The role of three-dimensional transesophageal echocardiography in predicting the effect of cardiac resynchronization therapy on mitral regurgitation in patients with low ejection fraction heart failure

Ayse Demirtola[1], Turkan Tan[2], Anar Mammadli[3], irem Muge Akbulut[4], Demet Gerede[5], and Irem Dincer[6]

[1]Basaksehir Cam ve Sakura City Hospital
[2]Ankara University Department of Cardiology
[3]Bayindir Hastanesi Sogutozu
[4]Ankara University Faculty of Medicine
[5]Ankara University
[6]Ankara University School of Medicine

June 18, 2021

Abstract

Purpose: Cardiac resynchronization therapy (CRT) has a positive effect on the improvement of functional mitral regurgitation in patients with heart failure with reduced ejection fraction. However geometric changes in the mitral valve apparatus, subvalvular structures and their contribution to the improvement of mitral regurgitation after CRT have not been clearly defined. The aim of our study was to evaluate the geometric parameters of mitral valve apparatus measured with 3Dimensional (3D) transesophageal echocardiography (TEE) before CRT implantation and to determine the parameters predicting the improvement of mitral regurgitation after CRT. Methods: In this prospective study thirty patients with moderate or severe mitral regurgitation with low EF heart failure planned for CRT implantation and had an indication for TEE were included. Effective regurgitant orifice (ERO) and regurgitant volume (RV) measurements were performed before CRT implantation. Detailed quantitative measurements of mitral valve were done from recorded images by 3D TEE. ERO, RV measurements were repeated to evaluate mitral regurgitation at the end of 3rd month. Results: There were no significant changes in left ventricular EF and left ventricular diameters at third month follow-up, whereas ERO and RV values were decreased. posterior leaflet angle was found higher in non-responder group compared to responder group. (28,93 ± 8,41 vs 41,25 ± 10,90, p = 0,006). Conclusion: Heart failure patients with moderate or severe functional mitral regurgitation who underwent CRT implantation were found lower posterior leaflet angle which was measured by 3D TEE in the patient group whose mitral regurgitation improved after CRT.

Introduction

Mitral regurgitation accompanies the heart failure with low ejection fraction at the rate of 30-50% (1). The coexistence of functional mitral regurgitation in patients with HfrEF is asscoiated with two fold increase in the mortality rates.(2) Progressive remodelling occurring in heart failure leads to left ventricular dilatation, increase in cavity sphericity, annulus expansion and displacement of papillary muscles result in improper coaptation of the leaflets and functional mitral regurgition. (3)-(4)

Although improvement in the mitral regurgitaion is expected after CRT implantation this is not the case in all of the patients. Several parameters were evaluated for the prediction of improvement of mitral regurgitation

after CRT implantation by 2D echocardiography. Tenting hight and interpapillary muscle distance were found to be related to improvement (5).

3D TEE is an integral part of the imaging in mitral valve disesases and has proven to be the most convincing method for understanding the complicated anatomy of the mitral valve and its dynamism.In addition to high quality real time imaging of the mitral valve it allows us to make quantitaive measurements by post process analysis.

Impact of CRT on geometric changes in mital valve apparatus and subvalvular structures and the parameters that would predict the improvement of mitral regurgitation still remain to be elucidated.

The aim of the this study was to evaluate the geometric parameters of mitral valve measured by three dimensional transosephageal echocardiography prior to CRT which would predict the improvement of mitral regurgitation after CRT implantation.

Methods

Study population

Among 72 patients who had CRT implantation were reviewed. 30 of them who had another indication for transeosephageal echocardiography (E.g. grading mitral regurgitation, trombus search etc.) and moderate to severe mitral regurgitaion were included to the study.

Patients with rheumatic mitral valve disease, severe annular calcifications, mitral valve prolapse and a history of mitral valve repair or replacement and those with inadequate acoustic windows were excluded from the study. Informed consent was obtained from the patients and approval from Clinical Investigation Ethics Committee in accordance with principles of Helsinki Declaration.

Echocardiographic analysis

Transthoracic and transosephageal echocardiograpy were performed with Vivid E9 Ultrasound system (GE Healtcare, Waukesha, WI, USA), which had both multiplane 2 dimensional and real time 3 dimensional imaging capacity. In accordance with the guides of American Echocardiography Association, left ventricle end systolic diameters (LVESD) and end-diastolic diamaters(LVEDD) were measured in the parasternal long-axis view in resting state , using transthoracic echocardiography (TTE) . Left ventricle ejection fraction (LVEF) was calculated with three dimensional echocardiographic method. In order to determine the severity of MR, proximal isovelocity surface area (PISA) method was utilized. ERO (Effective regurgitant orifice area) and RV (Regurgitant Volume) measurements were carried out at both before CRT implantation and at the end of 3. month follow up control.

Responder / Non-responder Definiton: As recommended by the guides, over 0.1 cm^2 decrease in ERO and 15ml and higher decrease in RV at the third month control TTE examination was regarded as improvement in MR and patients were divided into responder and non-responders according to this cutoff value.

Assesment with three dimensional TEE

In order to obtain values of mitral valve parameters before CRT implantation, real time 3 dimensional transesophageal echocardiography (TEE) Vivid 9 Ultrasound system was used. Using TEE probe in mid-esophageal position at full volume and in real time zoom mode with long axis view from left atrial perspective, images including mitral valve, aorta and LAA (left atrial appendix) and equivalent to surgical view were obtained. In order to increase temporal resolution multibeat images (at least 4 beat) (Frame rate: 8-12 Hz) in the region of interest, distance between sectors was decreased and gain was optimized to evaluate valve anatomy clearly and prevent artifacts. (Figure1)

Figure 1: .Evaluation of mitral valve apparatus with 3 dimensional transosephageal echocardiography

Data obtained in 3D zoom mode were recorded with EchoPac PC Software, Version 6.3 (GE Vingmed US, Horten, Norway), performing semi automated analysis. Detailed measurments of mitral valve was accessed

with 4D MVQ (Mitral Valve Quantification, GE Healthcare) program automatically and data were anlysed in offline mode. (Figure 2)

Figure 2: Three dimensional evaluation of mitral valve with EchoPac PC Software 4D MVQ program automatically

Statistical analysis

For statistical analysis, IBM SPSS Statistics v25 program was used. The evaluation of continuous variables was made with histogram diagrams and Kolmogorov-Smirnov test. .As continuous variables were not distributed normally and group frequencies and sample size was small, non-parametric methods were employed. Categorical (qualitative) variables were expreed with frequency (n) and percentage (%), and numerical variables with mean , standard deviation (sd) Changes in ERO, RV, LVEF, LVEDD, LVESD parameters before and three months after CRT were examined with Wilcoxon rank test. Improvement in MR was taken as dependent variable.

The difference in mean values of TEE between the group responders and non-responders was evaluated with Mann Whitney test. Logistic regression analysis was carried out so as to determine the variables predicting improvement in MR. *P value of* $< 0{,}05$ was considered statistically significant. .

Results

Baseline characteristics

Overall 30 patients (%70 male) were included to the study. Their mean age was 63,7, %36 had dilated cardiomyopathy while others had ishemic cardiomyopathy. Baseline demographic charecteristics were shown at Table 1.

In ECG examination, 17 (%56,7) patients had left bundle branch block, , 9 had right bundle branch block (%30) and 4 (%13.3) had interventriculer conduction delay with left bundle branch block variety .

All patients were using optimal medical heart failure treatment recommended by guidelines at baseline and at the end of 3rd month. At 3rd month control evaluation, there was no change in the use and the dosage of the drugs.

Pacemaker controls done at the baseline and 3rd month follow up evaluation, the rate of biventricular pace was at desired values i.e. (mean %95,6)

Baseline TTE Findings

At the baseline measurements mean EF value, mean LVEDD, mean LVESD, EROA value and mean RV value were found to be 22,83 ± 5,88%, 6,51 ± 0,68 cm, 5,38 ± 0,78 cm, 0,34 ± 0,15 cm2, 46,1 ± 15,73 mL respectively.

3D TEE Findings

In 3D TEE examination, mitral valve was accessed with 4D MVQ program automatically ; mean mitral annulus area was found to be 9,62 ± 2,73 cm2, mean postero-medial to antero-lateral diameter (PM-AL) was found to be 3,41 ± 0,47 cm, mean antero-posterior diameter was found to be 3,15 ± 0,53 cm, mean anterior leaflet angle was found to be 24,67° ± 8,06° and mean posterior leaflet angle was found to be 35,5° ± 11,5°. 3D Transosephageal echocardiographic findings of patients are illustrated in Table 2

Change in TTE parameters after CRT

There was no significant difference between baseline and 3rd month control measurments in terms of left ventricular size and EF values.However, significant difference was found in effective regurgitant orifice (ERO) and regurgitant volume (RV) measurements . ($p < 0{,}05$). Baseline and 3rd month control transthoracic echocardiography findings of patients are illustrated in Table 3.

Echocardiographic improvement in MR and TEE findings

In the present study, in accordance with the guides, at least 0,1 cm^2 reduction in ERO or at least 15ml decrease in RV was considered as echographic improvement of MR (Responder / Non-responder). There were 19 patients with at least 0,1 cm^2 reduction in ERO, 9 patients with at least 15ml decrease in RV and 8 patients who fulfilled both parameters.

No statistically significant difference was found between patients with and without at least 0.1 cm^2 decrease in ERO and between those with and without 15ml decrease in RV with regard to demographic characteristics. Table 4

No significant difference was found between patients in whom regarded as responder or non-responder according to status of change ERO, (Table 5) with respect to mitral annulus area, posteromedial and anterolateral diameter , antero-posterior diameter and anterior leaflet angle ($p > 0,05$). Yet, it was established that posterior leaflet angle was significantly lower in responder patients than that in non-responder patients. ($p = 0,029$) (40,73 vs. 32,47, $p = 0,029$).

No significant difference was found between three dimensional TEE paramers of patients in whom regarded as responder or non-responder according to status of change RV in terms of 3D TEE parameters. (Table6) However,, similar to the result obtained in ERO changes, in the responder group there was a trend towards lower posterior leaflet angle compared to non-responder group. . (respectively 29,22 vs. 38,19 $p = 0,063$)

In the group with whom regarded as responder or non-responder according to status of change ERO and RV both, When 3D TEE parameters were compared, statisicallly significant difference was found in posterior leaflet angle ($p < 0,05$). It was established that in non-responder group, posterior leaflet angle was higher. (38,05 vs. 28,5 $p = 0,049$). (Table 7)

Although posterior leaflet angle was found to be significantly different between responder and non-responder patients, in logistic regression analysis performed to determine the independent predictor parameters of MR improvement, it was not found to be significant.

Discussion

Aim of our study was to determine the parameters that will predict the improvement of mitral regurgitation after implatation of CRT in patinets with HFrRF with moderate or severe functional mitral regurgitation by measuring the geometric parameters of mitral valve with 3D TEE by 4D MVQ program automatically. Our results have shown that in patients with lower posterior leaflet angle, CRT resulted in the marked improvement of mitral regurgitation.

As it is known, functional mitral regurgitation arises as a consequance of the imbalance between closing and tethering forces responsible for valve competence. (4) Systolic dysfunction,ventricular remodelling, mitral annulus dysfunction, alteration in LV geometry and size and dyssnchrony are supposed to be the main causes of MR. (6)

Several echocardiogrphic parameters were found to be related to the significance of functional mitral regurgitation in patients with low EF heart failure. Posterior leaflet angle has been investigated many times as in our study. In a study echocardiography and cardiac MR were used in order to evaluate anterior and posterior leaflet angles, in the groups with severe MR; along with asymmetrical tethering, mean posterior leaflet angle was found to be a 38.37° and significant relation was demonstrated between RV and posterior leaflet angle. ($r = 0,90$ $p = 0,037$) (7)

Likewise, in the study of Kwan et al, in the evaluation of geomteric parameter measurements in ischemic cardiomyopathy, it was demonstrated that posteior leaflet angle of 47 degree was major predictor of severe MR with sensitivity of 96% and specifity of 84%. (positive predictive value 92%, negative predictive value 100%) (8)

CRT is a treatment option which can interrupt the vicious circle that deteriorates heart failure caused by MR.In acute period, resynchronization of papillary muscle enables the MR duration to be shortened and MR onset to be delayed , resulting in increase in transmitral pressure gradient and modification of mitral annulus

contraction via increased con tractility. (6) Moreover, in chronic period, resynchronization associated with remodelling brings about increase in closing forces within weeks to months and restores more coordinated movements of mitral valve components. (9) Beside this, there is an improvement in ejection fraction in the long term after CRT and it provides improvement in MR. However in our study we have evaluated the short term improvent at the end of three month and there was no change in LVEF and LV sizes and the improvement is only related to the CRT treatment. Although long term studies would be more valuable, results of our study shows solely effect of CRT on mitral regurgitaion is related to posterior mitral valve angle.

In the study of Kanzaki et al investigating the impact of CRT on early MR, it was revelaed through longitudinal strain measurements that after CRT implantation, mechnical activation of papillary muscles retension zone, became more coordinated and temporal delay between papillary muscles was decreased and improvement in dysynchrony was linked to improvement in MR.(10)

Three dimensional TEE, which has recently become popular in clinical practice, yields quite objective data in the evaluation of mitral valve. In a study including 112 patients with mitral valve prolapsus and severe MR, 2D and 3D TEE were compared and it was stated that measurements made with 3D TEE were superior in the determination of pathology. (11)

In addition to 3D TEE, full automated mitral analysis softwares enabling detailed evaluation of mitral valve has become more common in clinical practice. In the study of Nobuyuki et al comparing manual screening software with fully automated software in the three dimensional evaluation of mitral valve, it was stated that automated software had comparable accuracy to manual software as well as being time saving. (12)

Many measurements of the mitral valve can be made with these full automated mitral analysis softwares. And these reveal the effects of CRT on the mitral valve. Previous studies have demonstrated that the tenting hight and tenting area are related to both severity of mitral regurgitaiton and the response, by reason of tenting hight and the tenting area are the final results of the all the geometrical changes seen in dilated ventricle and accused for the development of mitral regurgitaiton annulus also has an adjuctive role by seperating the mitral leafleats.(13) However we had few number of the patients we could not included all the parameters that we would be measured with 3D TEE, we have included the parameters that are related to functional mitral regurgitaiton such as annulus size and diameters, anterior leaflet angle and as our results clinically important posterior leaflet angles.

Posterior leaflet angle is an indicator of posterior tethering. In dilated ventricle, the displacement of posterior papilary muscle will lead to increase in posterior tethering forces and in posterior leaflet angle and the resulting imbalance between tethering and closing forces will give rise to mitral regurgitation. Hence, in mitral valve complex with higher posterior leaflet angle, the response to treatment with CRT will be at a lower degree.

In conclusion, in heart failure patients with low ejection fraction, the accompanying moderate or severe mitral regurgitation portends poor prognosis and it is reduced after after CRT implantataion in about two thirds of the patients, which yields clinical benefit with decrease in mortality. Mitral valve measurments that will be made with 3D TEE prior to implantation may help to predict the response of MR to CRT. Hence, in the present study, we have tried to find out the parameters that will predict reponse to treatment of MR by evaluating mitral valve anatomy with 3D TEE and concluded that posterior leaflet angle may be an important parameter influencing the improvement in mitral regurgitation following CRT. (28,93 $\pm$ 8,41 vs. 41,25 $\pm$ 10,90, p = 0,006). Three dimensional TEE and is a highly valuable method for the both visual evaluation and quantitative analysis of mitral valve and further studies would be done with larger number of the patients to predict the mitral regurgitaiton responce to CRT implantation.

Study limitations

One of the limitatations, which may have influenced study results, is that patient number was low and the etiology of low ejection fraction was both ischemic and dialted cardiomyopathy, furthermore were dont have

only patients with LBBB but we also have patients with RBBB and LBBB type interventricular conduction delay. All of these may have an influence on the improvement of mitral regurgitaiton after CRT implantation. Another limitation was follow up period restricted to three months, as this period is not adequate to predict improvement either in LVEF or in mitral regurgitation. In three months follow up, no marked change was found in LVEF and volumes but in the long term, improvement in these parameters associated with left ventricle reverse remodelling, may decrease the degree of MR. For its evaluation, long term follow up will be more appropriate.

In addition, although the severity of mitral regurgitation was evaluated with transthoracic echocardiography at the third month follow up , as the patients did not undergo control TEE examination, the parameters of mitral valve, which are evaluated with TEE, improving and influencing the response to treatment of mitral regurgitataion, could not be determined.

Conclusion

In the present study, in patients with moderate and severe mitral regurgitataion, 3D TEE parameters, which could predict the improvement in MR after CRT, were investigated and it was established that patients with lower posterior leaflet angle can derive more benefit from CRT.

Conflicting interest: The authors declare that there is no conflict of interest.

References

1. Robbins JD, Maniar PB, Cotts W, Parker MA, Bonow RO, Gheorghiade M. Prevalence and severity of mitral regurgitation in chronic systolic heart failure. Am J Cardiol [Internet]. 2003 Feb [cited 2019 Aug 28];91(3):360–2. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0002914902031727

2. Junker A, Thayssen P, Nielsen B, Andersen PE. The Hemodynamic and Prognostic Significance of Echo-Doppler-Proven Mitral Regurgitation in Patients with Dilated Cardiomyopathy. Cardiology [Internet]. 1993 [cited 2019 Aug 28];83(1–2):14–20. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8261482

3. Agricola E, Oppizzi M, Maisano F, De Bonis M, Schinkel AFL, Torracca L, et al. Echocardiographic classification of chronic ischemic mitral regurgitation caused by restricted motion according to tethering pattern. Eur J Echocardiogr [Internet]. 2004 Oct [cited 2020 Apr 12];5(5):326–34. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15341868

4. Di Biase L, Auricchio A, Mohanty P, Bai R, Kautzner J, Pieragnoli P, et al. Impact of cardiac resynchronization therapy on the severity of mitral regurgitation. Europace [Internet]. 2011 Jun 1 [cited 2019 Aug 28];13(6):829–38. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21486916

5. Do CGM, Singh JP, Picard MH. Impact of cardiac resynchronization therapy on mitral valve apparatus geometry and clinical outcomes in patients with secondary mitral regurgitation. 2017;(Lv):1561–7.

6. PORCIANI M, MACIOCE R, DEMARCHI G, CHIOSTRI M, MUSILLI N, CAPPELLI F, et al. Effects of cardiac resynchronization therapy on the mechanisms underlying functional mitral regurgitation in congestive heart failure. Eur J Echocardiogr [Internet]. 2006 Jan [cited 2019 Aug 28];7(1):31–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16378918

7. Leśniak-Sobelga A, Wicher-Muniak E, Kostkiewicz M, Olszowska M, Musiałek P, Klimeczek P, et al. Relationship between mitral leaflets angles, left ventricular geometry and mitral deformation indices in patients with ischemic mitral regurgitation: Imaging by echocardiography and cardiac magnetic resonance. Int J Cardiovasc Imaging. 2012;28(1):59–67.

8. Kwan J, Gillinov MA, Thomas JD, Shiota T. Geometric predictor of significant mitral regurgitation in patients with severe ischemic cardiomyopathy, undergoing Dor procedure: a real-time 3D echocardiographic study. Eur J Echocardiogr [Internet]. 2007 Jun [cited 2019 Oct 24];8(3):195–203. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16621721

9. Linde C, Leclercq C, Rex S, Garrigue S, Lavergne T, Cazeau S, et al. Long-term benefits of biventricular pacing in congestive heart failure: results from the MUltisite STimulation in cardiomyopathy (MUSTIC) study. J Am Coll Cardiol [Internet]. 2002 Jul 3 [cited 2019 Jul 14];40(1):111–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0735109702019320

10. Kanzaki H, Bazaz R, Schwartzman D, Dohi K, Sade LE, Gorcsan J. A mechanism for immediate reduction in mitral regurgitation after cardiac resynchronization therapy. J Am Coll Cardiol [Internet]. 2004 Oct 19 [cited 2019 Oct 5];44(8):1619–25. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15489094

11. Pepi M, Tamborini G, Maltagliati A, Galli CA, Sisillo E, Salvi L, et al. Head-to-Head Comparison of Two- and Three-Dimensional Transthoracic and Transesophageal Echocardiography in the Localization of Mitral Valve Prolapse. J Am Coll Cardiol [Internet]. 2006 Dec 19 [cited 2019 Aug 8];48(12):2524–30. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17174193

12. Kagiyama N, Toki M, Hara M, Fukuda S, Aritaka S, Miki T, et al. Efficacy and Accuracy of Novel Automated Mitral Valve Quantification: Three-Dimensional Transesophageal Echocardiographic Study. Echocardiography [Internet]. 2016 May [cited 2019 Aug 11];33(5):756–63. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26661528

13. Karaca O, Cakal B, Omaygenc MO, Gunes HM, Kizilirmak F, Cakal SD, et al. Effect of cardiac resynchronization therapy on mitral valve geometry: a novel aspect as "reversed mitral remodeling." Int J Cardiovasc Imaging [Internet]. 2018 Jul 1 [cited 2020 Apr 12];34(7):1029–40. Available from: http://link.springer.com/10.1007/s10554-018-1308-2