a total of 180°. These images were downloaded onto a 5.25" magneto-optical disk and sent to the Core Laboratory, where analysis was performed in blinded fashion using custom software (Omni4D, Massachusetts General Hospital, Boston, MA). This offered several advantages with regard to quality control. First, this software has been previously validated *in vitro* and *in vivo*.^{10–13} Second, it allowed the different TEE operators at different STICH sites to get consistent high-quality data from a single mid-esophageal probe position during quiet respiration or breath hold. Third, it allowed more accurate measurements without confounding by foreshortened or off-axis views or flattening of 3-dimensional measurements onto a 2-dimensional display screen.

The mechanism(s) of functional MR was assessed by quantitative measures including leaflet tethering distance, tethering angle, tenting area, papillary muscle displacement, and annulus area at end-diastole and end-systole. 3D TEE datasets were analyzed by the method of Otsuji et al.¹¹ Manual tracing was used to identify the hinge points of the mitral leaflet insertion to identify the mitral annulus in each rotational imaging plane. The aortic annulus was identified by the hinge points of aortic leaflet insertion, and the intersection of the aortic and mitral annulus allowed identification of the medial and lateral fibrous trigones. The tips of the papillary muscles were also identified. In cases with complex papillary muscle anatomy, the largest papillary muscle head, which was most centrally located was selected. All of these points were assigned different colors by the Omni4D software, so that they could be tracked in 3 dimensions (Fig. 1). The computer allowed rotation of the images to facilitate analysis. The software then automatically calculated the mitral annulus area at end-diastole and end-systole, the percent systolic contraction of the mitral annulus, the papillary muscle separation distance, the mitral tenting area and height, the papillary muscle separation angle (angle from the posteromedial papillary muscle to the medial trigone to the anterolateral papillary muscle), and the distances between the medial trigone and the posteromedial and anterolateral papillary muscles.

In addition to the mechanistic variables measured from TEE images, core laboratory evaluations of LV end-diastolic volume index and end-systolic volume index, LVEF, and sphericity index were available from the STICH trial database. In the main STICH trial, all patients underwent baseline echocardiography, while magnetic resonance imaging and radionuclide imaging were optional. Using methodology described previously, optimal LV volumes and LVEF were determined using an approach that incorporated all modalities with the best correlation to overall mortality.²²

Quantitative measurements of MR severity, effective regurgitant orifice area (EROA) and vena contracta width (VCW) were used. MR was considered to be absent if no color flow signal was detectable superior to the mitral coaptation line during systole by color flow mapping. Trace MR was considered to be present when a few color pixels were present but no defined jet morphology was observed. For purposes of data analysis, none and trace were grouped together. If a defined systolic color flow jet was present, the severity of MR was classified using a hierarchical approach. Accordingly, EROA by the PISA method was used to classify MR severity, unless it was of poor technical quality or could not be measured. If no MR was present, EROA was assigned a value of zero. As per the guidelines of the American Society of Echocardiography (ASE)²³ and European Association of Echocardiography (EAE),²⁴ mild MR was considered to be an EROA 0.2 cm², moderate MR 0.2 to 0.39 cm², and severe MR 0.4 cm² (31,32). If EROA was not available or

measureable, VCW was next used to classify MR severity with <0.3 cm being mild MR, and 0.7 cm being severe MR. If neither EROA nor VCW were available, regurgitant volume by quantitative Doppler was used. If no quantitative measures were available, the size of the color flow jet was used with 4.0 cm² denoting mild MR, and 8.0 cm² severe MR. Jet eccentricity, E wave velocity, pulmonary vein pattern were used to adjust the MR severity up or down by one grade using the integrative method described by the American Society of Echocardiography and European Association of Echocardiography guidelines.^{23,24} All patients graded as moderate or severe MR had quantitative assessment of EROA.

Quantitative measurements of annulus size and leaflet tethering were compared in three groups of patients – those without MR, those with mild MR (EROA < 0.2 cm²) and those with at least moderate MR (EROA ≥ 0.2 cm²). Specific measurements of MR mechanism were compared across MR grades. Analysis of variance was used to compare continuous variables of MR mechanism among three groups of MR severity. Multivariable regression analysis was performed to evaluate which measurements of the mechanism of MR are independent predictors of MR severity as defined by a) EROA and b) vena contracta width. For purposes of the multivariable analysis, EROA and VCW were assigned a value of 0 if MR was graded as none or trace.

Results

TEE studies were obtained in 214 subjects, of whom 81 had both 2D and 3D TEE performed and 134 had only 2D TEE. Of these, 210 (97.7%) studies were of sufficient quality to assess MR severity. There were 57 patients with no MR, 120 with mild, 29 with moderate, and 4 patients with severe MR. Of the subset of patients with 3D TEE, 26 had no MR, 44 had mild MR, and 11 had moderate or severe MR. Given the small sample of severe MR and the fact that even moderate MR portends a poor prognosis in heart failure (33), the moderate and severe MR grades were combined for statistical analysis.

Table 1 shows the demographic and clinical characteristics of the patients in the MR substudy compared to the STICH main trial population not included in the substudy. In general, MR substudy patients were similar to those in the parent trial, being predominantly white men with a median age of 60 years. There was a higher predominance of whites in the substudy compared to the main trial (91.1 vs. 76.6%, $p<0.0001$), more patients without angina (37.4 vs. 30.5%, $p=0.006$), and more patients with NYHA Class I heart failure symptoms (20.1 vs. 9.1%, $p<0.0001$). MR substudy patients tended to have higher diastolic blood pressure (median of 80 vs. 75 mmHg, $p=0.016$) and higher LV end-systolic volume index (median of 82.5 vs. 77.9 ml/m², $p=0.018$). MR severity (as graded by the sites) tended to be slightly worse in MR substudy patients (moderate/severe MR in 27.8 vs. 16.9%, $p<0.001$). Finally, patients in the MR substudy had slightly higher usage of the following medications: beta-blockers, ACE inhibitors, diuretics, aspirin, aspirin or warfarin, and statins ($p<0.05$ for all).

Table 2 shows the MR mechanistic variables by MR severity grades in the patients with 2D TEE studies. Multiple measurements were statistically significantly different across MR severity grades, including leaflet angle, posterior leaflet angle, mitral annulus diameter in the long-axis view (anteroposterior diameter), LV end-systolic volume index, LVEF, and sphericity index ($p<0.05$ for all). The most strongly predictive measurement of MR grade was LV end-systolic volume index (77 ml/m² for none/trace MR, 81 ml/m² for mild MR, and 99.9 ml/m² for moderate/severe MR, $p<0.001$).

Table 3 shows the results of MR mechanistic variables for the different grades of MR severity by 3D TEE. As with 2D TEE, multiple measurements showed statistically

significant differences between MR grades, including end-diastolic and end-systolic mitral annulus areas, leaflet tenting area, LV end-systolic volume index, LVEF and sphericity index ($p < 0.05$ for all). Leaflet tethering distance (lateral trigone to lateral papillary muscle) tended to be longer in moderate/severe MR, but was not statistically significant ($p=0.092$). The strongest association was with leaflet tenting area (1.6 cm^2 for none/trace MR, 1.9 cm^2 for mild MR, and 2.4 cm^2 for moderate/severe MR, $p<0.001$).

Table 4 shows the results of a univariate analysis of various MR mechanistic variables as predictors of quantitative MR severity by EROA and VCW, as pre-specified in the statistical analysis plan of the MR substudy. Statistically significant correlations were present between EROA and end-diastolic and end-systolic mitral annulus area, leaflet tenting area, baseline LV end-systolic volume index, and sphericity index. Statistically significant correlations existed between VCW and end-diastolic and end-systolic mitral annulus area by 3D TEE, leaflet tenting area, tethering distance from lateral trigone to lateral papillary muscle, baseline LV end-systolic volume index, and sphericity index.

Table 5 shows the results of multivariable analysis using the variables that were statistically significant by univariate analysis. A trend was found between EROA and end-diastolic mitral annulus area ($p=0.069$) and LV end-systolic volume index ($p=0.071$). However, R-square values were weak, indicating that none of these variables were strong predictors of EROA. For VCW, only end-systolic annulus area was statistically significant ($p=0.018$) with a trend for LV end-systolic volume index ($p=0.073$).

Discussion

It has been well accepted that in ischemic cardiomyopathy, functional MR is primarily caused by left ventricular dilation and/or dysfunction, such that coaptation of normal or nearly normal mitral leaflets is prevented by a combination of reduced systolic closing force, leaflet tethering, and mitral annular dilation. This ancillary study of the STICH trial offered the opportunity to systematically assess many of these variables using high resolution measurements of the mitral leaflets and annulus by TEE. The results showed that multiple 2D and 3D TEE measurements were associated with MR severity, emphasizing the complex and heterogeneous nature of ischemic functional MR.

Multiple mechanistic variables were associated with qualitative MR grade, including anterior and posterior leaflet angles, anteroposterior mitral annulus diameter, LV end-systolic volume index, LVEF and sphericity index in the subset of patients who had 2D TEE studies. The strongest of these were leaflet tenting area and LV end-systolic volume index, the only two variables with p values < 0.001 . In a smaller subset of 81 patients with 3D TEE, end-diastolic and end-systolic mitral annulus area, leaflet tenting area, LV end-systolic volume index, LVEF, and sphericity index were statistically significantly associated with MR grade. The strongest of these were end-systolic mitral annulus area and mitral leaflet tenting area, both with p values < 0.001 .

For patients in whom EROA could be assessed quantitatively, significant correlations were found for annulus area, leaflet tenting area, LV end-systolic volume index, and sphericity index on univariate analysis. However, on multivariate analysis, none of these variables were significantly related to EROA, although there was a trend for end-diastolic annulus area and LV end-systolic volume index. Similar findings were present for VCW, where only end-systolic annulus area was statistically significant and there was a trend for LV end-systolic volume index. This is probably explained by a strong degree of correlation between the mechanistic variables, which is consistent with the prevailing hypothesis that functional MR is a consequence of LV dilation and dysfunction.

The majority of our data comes from 2D TEE because many of the participating sites did not have 3D capability. At the time of recruitment into the STICH trial, the 3D rotational imaging used in this study was state of the art. However, current 3D imaging techniques use real-time imaging, which is less prone to translational artifacts and is recommended for evaluation of mitral valve morphology²⁵ and for quantitation of functional MR severity by planimetry of the vena contracta area.²⁶

The final analysis was conducted based on the data taken from 3 different sources: 2D TEE, 3D TEE and assessment of LV size and by 2D transthoracic echocardiography, radionuclide angiography, and cine magnetic resonance. This may raise doubts about the homogeneity of data.

Finally, the STICH inclusion criteria stipulated enrolling patients with heart failure due to ischemic cardiomyopathy, LVEF $\geq 35\%$, and anterior akinesis. Patients with functional MR due to isolated inferior or posterolateral wall motion abnormalities are not represented. In such patients, leaflet tethering is likely to play a larger role in the mechanism of functional MR.

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Fig. 1.

3D reconstruction of TEE images using Omni4D software. Blue line represents mitral annulus, green and white lines represent the leaflet area, The medial fibrous trigone (MT, orange dot), lateral fibrous trigone (LT, dark blue dot), medial papillary muscle (Mpm, yellow dot) and lateral papillary muscle (Lpm, light blue dot) are shown.

Table 1

Baseline Demographic and Clinical Characteristics: Comparison of Patients in MR Substudy vs. Not in MR Substudy

Variable	STICH H1/H2 Population		P value
	MR Substudy (n=214)	Not in MR Substudy (n=1922)	
Age (years)	60.4 (52.7, 68.0)	60.5 (54.0, 68.1)	0.317
Male	188/214 (87.9%)	1662/1922 (86.5%)	0.574
Female	26/214 (12.1%)	260/1922 (13.5%)	
White	195/214 (91.1%)	1473/1922 (76.6%)	<0.001
Black	5/214 (2.3%)	45/1922 (2.3%)	
Asian	5/214 (2.3%)	235/1922 (12.2%)	
Other	9/214 (4.2%)	164/1922 (8.5%)	
Multi-racial		5/1922 (0.3%)	
Body Mass Index (kg/m ²)	27.0 (24.5, 29.4%)	26.9 (24.2, 30.1%)	0.856
Prior myocardial infarction	183/214 (85.5%)	1559/1922 (81.1%)	0.115
History of hyperlipidemia	147/214 (68.7%)	1245/1918 (64.9%)	0.271
History of hypertension	129/214 (60.3%)	1147/1922 (59.7%)	0.865
Diabetes mellitus	70/214 (32.7%)	729/1922 (37.9%)	0.134
Current smoker	39/214 (18.2%)	406/1921 (21.1%)	0.320
Prior percutaneous coronary intervention	38/214 (17.8%)	294/1922 (15.3%)	0.346
Chronic renal insufficiency	8/214 (3.7%)	164/1920 (8.5%)	0.014
Stroke	18/214 (8.4%)	123/1922 (6.4%)	0.261
Prior coronary bypass	2/214 (0.9%)	58/1922 (3.0%)	0.080
Current Canadian Cardiovascular Society Angina Class	1.0 (0.0, 3.0)	2.0 (0.0, 3.0)	0.047
None	80/214 (37.4%)	586/1922 (30.5%)	0.006
I	29/214 (13.6%)	216/1922 (11.2%)	
II	51/214 (23.8%)	629/1922 (32.7%)	
III	51/214 (23.8%)	400/1922 (20.8%)	
IV	3/214 (1.4%)	91/1922 (4.7%)	
Current NYHA heart failure class	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	<0.001
I	43/214 (20.1%)	174/1922 (9.1%)	<0.001
II	111/214 (51.9%)	903/1922 (47.0%)	
III	54/214 (25.2%)	765/1922 (39.8%)	
IV	6/214 (2.8%)	80/1922 (4.2%)	
Blood pressure: systolic (mmHg)	120.0 (110.0, 130.0)	120.0 (110.0, 130.0)	0.123
Blood pressure: diastolic (mmHg)	80.0 (70.0, 80.0)	75.0 (69.0, 80.0)	0.016
Heart rate (bpm)	72.0 (66.0, 80.0)	72.0 (65.0, 80.0)	0.433
Creatinine (mg/dL)	1.1 (0.9, 1.2)	1.1 (0.9, 1.3)	0.067
Baseline LVEF (%) CMR/RN/ECHO/Site	26.1 (20.2, 32.0)	27.4 (22.0, 33.7)	0.056
End-systolic volume index (ml/m ²)	82.5 (65.0, 103.2)	77.9 (59.6, 98.6)	0.018
Anterior akinesia or dyskinesia (%)	47.0 (29.0, 57.0)	43.0 (35.0, 60.0)	0.382

Variable	STICH H1/H2 Population		P value
	MR Substudy (n=214)	Not in MR Substudy (n=1922)	
MR Severity Grade *			
None/Trace	66/212 (31.1%)	702/1912 (36.7%)	<0.001
Mild	87/212 (41.0%)	886/1912 (46.3%)	
Moderate/Severe	59/212 (27.8%)	324/1912 (16.9%)	
Baseline Medications			
Beta blocker	195/214 (91.1%)	1631/1922 (84.9%)	0.014
ACE inhibitor or ARB	193/214 (90.2%)	1698/1922 (88.3%)	0.423
ACE inhibitor	187/214 (87.4%)	1550/1922 (80.6%)	0.016
Digoxin	33/214 (15.4%)	351/1922 (18.3%)	0.304
Diuretic (potassium sparing)	137/214 (64.0%)	752/1922 (39.1%)	<0.001
Diuretic (loop/thiazide or potassium sparing)	169/214 (79.0%)	1360/1922 (70.8%)	0.012
Aspirin (daily)	190/214 (88.8%)	1521/1922 (79.1%)	<0.001
Aspirin or Warfarin	197/214 (92.1%)	1625/1922 (84.5%)	0.003
Statin	195/214 (91.1%)	1491/1922 (77.6%)	<0.001

N / Median (25th, 75th percentiles) for continuous variables, n/N (%) for categorical variables.

* MR grade by transthoracic echocardiography as determined by study site investigators.

Table 2

2-D Transesophageal Echocardiographic Measurements of Mitral Regurgitation Mechanism According to Mitral Regurgitation Grade

Variable	None/Trace (n=57)	Mild (n=120)	Moderate/Severe (n=33)	P value
Leaflet tenting area (cm ²)	1.5 (1.2, 1.8)	1.6 (1.4, 2.0)	2.1 (1.4, 2.2)	0.080
Leaflet tenting height (cm)	0.7 (0.6, 0.8)	0.8 (0.7, 0.9)	0.8 (0.7, 1.0)	0.611
Anterior leaflet angle (degrees)	40.0 (29.0, 44.0)	38.0 (32.0, 45.0)	38.0 (29.0, 46.0)	0.005
Mid-anterior leaflet angle (degrees)	148.0 (142.0, 158.0)	149.0 (140.0, 158.0)	147.0 (137.0, 158.0)	0.122
Posterior leaflet angle (degrees)	55.0 (46.0, 65.0)	54.0 (44.0, 64.0)	54.0 (45.0, 69.0)	0.028
Annulus diameter 4 chamber view (cm)	3.4 (3.3, 3.5)	3.4 (3.1, 3.6)	3.5 (3.2, 3.8)	0.654
Annulus diameter long-axis view (cm)	3.2 (2.9, 3.4)	3.3 (3.0, 3.5)	3.5 (3.4, 3.7)	0.004
Left ventricular end-systolic volume index (ml/m ²)	77.0 (57.3, 99.6)	81.0 (66.3, 100.2)	99.9 (82.6, 128.9)	<0.001
Baseline left ventricular ejection fraction (%)	27.0 (21.8, 33.1)	27.8 (20.0, 32.0)	22.7 (18.8, 26.0)	0.017
Sphericity Index	1.4 (1.4, 1.6)	1.4 (1.3, 1.6)	1.3 (1.2, 1.4)	0.008

N / Median (25th, 75th percentiles) for continuous variables.

Table 3

3-D Transesophageal Echocardiographic Measurements of Mitral Regurgitation Mechanism According to Mitral Regurgitation Grade

Variable	None/Trace (n=26)	Mild (n=44)	Moderate/Severe (n=11)	P value
Annulus area diastole (cm ²)	9.8 (9.0, 11.7)	11.8 (10.2, 13.0)	12.0 (11.4, 12.1)	0.002
Annulus area systole (cm ²)	10.1 (9.1, 11.4)	11.5 (10.2, 12.6)	12.2 (11.5, 13.3)	0.001
Annular contraction (%)	-2.3 (-7.9, 0.7)	1.9 (-2.8, 6.8)	-4.9 (-7.4, -3.6)	0.600
Leaflet tenting area (cm ²)	1.6 (1.3, 2.0)	1.9 (1.6, 2.4)	2.4 (2.2, 2.9)	<0.001
Medial trigone-medial papillary muscle distance (mm)	42.5 (41.0, 47.0)	44.6 (40.7, 48.0)	45.1 (43.5, 47.0)	0.295
Lateral trigone-lateral papillary muscle distance (mm)	25.1 (21.7, 29.6)	26.8 (23.3, 30.8)	29.9 (24.9, 34.4)	0.092
Primary chordal separation angle (degrees)	35.4 (28.2, 43.4)	37.3 (30.9, 41.3)	38.9 (33.6, 44.8)	0.082
Left ventricular end-systolic volume index (ml/m ²)	80.8 (59.9, 101.7)	88.1 (68.8, 108.3)	114.3 (93.8, 138.1)	0.006
Baseline left ventricular ejection fraction (%)	28.5 (21.9, 33.0)	27.0 (21.1, 31.3)	24.2 (18.7, 25.7)	0.050
Sphericity Index	1.5 (1.4, 1.5)	1.4 (1.2, 1.6)	1.4 (1.2, 1.5)	0.017

N / Median (25th, 75th percentiles) for continuous variables.

Table 4

Univariate Analysis of the Correlation between Mechanism and Quantitative Severity of MR.

Independent Variable	Dependent Variable	DF	P-value
Effective regurgitant orifice area by PISA method (cm ²)	Annulus area diastole (cm ²)	56	0.006
	Annulus area systole (cm ²)	55	0.007
	Annular contraction (%)	55	0.674
	3D: Leaflet tenting area (cm ²)	56	0.015
	Medial trigone-medial papillary muscle distance (mm)	55	0.173
	Lateral trigone-lateral papillary muscle distance (mm)	55	0.350
	Primary chordal separation angle (degrees)	55	0.775
	LVESVI (ml)	114	0.043
	Baseline LVEF (%)	114	0.157
	Sphericity Index	72	0.050
Vena contracta width (cm)	Annulus area diastole (cm ²)	78	0.002
	Annulus area systole (cm ²)	77	<0.001
	Annular contraction (%)	77	0.917
	3D: Leaflet tenting area (cm ²)	77	0.004
	Medial trigone-medial papillary muscle distance (mm)	77	0.075
	Lateral trigone-lateral papillary muscle distance (mm)	77	0.047
	Primary chordal separation angle (degrees)	77	0.312
	LVESVI (ml)	203	0.002
	Baseline LVEF (%)	203	0.061
	Sphericity Index	110	0.008

LVESVI - left ventricular end-systolic volume index; LVEF - left ventricular ejection fraction.

Table 5

Multivariable Analyses of the Correlation between Mechanism and Quantitative Severity of MR.

Dependent Variable	Variables	T value	P value
Effective Regurgitant Orifice Area	Mitral annulus area at end- diastole (cm ²)	1.86	0.069
	LVESVI (ml)	1.84	0.071
Vena Contracta Width	Mitral annulus area at end-systole (cm ²)	2.42	0.018
	LVESVI (ml)	1.82	0.073

LVESVI - left ventricular end-systolic volume index.