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Left ventricle assessment by three-dimensional HeartModel software in different types of mitral valve prolapse (Barlow's disease and fibroelastic deficiency) with severe mitral regurgitation

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Original Article

Abstract

BACKGROUND: Mitral valve prolapse (MVP) is the most common cause of isolated mitral regurgitation (MR) requiring surgical repair. Therapeutic interventions should be considered before irreversible left ventricular (LV) dysfunction in asymptomatic patients. Measurement of LV volume and function is very important. Because of two-dimensional (2D) echocardiography limitations, three-dimensional (3D) measurement is preferred on the strength of its speed, accuracy, and reproducibility, which are comparable with those of magnetic resonance imaging (MRI).

METHODS: This study was conducted between April 2018 and February 2019 on 50 patients with different MVP types and severe MR scheduled for valve surgery at Rajaie Cardiovascular Research Center, Tehran, Iran, with the aid of the HeartModel$^{\text{Anatomical intelligence (A.I.)}}$ (EPIQ 7: new 3D software) for measurement of LV volume indices and function.

RESULTS: Patients with the Barlow syndrome had a greater drop in LV ejection fraction (LVEF) than those with fibroelastic deficiency (FED) (57.05% ± 6.00% vs. 65.00% ± 4.08%; P = 0.001). LV volume was larger in patients with flail mitral valve (MV) than in those with non-flail MV (165 cc vs. 118 cc; P = 0.001). LVEF declined more in patients with the involvement of both leaflets than in those with the involvement of the anterior leaflet alone (56.00% ± 7.10% vs. 57.70% ± 4.30%; P = 0.021).

CONCLUSION: The LVEF drop was more remarkable in patients with the Barlow syndrome (both flail and non-flail MV) than in those with FED. It is, therefore, advisable that such patients be monitored more meticulously via the 3D HeartModel$^{\text{A.I.}}$ method in terms of LVEF and LV size to prevent irreversible effects on LV function and to reduce mortality.

Keywords: Three-Dimensional Echocardiography; Mitral Valve Prolapse; Mitral Regurgitation; Left Ventricular Function

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Introduction

The main components of the mitral valve (MV) apparatus are the leaflets, the mitral annulus, the chordae tendineae, and the papillary muscles attached to left ventricular (LV) wall.[1] Failure in any component of this system results in mitral regurgitation (MR) from the LV to the left atrium (LA) in systole. The MV has 2 leaflets: the anterior leaflet with 3 segments: A1, A2, and A3, without distinctive separation between them and a posterior leaflet with 3 scallops: P1 (anterolateral), P2 (middle), and P3 (posteromedial).[2]

MR is categorized as primary and secondary. Whereas an intrinsic pathology in the leaflets causes primary MR, the distortion of the MV apparatus due to LV or LA remodeling is the main culprit for secondary MR.[3] The prevalence of MR is more than 10% in adults over 75 years.[4] In the Euro Heart Survey, MR was the second most common cause of valvular diseases (31.5%) after aortic stenosis

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necessitating surgery.[4] Primary MR is mainly caused by mitral valve prolapse (MVP) with myxomatous degeneration, the 2 most common forms of which are fibroelastic deficiency (FED) (focal segmental thinning of the leaflets) and the Barlow syndrome (diffuse thickening and redundancy of several segments of both leaflets and chordae).[3]

MVP is a common disorder with a prevalence rate of 2% to 3% in the general population and is the most common cause of isolated MR requiring surgical repair.[5] This pathology is due to free-edge prolapse with scallop billowing or flail MV. The flail valve is accompanied by chordal rupture and sometimes by chordal elongation without complete rupture (partial flail).[2]

MVP may be familial or sporadic. Most data indicate an autosomal dominant pattern of inheritance.[5] Among patients with MVP, fewer than 10% have progression to severe MR, with the rest remaining asymptomatic with a normal life expectancy.[6]

MR leads to increasingly more severe MR and irreversible LV dysfunction. An LV end-systolic dimension (LVESD) of 40 mm or more independently predicts overall and cardiac mortality, even after surgery.[7] Most guidelines state that intervention is prudent in patients who are not symptomatic but have a progressive decrease in the LV ejection fraction (LVEF) toward 60% or an increase in LVESD to 40 mm.[8,9]

Two-dimensional (2D) echocardiography is used to study LV volume and function. This modality, nonetheless, has some limitations for LV imaging such as foreshortening, malrotation, and angulation. A suboptimal acquisition of 2D images yields incorrect volume measurements.[10] Three-dimensional (3D) echocardiography is preferred to its 2D counterpart insofar as the former is comparable with cardiac magnetic resonance (CMR) in terms of speed, accuracy, and reproducibility.[10,11]

There is no extensive study in the literature that has compared 2 groups of patients suffering from MVP (the Barlow syndrome vs. FED) with severe regurgitation using advanced 3D methods in such details.

The salient point vis-à-vis the 3D full-volume mode is its operator dependency in border detection, despite its ability to offer the largest acquisition sector.

In the HeartModel[Anatomical intelligence (A.I.)], a novel software in Philips system (EPIQ 7) automatically detects the segments and quantifies the LV and LA from a live 3D volume. With a single button, the HeartModel[A.I.] overcomes the time it takes to perform 3D transthoracic echocardiography (TTE) and automatically-designed visualization and editing interface illustrates the standard AP2, AP3, and AP4 views in a comparatively short time and without foreshortening. Similar to a routine 2D examination, users are not required to have significant experience in navigating around 3D ultrasound volumes to align the views to the standard views.[12]

Materials and Methods

This cross-sectional study was conducted from April 2018 to February 2019 at Rajaie Cardiovascular, Medical, and Research Center, Tehran, Iran. Initially, patients with MVP and severe MR that were referred for transesophageal echocardiography (TEE) were chosen randomly. Next, patients were excluded if they had one of the following criteria: LVEF less than 45%, coronary artery disease (CAD), other more-than-mild valvular problems, and atrial fibrillation (AF) rhythms. Consequently, using convenience sampling, 50 patients were enrolled in the study. The sample size was calculated using the formula regarding to previous studies that compared 2D and 3D TEE in MVP with severe MR. The study protocol was approved by the Ethics Committee of Rajaie Cardiovascular, Medical, and Research Center, and written informed consent was obtained from all the participants that included information about procedure, ensuring data protection, confidentiality, privacy, and reference contacts for any further answers to questions and opportunity to withdraw at any time from research without any consequences.

Echocardiography: Following the collection of the study population's general information such as age, sex, body surface area (BSA), and functional capacity (FC), an echocardiologist performed standard 2D TTE studies using a Philips EPIQ 7 ultrasound system for cardiology equipped with xMATRIX ultrasound transducer technology. LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and LVEF were calculated via eyeball estimation and the Simpson's biplane method. Afterward, LV volumetric indices and function were assessed using the 3D HeartModel[A.I.] software (EPIQ 7). Finally, other MV parameters such as regurgitation severity, MR jet direction in the LA, and the leaflets and scallops involved were recorded by TEE.

Statistical analysis: All the continuous variables were expressed as the mean ± standard deviation (SD). Normal distribution was tested using the Kolmogorov-Smirnov test. The distribution of

ejection fraction (EF) and end-systolic volume (ESV) calculated by HeartModel and also LVEDV was normal. The continuous variables were compared using the independent samples t-test or the one-way analysis of variance (ANOVA). A P-value of less than 0.05 was considered statistically significant. All the statistical analyses were performed using SPSS software (version 22.0, IBM Corporation, Armonk, NY, USA) released in 2013.

Results

The general information of the study population is summarized in table 1. The majority of the patients were men (66%), and the mean age was 46.0 ± 15.2 years. Most patients (64%) had little activity restriction [New York Heart Association (NYHA) functional class II].

Table 1. General information of the study population (n = 50)

Variable	n (%)
Sex (male)	33 (66)
FC	
I	15 (30)
II	32 (64)
III	3 (6)
Etiology (1)	
Barlow	43 (86)
FED	7 (14)
Etiology (2)	
Flail	29 (58)
Non-flail	21 (42)
Variable	**Mean ± SD**
Age (year)	46.50 ± 15.00
BSA (m^2)	1.79 ± 0.21
EF (%)	
2D	55.50 ± 4.00
Simpson	60.10 ± 6.00
3D HM	58.20 ± 6.80
LVEDV (cc)	
Simpson	147.40 ± 49.10
3D HM	146.50 ± 49.00
LVESV (cc)	
Simpson	55.80 ± 19.80
3D HM	58.70 ± 21.80

Data are reported as mean ± standard deviation (SD) or number (percentage)
BSA: Body surface area; FC: Functional capacity; FED: Fibroelastic deficiency; EF: Ejection fraction; 2D: Two-dimensional; 3D: Three-dimensional; HM: HeartModel$^{A.I.}$; LVEDV: Left ventricular end-diastolic volume; LVESV: Left ventricular end-systolic volume

Valve involvement was chiefly due to the Barlow syndrome (86%) with a lower prevalence of FED (14%). Flail MV was more prevalent than non-flail MV (58% vs. 42%). In two-thirds of the study population, the involvement was seen in both anterior and posterior leaflets; and in the remainder, only the posterior (26%) and anterior (8%) cusps were affected. Multi-scallop involvement was reported in 56% of the patients. Of all the scallops, the P2 was the most frequently involved one (28%).

In our study, the agreement rate according to the Bland-Altman plot (difference plot) between different 2D and 3D methods in the analysis of LVEF and LV volumetric indices showed that the HeartModel$^{A.I.}$ had a high agreement with the Simpson's biplane method [intraclass correlation (ICC): 0.859, 95% confidence interval (CI): 0.745-0.922].

We assessed most of the LV indices using the 3D HeartModel$^{A.I.}$ rather than the Simpson's biplane method, because the former required less manual intervention and conferred higher speed and accuracy.

A: Comparisons of LV function and volumetric indices using the HeartModel$^{A.I.}$ between patients with the Barlow syndrome and those with FED

LVEF measurements with the HeartModel$^{A.I.}$ showed a lower mean LVEF in patients with the Barlow syndrome than in those with FED (57.05% ± 6.00% vs. 65.00% ± 4.08%; P = 0.001) (Figure 1). However, the difference between the 2 groups concerning LVESV and LVEDV did not constitute statistical significance (Barlow LVESV = 60.6 ± 22.0 cc vs. FED LVESV = 48.0 ± 16.0 cc; P = 0.124 and Barlow LVEDV = 144.0 ± 49.0 cc vs. FED LVEDV = 167.0 ± 42.0 cc; P = 0.231).

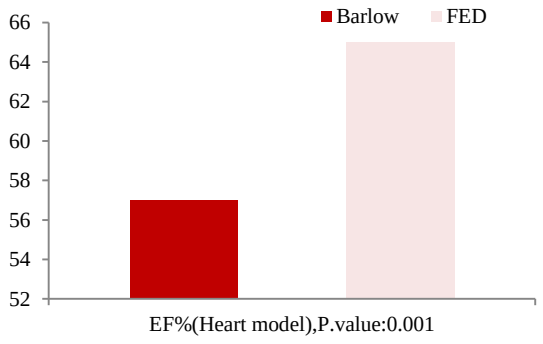

Figure 1. Comparison of left ventricular (LV) function between the patients with the Barlow syndrome and those with fibroelastic deficiency (FED) using the HeartModel$^{A.I.}$
EF: Ejection fraction; FED: Fibroelastic deficienc

B: Comparisons between patients with flail MV and those with non-flail MV

LVEDV and LVESV measurements with the HeartModel$^{A.I.}$ indicated greater volumes in patients

with flail MV than in those with non-flail MV (P = 0.001 and P = 0.043) (Figure 2). However, the difference between the 2 groups apropos of LVEF was not statistically significant (non-flail LVEF = 57% ± 7% vs. flail LVEF = 61% ± 6%; P = 0.112).

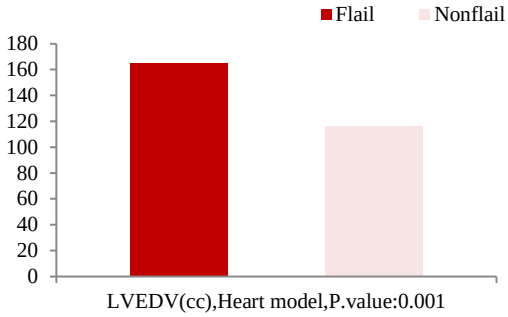

Figure 2. Comparison of left ventricular end-diastolic volume (LVEDV) between patients with flail mitral valve (MV) and those with non-flail MV using the HeartModel[A.I.]
LVEDV: Left ventricular end-diastolic volume

Additionally, by dividing patients with flail MV into FED and Barlow groups, we concluded that LVEF measurements with the HeartModel[A.I.] in patients with flail-Barlow were significantly lower than those in patients with flail-FED (flail-Barlow LVEF = 58.0% ± 5.0% vs. flail-FED LVEF = 65.0% ± 4.0%; P = 0.003). In terms of other measurements, the differences between these 2 subgroups were not statistically significant (flail-Barlow LVEDV = 166.0 ± 52.0 cc vs. flail-FED LVEDV = 167.0 ± 42.0 cc; P = 0.980).

C: Comparisons between patients with different leaflet involvements

LVEF declined significantly more in patients with the involvement of both anterior and posterior leaflets than in those with anterior leaflet involvement alone (56.0% ± 7.1% vs. 57.7% ± 4.3%; P = 0.021). Patients with posterior leaflet involvement alone had higher LVEF (mean LVEF = 62.6% ± 5.02%). This difference was not significant in the case of LVESV and LVEDV (P = 0.700 and P = 0.150).

D: Comparisons between patients with single-, double-, and multi-scallop involvements

No significant differences were found concerning LVEF, LVESD, and LVEDV between patients with the involvement of 1, 2, and multi scallops (P = 0.130, P = 0.090, and P = 0.100).

E: Comparisons of volumetric indices and cardiac function based on MR jet direction

The results of the HeartModel[A.I.] demonstrated the lowest and highest LVEF in patients with central jets and those with anterior jets, respectively (mean LVEF = 52.66% ± 2.50% vs. 60.62% ± 5.70%; P = 0.034) (Figure 3). Moreover, patients with central jets, despite their lower LVEF, had lower LVEDV (mean volume = 105 cc) than their counterparts with posterior jets (mean volume = 145 cc) and anterior jets (mean volume = 154 cc) (P = 0.043). In patients with medial jets, LVEDV was greater than that in patients with lateral jets (158.00 ± 45.87 cc vs. 119.00 ± 25.12 cc; P = 0.005). Further, according to the HeartModel[A.I.], LVEF in patients with medial jets was greater than that in those with lateral jets (60.13% ± 5.80% vs. 54.15% ± 7.20%; P = 0.019).

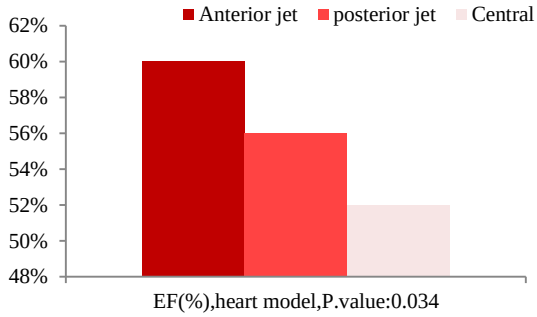

Figure 3. Comparison of left ventricular (LV) function using the HeartModel[A.I.] regarding mitral regurgitation (MR) jet direction
EF: Ejection fraction

Discussion

A study published in the Journal of the American College of Cardiology (ACC) examined the ICC between the different methods of measurement and reported that both 2D and 3D methods had a significant agreement with computed tomography (CT) and magnetic resonance imaging (MRI) (> 80%).[12] The 3D method has been employed in previous studies for volume measurement. Not only this method benefits from a good agreement rate with MRI as a reference method in volume measurement, but also it confers a high ICC.[13] Of all 3D methods in current use, the HeartModel[A.I.] requires the least manual intervention and enjoys the highest speed and accuracy; accordingly, we utilized this method for volume measurement in our study. In addition, worthy of note is the absence of extensive research in the literature on the comparison of 2 groups of patients suffering from MVP (the Barlow syndrome vs. FED) with severe regurgitation via the 3D method with as many details as are found in the current investigation.

In our study, patients with the Barlow syndrome had lower LVEF than their counterparts with FED. Our subgroup analysis revealed that LVEF measurements with the HeartModel[A.I.] in patients with flail-Barlow were significantly lower than those in patients with flail-FED (P = 0.003).

Malev et al.[14] compared 2 groups of patients with MVP using the global longitudinal strain method and found that LV function was lower in patients with the Barlow syndrome than in those with FED. Garbi et al.[15] reported evidence of LV fibrosis in patients with the Barlow syndrome, indicating the emergence of cardiomyopathy and increasing the risk of sudden cardiac death. Indeed, there is a growing body of evidence denoting a predisposition toward cardiomyopathy and fibrosis in patients with the advanced forms of MVP.[16]

Most guidelines including those from the ACC and the European Society of Cardiology (ESC) underscore the significance of LV size and EF in opting for surgery in patients with MR who are without symptoms.[8,9] Patients with severe MR and with LVEF less than 60% or LVESD more than 40 mm are considered to have already developed LV systolic dysfunction.

As has been repeated frequently in the literature, "MR begets MR". In other words, MR leads to LV dilation, which exerts more stress on the mitral apparatus and LV geometry and, thus, causes further damage to it. The upshot is the creation of a perpetual cycle that induces more LV dilation, progressively severe MR, and ultimately irreversible LV dysfunction.

In the Mitral Regurgitation International Database (MIDA) registry, which is a large-scale multicenter registry, 739 patients with flail MV and MR were evaluated.[7] The results demonstrated that in patients under medical treatment, LVESD of 40 mm or greater independently predicted overall mortality [hazard ratio (HR): 1.95, 95% CI: 1.01-3.83] and cardiac mortality (HR: 3.09, 95% CI: 1.35-7.09). Moreover, mortality risk increased linearly (HR: 1.15, 95% CI: 1.04-1.27 per 1-mm increment). Even with surgery, LVESD of 40 mm or greater independently predicted overall mortality (HR: 1.86, 95% CI: 1.24-2.80) and cardiac mortality (HR: 2.14, 95% CI: 1.29-3.56). As a consequence, the guidelines of both the ACC and the ESC recommend intervention in patients who are not symptomatic but exhibit a progressive decrease in LVEF toward 60% or an increase in LVESD to 40 mm.[8,9]

Given that our results revealed a greater drop in LVEF in patients with the Barlow syndrome (both flail and non-flail) than in those with FED, it seems reasonable to monitor these patients more accurately in terms of LVEF with a view to preventing irreversible effects on the long-term LV function and reducing mortality.

In the context of a paucity of data in the existing literature on comparisons between patients with flail and non-flail MV, we found that patients with flail MV had larger LVESV and LVEDV than those with non-flail MV. It can, therefore, be concluded that patients with flail MV who are asymptomatic should be accorded more attention because of the greater rate of ventricular enlargement and the resultant long-term effects on increased mortality and decreased cardiac function, even after surgery. It is deserving of note that previous studies have reached a cutoff point of 40 mm using ventricular measurements via the 2D method; consequently, future investigations are required to determine more accurate cutoff points for LV volume and EF.

Suzuki et al.[17] compared the outcome of their patients in terms of the involved leaflet and found that patients with posterior leaflet involvement had a larger ventricular size and a worse outcome than those with the involvement of the anterior leaflet or both leaflets. LVEF measurements with the HeartModel[A.I.] in our study demonstrated that the LVEF drop was significantly greater in patients with the involvement of both anterior and posterior leaflets than in those with anterior leaflet involvement alone (P = 0.021). Additionally, patients with posterior leaflet involvement alone had higher LVEF.

Unlike the Suzuki et al.[17] study, this issue was not statistically significant regarding ventricular volume in our study. Although we did not follow our study population with respect to outcomes, our measurements made with the advanced method of the HeartModel[A.I.] confirmed that cardiac function was further reduced in patients with the involvement of both valve leaflets in consequence of the increased hemodynamic effects on the heart. The difference between the results of our study and those reported by the previous studies on the posterior leaflet warrants further research with advanced 3D techniques since the latter studies made all their measurements via the conventional methods.

Low LVEF is associated with worse outcomes.[8] According to our findings based on the HeartModel[A.I.], the lowest and highest LVEF levels were detected in patients with central MR jets and those with anterior MR jets, correspondingly (P = 0.034).

Central MR is more likely to develop in patients suffering from the Barlow syndrome with multi-scallop involvement, which is not amenable to surgical repair. Hence, patients with central MR jets should be followed meticulously at shorter intervals.

Conclusion

In light of the results of the current study, the 3D HeartModel[A.I.], which needs the least manual intervention but confers the highest speed of all 3D methods in current use, can be drawn upon as a proper modality along with other conventional methods (e.g., 2D and the Simpson's biplane) in patients with MV regurgitation for the timely and accurate diagnosis of LV size increase. Some patients have poor echo window and dependency of 3D study on image quality is one of the main limitations in our study. Some patients with MVP are thin with some degrees of chest deformity which affects the 3D image acquisition.

That LVEF drop was greater in our patients with the Barlow syndrome (both flail and non-flail) than in those with FED which indicates that the prevention of irreversible effects on the long-term LV function and mortality among these patients requires accurate LVEF evaluations.

Further, our patients with flail MV had greater LVESV and LVEDV than those with non-flail MV, suggesting the need for close follow-ups of asymptomatic patients with flail MV, especially in view of the fact that they are at higher risk of ventricular enlargement and the ensuing long-term effects on increased mortality and compromised cardiac function, even after surgery.

Previous studies have reached a cutoff point of 40 mm in patients with severe MR merely by using ventricular measurements via the 2D method in their attempts to assess the increased risk of postoperative heart failure and increased mortality. Future investigations may determine more accurate cutoff points for LV volume and EF with the aid of advanced 3D modalities.

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Conflict of Interests

Authors have no conflict of interests.

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