DOI: http://dx.doi.org/10.22122/arya.v14i1.1404

Prediction of the ischemic origin of functional mitral regurgitation in patients with systolic heart failure through posterior mitral leaflet angle

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Original Article

Abstract

BACKGROUND: Differentiating ischemic from non-ischemic functional mitral regurgitation (FMR) in patients with cardiomyopathy is important in terms of the therapeutic decision-making and prognosis, but might be clinically challenging. In this study, the deformation of mitral valve (MV) indices in the prediction of the etiology of FMR was assessed using 2D transthoracic and tissue Doppler echocardiography.

METHODS: This case-control study was conducted from April 2015 to January 2016 in Imam Reza Hospital in Mashhad, Iran. The participants consisted of 40 patients with ischemic cardiomyopathy (ICM) and 22 with non-ischemic dilated cardiomyopathy (DCM) who referred to the heart failure clinic. Transthoracic echocardiography was performed using the conventional 2D and tissue Doppler imaging (TDI). MV tenting area (TA), coaptation distance (CD), anterior and posterior mitral leaflet angles (AMLA and PMLA), and regional systolic myocardial velocity (Sm) were measured.

RESULTS: There were no significant differences in echocardiographic indices between the two groups, besides Sm and PMLA which were significantly lower and higher, respectively, in ICM subjects in comparison with DCM patients (P = 0.002). PMLA ≥ 40 degrees and Sm ≤ 4 cm/second have a relatively high value for discriminating the ischemic from non-ischemic origin of functional MR in subjects with systolic heart failure (sensitivity: 80.0% and 70.0%, specificity: 73.0% and 77.3%; P = 0.001 and P < 0.001; respectively). Multivariable logistic regression identified PMLA and anterior Sm as major determinants for ischemic MR {Odds ratio (OR) [95% confidence interval (CI)] = 0.89 (0.82-0.96), P = 0.003, OR (95% CI) = 0.29 (0.14-0.60), P = 0.001, respectively}.

CONCLUSION: The present study showed that PMLA and Sm had an independent significant association with the mechanism of FMR. These findings are suggestive of the predictive role of mitral deformation echocardiographic indices in the determination of the etiology of FMR in systolic heart failure.

Keywords: Cardiomyopathies, Systolic Heart Failure, Mitral Regurgitation, Transthoracic Echocardiography

Date of submission: 24 Apr. 2016, *Date of acceptance:* 25 Dec. 2017

Introduction

The mitral valve (MV) apparatus includes the mitral leaflets, chordae tendineae, papillary muscles, and mitral annulus. Abnormalities of any of these structures may cause mitral regurgitation (MR).

For clinical purposes, MR is classified as primary organic MR caused by intrinsic disease of the mitral leaflets, and secondary functional MR caused by diseases of the left ventricle (LV) and/or dilatation of MV annulus. Functional MR is further classified

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as ischemic or non-ischemic MR, depending on the contribution of coronary artery disease (CAD) to left ventricular myocardial dysfunction. These are two distinctly different disease conditions, with different pathophysiologies, outcomes, and management considerations.[1,2]

Patients with non-ischemic dilated cardiomyopathy (DCM) have a greater and more significant improvement in functional status during follow-up than those with ischemic cardiomyopathy (ICM), despite the use of similar cardiovascular medical treatments. The current optimal medical therapy (OMT) produces more favorable ventricular remodeling in DCM than ICM.[3]

LV systolic dysfunction and LV remodeling can result in the occurrence of functional mitral regurgitation (FMR). Moreover, the degree of severity of FMR is believed to be associated with morbidity and mortality outcomes.[2-4]

Several echocardiographic parameters including tenting area (TA), inter-papillary muscle distance (IPMD), coaptation distance (CD), and mitral leaflet angle (MLA) have been studied in patients with FMR.[3-7] Some studies have evaluated the correlation between MLA and other deformation indices for the evaluation of MR severity.[6,8,9]

Different complicated methods have been introduced to calculate the degree of severity of MR; however, the use of two-dimensional echocardiographic indices is relatively simple and has been proven to be a reliable method to accurately determine the degree of severity of FMR. Moreover, there is only limited evidence to suggest the predictive role of mitral deformation echocardiographic indices in determining the etiology of FMR in systolic heart failure.

The aim of this study was to elucidate differences in MV deformation indices between patients with ischemic and non-ischemic moderate FMR using transthoracic echocardiography.

Materials and Methods

This case-control study was conducted from April 2015 to January 2016 at Imam Reza Hospital in Mashhad, Iran. All subjects with clinical features of heart failure who had undergone Doppler echocardiography were assessed for eligibility.

Only patients who had been previously diagnosed with chronic heart failure (CHF), a severely reduced LV ejection fraction (LVEF) (EF ≤ 30%), and a moderate functional MR were included in the study. Patients with acute coronary syndrome (ACS), acute myocarditis, organic MV disease, and significant aortic valve disease, and patients undergoing cardiac resynchronization therapy (CRT) or with implantable cardioverter defibrillator (ICD) devices were excluded. All subjects were in sinus rhythm at the time of the study. The local Ethics Committee approved this study and all patients consented to participate in the study (code number: 93516).

All included subjects underwent selective coronary angiography (SCA) by the same experienced cardiologist at the Cath lab of Imam Reza Hospital, to differentiate the etiology of heart failure, and hence, determine the cause of FMR as being either ICM or DCM. Patients with a history of old myocardial infarction as well as subjects presenting with arterial narrowing of ≥ 50% on the proximal of any of the main three coronary arteries on SCA studies were defined as having CAD and categorized as subjects with ICM. Moreover, patients with DCM were defined as those with systolic heart failure in the presence of normal coronary arteries in SCA and no clinical history of myocardial ischemia. Accordingly, the study population was divided into two groups of ICM and DCM.

In addition to SCA, all included patients also underwent conventional as well as tissue Doppler imaging (TDI) as a second modality to assess different echocardiographic parameters, including systolic myocardial velocity (Sm), TA, CD, and MLA, in order to determine which parameter has the best predictive role by analysis considering SCA findings.

Conventional DI and TDI were performed using a Vivid Seven (GE Healthcare, Milwaukee, USA) with a 4S probe by an expert echocardiologist who was blinded to the angiographic data. Three loops of 2D and TDI images were stored for offline analysis. The severity of MR was determined using the proximal isovelocity surface area (PISA) method.

The modified biplane Simpson method determined LV end-diastolic volume (LVEDV) and LVEF.

Anterior and inferior Sm were measured using TDI at mid-anterior and inferior walls in the apical two-chamber view (Figure 1).

MV deformation indices were assessed in mid-systole using the parasternal long-axis and 4-chamber views (Figure 2). The TA of the MV was measured as the area enclosed by the annular line and MV leaflets. The CD was defined as the distance between the annular line and the leaflet's coaptation point. The posterior and anterior MLA (PMLA and AMLA, respectively) were measured directly between the mitral leaflets and mitral annulus plane in the 4-chamber view as shown in figure 2.

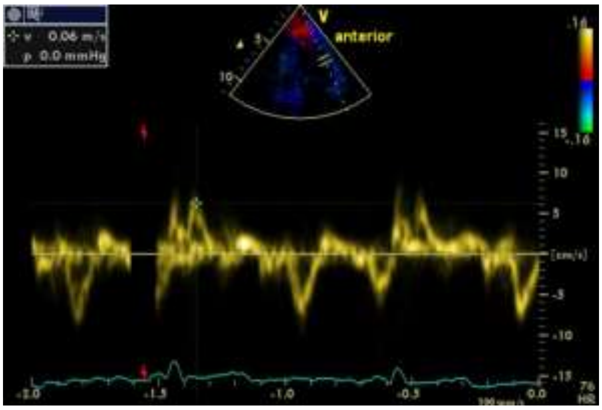

Figure 1. Systolic myocardial velocity measured by PW-based tissue Doppler imaging at the mid-anterior wall in two-chamber view

Standard parasternal and apical views were recorded as three consecutive beats for offline analysis according to the American Society of Echocardiography guidelines.[10]

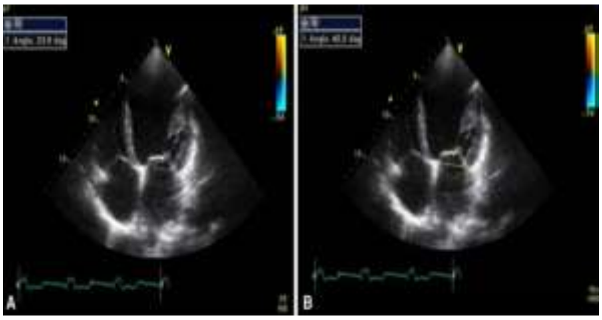

Figure 2. Anterior mitral leaflet angle (a) and posterior mitral leaflet angle (b) at mid-systole in apical four-chamber view

In the present text, continuous data are expressed as mean ± standard deviation (SD) and qualitative parameters are expressed as number (percentage). One-sample Kolmogorov-Smirnov test was used in order to evaluate the normality of parameters. Differences between groups were assessed by independent student's t-test for the normally distributed parameters and Mann-Whitney test for non-normally distributed variables. Categorical variables were compared using the chi-square test. Multivariable stepwise logistic regression analysis was performed with adjustments for age, gender, hyperlipidemia, hypertension, smoking status, anterior and inferior Sm, posterior MLA, and other variables with marginally significant differences ($P < 0.100$) in univariate analyses in order to investigate the independent determinant of functional ischemic MR. A receiver operating characteristic (ROC) curve was constructed to determine the best cut-off values for tissue Doppler echocardiographic parameters. ROC curve shows the relation between true positive (sensitivity) and false positive (1-specificity) for each echocardiographic parameter. The area under the ROC curve was measured. A large area under the ROC curve represents more reliability and good discrimination of the echocardiographic parameter. Youden's index specifies the best cutoff point. Its value ranges from 0 to 1, and has a 0 value when a diagnostic test gives the same proportion of positive results for groups with and without the disease. A value of 1 indicates that there are no false positives or false negatives. The index gives equal weight to false positive and false negative values, so all tests with the same value of the index give the same proportion of total misclassified results.

A two-tailed P-value < 0.05 was considered significant. SPSS statistical software (version 12.0, SPSS Inc., Chicago, IL, USA) and MedCalc Software (version 12.1.4.0, MedCalc Software, Mariakerke, Belgium) were used.

Results

The study population consisted of 62 patients (mean age: 57.21 ± 16.41 years, 37.1% women) with chronic CHF (including 40 suffering from ICM and 22 from DCM). The baseline demographic and clinical characteristics of the two groups are shown in table 1. There were no statistically significant differences between the two groups in terms of NYHA functional class, body surface area (BSA), hypertension (HTN), and bundle branch block (BBB), even though patients with ICM were significantly older and more often had a history of diabetes mellitus (DM), hyperlipidemia (HLP), and smoking compared to patients with DCM ($P < 0.050$).

The severity of LV systolic dysfunction, LVEDV, LVESV, and LVEF were similar in the two groups ($P > 0.050$). In addition, some other echocardiographic parameters such as TA, CD, and AMLA were not significantly different between patients with ICM and DCM (P = 0.690, 0.420, and 0.670, respectively). It is noteworthy that patients with ischemic FMR had significantly lower anterior Sm, lower inferior Sm, and a higher degree of PMLA in comparison with patients with DCM ($P < 0.050$). All echocardiographic measurements are shown in table 2.

Table 1. Demographic and clinical characteristics of patients with ischemic cardiomyopathy and non-ischemic cardiomyopathy

Parameter		ICM (n = 40)	NICM (n = 22)	P
Demographic/Clinical	Age (years)	59.28 ± 17.21	47.41 ± 19.24	0.017
	Gender (female %)	10 (25.0)	13 (59.0)	0.008
	NYHA Class- II/III	22 (55.0)	13 (59.0)	0.780
	BSA (m^2)	1.74	1.71	0.190
	Diabetes Mellitus	14 (35.0)	2 (9.1)	0.026
	Hyperlipidemia	6 (15.0)	0 (0.0)	0.001
	HTN	18 (45.0)	5 (22.7)	0.080
	Smoking	23 (57.5)	3 (13.6)	0.001
ECG	Sinus Rhythm	38 (95.0)	20 (90.9)	0.600
	LBBB	15 (37.5)	6 (27.2)	0.780
	RBBB	4 (10.0)	3 (13.6)	0.690

Data are presented as mean ± standard deviation for quantitative variables and n (%) for qualitative variables.
Diabetes: Fasting blood sugar ≥ 126 mg/dl or use of diabetes medications; Hyperlipidemia: LDL > 160 mg/dl or total cholesterol > 240 mg/dl
ICM: Ischemic cardiomyopathy; NICM: Non-ischemic cardiomyopathy; NYHA: New York Heart Association; BSA: Body surface area; HTN: Hypertension; LBBB: Left bundle branch block; RBBB: Right bundle branch block; ECG: Electrocardiography

Among clinical and echocardiographic parameters, age, gender, DM, HLP, smoking, PMLA, and anterior and inferior Sm were shown to have significant associations with ischemic MR by univariate analysis ($P < 0.050$). Table 3 reveals the results of multiple logistic regression analysis regarding the significant predictors of ischemic MR. Smoking was identified as a strong determinant of ischemic MR (OR = 3.16, 95% confidence interval (CI): 2.77-198.52, P = 0.004). Moreover, echocardiographic parameters of PMLA and anterior Sm were identified as determinants with significant prediction value for ischemic MR (OR = 0.89, 95% CI: 0.82-0.96, P = 0.003; OR = 0.29, 95% CI: 0.14-0.60, P = 0.001, respectively).

According to the ROC curve analysis for PMLA and anterior Sm, the optimal cut-off point for discriminating ischemic MR from non-ischemic MR was ≤ 4 cm/second with the sensitivity and specificity of 80.0% (95% CI: 64.5-91.0), and 73% (95% CI: 50.0-91.0), respectively, and area under the curve (AUC) of 0.77 (95% CI: 0.63-0.91, $P < 0.001$). On the other hand, PMLA ≥ 40 degrees had the sensitivity of 70.0% (95% CI: 53.5-83.4), specificity of 77.3% (95% CI: 54.6-92.2), and AUC of 0.73 (95% CI: 0.59-0.86, P = 0.001) for predicting the ischemic etiology of FMR (Table 4) (Figure 3). Although PMLA had a higher positive predictive value (95% CI) than anterior Sm [0.75 (0.67-0.81) vs. 0.74 (0.67-0.80), respectively], this difference was not significant.

Table 2. Echocardiographic indices of patients with ischemic cardiomyopathy and non-ischemic cardiomyopathy

Parameter	ICM (n = 40)	NICM (n = 22)	P
LVEDV/BSA (ml/m^2)	119.32 ± 48.79	120.81 ± 42.72	0.790
LVESV/BSA(ml/m^2)	91.95 ± 38.64	96.49 ± 31.20	0.950
LVEF (%)	23.10 ± 6.60	19.80 ± 9.00	0.105
Tenting area	2.30 ± 0.90	2.30 ± 0.80	0.690
Coaptation depth	10.00 ± 0.40	9.30 ± 0.20	0.420
Anterior Sm (cm/second)	3.75 ± 1.14	5.00 ± 1.53	0.002
Inferior Sm (cm/second)	3.72 ± 1.11	4.80 ± 1.20	0.002
Anterior MLA (degree)	35.21 ± 9.80	34.32 ± 11.76	0.670
Posterior MLA (degree)	50.70 ± 12.21	40.10 ± 11.37	0.002

Data are presented as mean ± standard deviation.
ICM: Ischemic cardiomyopathy; NICM: Non-ischemic cardiomyopathy; LVEDV: Left ventricle end-diastolic volume; LVESV: Left ventricle end-systolic volume; LVEF: Left ventricle ejection fraction; BSA: Body surface area; Sm: Systolic myocardial velocity; MTA: Mitral leaflet angle; AMLA: Anterior mitral leaflet angle; PMLA: Posterior mitral leaflet angle; NS: Non-significant (P > 0.050)

Table 3. Logistic regression analysis for the prediction of ischemic functional mitral regurgitation*

Parameter	OR (95% CI)	P
Univariate		
Age (year)	1.07 (1.02-1.21)	0.010
Gender (male)	1.15 (0.76-1.74)	0.490
Hyperlipidemia	1.73 (1.10-2.72)	0.020
Hypertension	0.66 (0.28-1.50)	0.320
Smoking	3.13 (1.04-9.42)	0.040
Anterior Sm (cm/second)	0.22 (0.11-0.45)	< 0.001
Inferior Sm (degree)	0.99 (0.98-1.00)	0.340
PMLA (degree)	1.16 (1.13-1.19)	0.001
Multivariable		
Age(y)	0.99 (0.94-1.04)	0.740
Hyperlipidemia	1.26 (0.58-2.74)	0.550
Anterior Sm (cm/second)	0.29 (0.14-0.60)	0.001
PMLA (degree)	0.89 (0.82-0.96)	0.003
Smoking	23.46 (2.77-198.52)	0.004

CI: Confidence interval; OR: Odds Ratio; Sm: Systolic myocardial velocity; PMLA: Posterior mitral leaflet angle;
* Stepwise logistic regression was done.

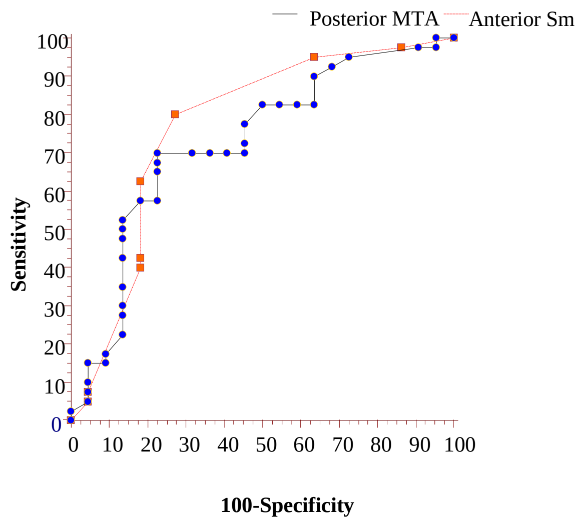

Figure 3. Receiver–Operating Characteristics curve illustrating accuracy of anterior systolic myocardial velocity and posterior mitral leaflet angle for the prediction of the ischemic etiology of functional mitral regurgitation

Discussion

The aim of this study was to evaluate echocardiographic parameters including 2D deformation MV indices and TDI in patients diagnosed with ICM and DCM. Echocardiographic differences were assessed with respect to FMR indices between these two groups. There were no significant differences in MR severity, and LV size and function (as measured by LVEF) between the two groups. The present study showed significant differences in PMLA and Sm between individuals with ICM and DCM. There were no significant differences in AMVL, TA, and CD between ICM and DCM groups. Multivariable logistic analysis demonstrated that PMLA and Sm could predict the etiology of FMR in patients with systolic heart failure. Many studies which have assessed echocardiographic characteristics in subjects with ICM and DCM have mainly focused on the relation of MV indices to MR severity. Konstantinou et al. studied the relation of MV echocardiographic deformation parameters with the severity of MR in ICM and DCM.[10] They found that FMR severity was chiefly determined by the extent of mitral apparatus deformity, and CD and regional myocardial systolic velocity had a significant association with FMR severity.

Table 4. Sensitivity and specificity of the anterior systolic myocardial velocity and posterior mitral leaflet angle for the identification of ischemic etiology in patients with functional mitral regurgitation

Parameter	Cut-off point	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	Positive Predictive value (95% CI)	Negative Predictive Value (95% CI)	P
Anterior Sm	4 (cm/second)	0.80 (0.64-0.91)	0.73 (0.50-0.89)	0.77 (0.63-0.91)	0.74 (0.67-0.80)	0.78 (0.70-0.84)	< 0.001
PMLA	40 (degree)	0.70 (0.53-0.83)	0.77 (0.54-0.92)	0.73 (0.59-0.86)	0.75 (0.67-0.81)	0.71 (0.65-0.77)	0.001

CI: Confidence interval; AUC: Area under the curve; Sm: Systolic myocardial velocity; PMLA: Posterior mitral leaflet angle

In the study by Papadopoulou et al., there were significant differences in LV and MV indices between ICM and DCM with functional MR.[11] In the logistic regression analysis, CD and TA were significantly larger in patients with ICM than those with DCM. TA > 1.27 cm^2 exhibited the highest sensitivity for predicting the ischemic etiology of LV dysfunction. However, this study evaluated patients with varying degrees of MR severity, which can have a confounding effect on the results reported. Therefore, the relatively similar CD and TA between ICM and DCM in our study could be due to the inclusion of subjects with no significant differences in MR severity, LV size, and function.

Upon evaluating the myocardial systolic velocity by TDI at mid-segments of anterior and inferior walls in ischemic and non-ischemic LV dysfunction, significant differences were observed in anterior and inferior Sm between ICM and DCM. Although the two groups had similar LVEF, patients with ICM exhibited lower systolic myocardial velocities, which could be explained by the regional wall motion abnormality detected in TDI. Significantly lower values of Sm were observed in patients with ICM compared to DCM, which was in agreement with previous studies.[8,12,13] MR severity affects Sm,[1] even though all patients in the present study had MR with similar moderate severity. In fact, longitudinal LV contraction could be attenuated in myocardial ischemia. Obstructive CAD leads to regional hypoperfusion of the myocardium which is detected by TDI earlier than visual assessment, presenting with attenuated Sm. In the present study, it was found that Sm values of less than 4 cm/second were independently associated with the probability of diagnosis of ICM rather than DCM.

In the current study, patients with ICM had a higher degree of PMLA angle in comparison with subjects with DCM, which could be explained by the predominant role of posteromedial dysfunction in ischemic MR. Therefore, in addition to the predictive role of Sm in identifying ICM and DCM, PMLA of more than 40 degrees with a high sensitivity and specificity in predicting the ischemic origin of functional MR was observed. This independent predictive role for PMLA in the present survey can be explained by the mechanism of FMR in patients with ICM. Mitral valve tenting is a major determinant of FMR and is directly determined by local LV remodeling, particularly by the displacement of the apical and posterior papillary muscles (PM). The pattern of mitral apparatus deformation is asymmetrical in ICM-related FMR. This could result in augmented tethering of the posterior MV leaflet rather than anterior MV leaflet in patients with ICM because of regional change in LV dysfunction. In contrast, in patients with DCM, global LV dysfunction results in bilateral symmetrical PM displacement.[14-16]

Gorman et al. suggested that, in a sheep model, LV dilatation without prominent geometric changes in the MV apparatus does not cause significant ischemic MR, while with MV annular and posteromedial PM geometric changes, especially in subjects with posterior MI, MR develops.[17] Therefore, ischemic MR is proportional to the degree of deformity of the MV complex, especially the outward displacement of the posteromedial PM, rather than to global LV dilatation. Magne et al. conducted a study on patients with ischemic MR who underwent surgical MV repair.[18] Patients with PMLA of more than 45 degrees had unfavorable results and recurrence of MR was seen frequently in these patients. Their study suggested that a higher degree of PMLA indicates the greater tethering of MV leaflets, resulting in unsuccessful MV repair.

Limitation: The main limitation of this study was that the patient population was relatively small; thus, further studies with larger samples are needed. Moreover, the present study findings were limited to patients with moderate severity of functional MR.

Conclusion

PMLA ≥ 40 degrees in echocardiography could be used with reasonable accuracy to predict the ischemic entity of MR in patients with systolic heart failure. In addition, Sm ≤ 4 cm/second measured by TDI can predict MR of ischemic origin in patients with systolic heart failure.

Acknowledgments

The authors wish to thank Mr. Aminreza Amini for his assistance in data interpretation in this survey. This study was supported by a grant from the Vice Chancellor for Research of Mashhad University of Medical Sciences as a medical student thesis with the approval number 93516.

Conflict of Interests

Authors have no conflict of interests.

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How to cite this article: Ghaderi F, Vakilian F, Nezafati P, Amini OR, Sheikh-Andalibi MS. **Prediction of the ischemic origin of functional mitral regurgitation in patients with systolic heart failure through posterior mitral leaflet angle.** ARYA Atheroscler 2018; 14(1): 17-23.